 Thyroid Function in Horses with Peripheral Cushing’s Syndrome

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Increases in serum thyroid hormone concentrations after administration of thyrotropin-releasing hormone were either not different or greater in horses with peripheral Cushing’s syndrome compared with control horses. These results indicate that function of the pituitary-thyroid gland axis is normal in horses with peripheral Cushing’s syndrome. Authors’ addresses: Department of Large Animal Clinical Sciences (Graves, Schott, Eberhart, Nachreiner, Nickels) and Animal Health Diagnostic Laboratory (Refsal), College of Veterinary Medicine, Michigan State University, East Lansing, MI 48824-1314; and Department of Veterinary Medicine and Surgery (Johnson, Messer, Ganjam) and Department of Veterinary Biomedical Science (Slight), College of Veterinary Medicine, University of Missouri, 379 East Campus Drive, Columbia, MO 65211. © 2002 AAEP.

1. Introduction

Obesity-associated laminitis is a widely recognized problem of middle-aged horses that are not in consistent work. Affected horses accumulate fat in the crest of the neck, over the rump, and in the sheath in male horses. Development of laminitis is insidious in onset, and other risk factors (e.g., grain overload, diarrhea, or pleuropneumonia) are generally absent. Treatment of affected horses is challenging because the severity of laminitis initially precludes use of exercise for weight loss, and clients are reluctant to limit feed intake. Because of the frustrating nature of this problem, equine practitioners have searched for medical disorders that may explain development of laminitis in these otherwise apparently healthy horses. Based on detection of low serum thyroid hormone concentrations in some horses, hypothyroidism has been implicated in the syndrome and supplementation with exogenous thyroid hormone is a common treatment. However, abnormal responses to thyroid stimulation tests have not been demonstrated in affected horses. Further, development of laminitis has not been observed in thyroidectomized horses, suggesting that hypothyroidism is not a risk factor for laminitis. Thus, the potential role of hypothyroidism in obesity-associated laminitis remains unclear.

Peripheral Cushing’s syndrome (PCS) is the term that has recently been introduced to describe an endocrinopathy that seems to be involved in obesity-associated laminitis in horses. In contrast to clas-
sic equine Cushing’s disease, attributable to pituitary pars intermedia dysfunction, PCS seems to be a syndrome of increased cortisol action in peripheral tissues, including skin, fat, and laminar tissue. PCS seems to be somewhat analogous to the syndrome of central or omental obesity in humans that has been termed “omental Cushing’s syndrome.”

In the latter disorder, pituitary gland function is normal but cortisol production in omental fat cells and other tissues is increased because of enhanced oxoreductase activity of the enzyme 11β-hydroxysteroid dehydrogenase (HSD). The oxoreductase activity of HSD converts inactive cortisone to active cortisol, leading to a syndrome of cortisol excess at the tissue level.

In humans, genetic predisposition seems to be an important risk factor in the development of omental obesity. Complications of this disorder include type II diabetes (accompanied by hyperinsulinemia), dyslipidemia, and increased risk of vascular disease.

With further endocrine testing of horses with PCS, it has been found that they usually have elevated serum insulin concentrations. In addition, preliminary data indicate that oxoreductase activity of HSD in skin, fat, and laminar tissue of horses with obesity-associated laminitis is also increased.

The purpose of this study was to evaluate thyroid gland function in horses with PCS. Specifically, we compared thyroid hormone responses with administration of thyrotropin-releasing hormone (TRH) in horses with obesity-associated laminitis and control horses with other musculoskeletal disorders.

2. Materials and Methods

Horses referred to Michigan State University’s Veterinary Teaching Hospital for evaluation of laminitis were initially included in the study if they were obese (body condition score 6 or greater on a scale to 9) or had abnormal fat deposition in the crest of the neck and over the tail head. Further inclusion criteria used to establish a diagnosis of PCS included an elevated fasting insulin concentration (>300 pmol/l) and a normal response to an overnight dexamethasone suppression test (DST; suppression of plasma cortisol concentration to <30 pmol/l 17–19 h after administration of 0.02 mg/kg dexamethasone IM). Control horses were matched on the basis of age, sex, and presence of a musculoskeletal disorder resulting in chronic lameness (usually osteoarthritis). Further inclusion criteria for control horses included a normal fasting insulin concentration (<300 pmol/l) along with a normal response to an overnight DST.

