Equine Nutritional Secondary Hyperparathyroidism

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Equine nutritional secondary hyperparathyroidism (NSH) results from feeding a ration with an improper calcium:phosphorus ratio, which causes hypersecretion of parathyroid hormone (PTH) and results in metabolic bone disease (fibrous osteodystrophy). Despite improvements in ration formulation and increased recognition of predisposing dietary factors, horses with NSH are still presented to practitioners. This article considers the causes, clinical signs, diagnosis, management, and prevention of NSH. Two affected horses that were recently examined at our clinic are described.

CAUSES

Nutritional secondary hyperparathyroidism results when an improper dietary calcium:phosphorus ratio leads to an increased concentration of serum phosphorus. The disease can be caused by a diet that is low in calcium, high in phosphorus, or low in vitamin D. In addition, animals that are pastured on grasses that contain excessive amounts of oxalate may develop clinical signs of NSH. Buffel grass (Cenchrus ciliaris), green and blue panic grasses (Panicum species), Argentine or Dallis grasses (Paspalum species), and Setaria sphacelata grass contain enough oxalate to diminish intestinal absorption of calcium by chelating calcium in the gastrointestinal tract but not enough oxalate to produce manifestations of oxalate toxicity (e.g., hypocalcemia and acute renal failure). In grass or hay, a calcium:oxalate ratio that exceeds 0.5% should be considered suspect.

The dietary imbalance of calcium and phosphorus may result either in a decreased serum concentration of ionized calcium or an increased serum concentration of phosphorus. The imbalance may be related to intestinal absorption of a decreased amount of calcium or an increased amount of phosphorus. The increased serum concentration of phosphorus or the decreased serum concentra-
tation of ionized calcium causes hypersecretion of PTH to maintain calcium homeostasis. Decreased serum concentration of ionized calcium directly stimulates secretion of PTH.

In current studies of secondary hyperparathyroidism in human and canine renal failure, the complex mechanism by which an increased concentration of serum phosphorus causes secretion of PTH remains controversial. One theory suggests that phosphorus combines with calcium in the serum, decreasing the ionized fraction of calcium and thereby stimulating secretion of PTH.

Another theory, not exclusive of the first, is that hyperphosphatemia decreases renal formation of calcitriol (1,25-dihydroxycholecalciferol), which results in decreased intestinal calcium absorption and removes the inhibitory effect of calcitriol on PTH secretion. The increased serum concentration of PTH in turn causes an increase in calcium mobilization from bone and an increase in renal excretion of phosphorus.

Increased activity of PTH directly results in increased resorption of calcium and phosphorus from bone and increased urinary excretion of phosphorus.

Increased activity of PTH also stimulates renal hydroxylation of 25-hydroxycholecalciferol to calcitriol. Calcitriol is very active and results in enhanced resorption of calcium and phosphorus from bone, increased intestinal absorption of calcium and phosphorus, and decreased urinary excretion