After discontinuation of phenylbutazone or other non-steroidal anti-inflammatory drugs (NSAIDs) for a minimum of 24 h, blood samples were collected for a complete blood count, a serum biochemistry profile, and measurement of serum concentrations of total thyroxine (TT4), free thyroxine (FT4), total triiodothyronine (TT3), and free triiodothyronine (FT3). Measurement of serum concentrations of TT4, FT4, TT3, and FT3 were repeated 2, 4, and 6 h after administration of TRH (1 mg IV; Sigma Chemical Co, St. Louis, MO). Changes in thyroid hormone concentrations in PCS and control horses were evaluated by a two-factor analysis of variance (main effects of group and time), and when F ratios were significant (p < 0.05), a Student-Newman-Keuls post hoc test was performed to detect specific differences. Differences between single measurements (e.g., serum insulin concentration and blood glucose concentration) between groups were compared by a non-paired t test.

3. Results

During the study period, nine horses with obesity-associated laminitis and hyperinsulinemia (909 ± 243 [SE] pmol/l) were diagnosed with PCS. Affected horses ranged in age from 8 to 20 yr (mean, 14.5 yr) and included a variety of breeds: Morgan (2), Paso Fino (2), Saddlebred (2), Appaloosa (1), and Standardbred (1). A sex predilection was not apparent because four were mares and five were geldings. In addition, seven control horses with normal serum insulin concentrations (110 ± 22 pmol/l) were also studied. Control horses ranged in age from 8 to 19 yr (mean, 13.1 yr) and also included a variety of breeds. Although serum glucose concentration remained within the reference range for all horses, the mean value for PCS-affected horses (99.9 ± 3.3 mg/dl) was greater (p < 0.05) than that of control horses (85.0 ± 5.8 mg/dl).

In both PCS-affected and control horses, TT4, FT4, TT3, and FT3 increased after administration of TRH (Table 1). In fact, the only significant differences between the groups were greater increases in TT3 at all times and in FT3 4 h after TRH administration in PCS-affected horses.

4. Discussion

The results of this study indicate that the pituitary-thyroid gland axis responds normally to administration of TRH in PCS-affected horses. Thus, support for hypothyroidism as a risk factor for development of obesity-associated laminitis was not found in this group of horses. Although we used chemical grade (rather than medical grade) TRH in this study, the thyroid gland clearly responded during this stimulation test. Furthermore, we have used chemical grade TRH (cost of ~$1/mg vs. ~$100/mg for medical grade TRH) in more than 50 horses over the past 5 yr with numerous horses undergoing repeated testing. Despite the fact that no adverse effects have been observed, we continue to gain informed client consent before administration of this agent in the diagnostic evaluation of horses with suspected endocrine disorders.

We used an elevated serum fasting insulin concentration as an inclusion criterion for a diagnosis of PCS. However, it is noteworthy to mention that only one of the horses with obesity/abnormal fat deposition and laminitis initially screened for inclu-
sion in the study had a serum insulin concentration <300 pmol/l. Further, three other laminitic horses with hyperinsulinemia but without hirsutism were also excluded on the basis of overnight DST results supportive of classic Cushing’s disease. These findings demonstrate that measurement of serum insulin concentration should be combined with an overnight DST to fully evaluate horses with obesity-associated laminitis. Further, it remains unknown whether horses with obesity-associated laminitis (PCS-affected horses) may be at greater risk for development of classic Cushing’s disease or whether o xooreductase activity of laminar tissue HSD may be elevated in laminitic horses with classic Cushing’s disease.

At present, it is important to recognize that the syndrome of obesity-associated laminitis in horses remains incompletely understood and that multiple metabolic/endocrine disorders may be involved. However, this study provides support for a disturbance in tissue cortisol metabolism (manifested in these horses by hyperinsulinemia and a higher serum glucose concentration) as a more likely endocrine cause of the disorder than hypothyroidism. Further, until measurement of HSD activity becomes a clinically available diagnostic test, measurement of serum insulin concentration seems to be a useful tool in both the initial evaluation and monitoring of horses with this problem. In our experience, appropriate corrective trimming and shoeing, judicious use of NSAIDs, and weight reduction (through diet and increased exercise) has proved a successful approach to treatment of horses with obesity-associated laminitis. Clinical improvement has also been accompanied by a reduction in serum insulin concentration; however, a milder degree of hyperinsulinemia appears to persist in many PCS-affected horses.

Finally, despite the fact that the pituitary-thyroid axis responded normally to TRH administration in these PCS-affected horses, it remains unknown whether administration of exogenous thyroid hormone may be a useful adjunct treatment of horses with obesity-associated laminitis. In theory, thyroid hormone supplementation could increase metabolic rate and potentate weight loss accompanying dietary restriction. However, a controlled experiment comparing weight loss in thyroid hormone-supplemented and non-supplemented horses with obesity-associated laminitis is needed to answer this question. Although thyroid hormone supplementation to euthyroid horses has generally been considered safe, it warrants mention that excessive thyroid hormone supplementation can have detrimental effects in humans.

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References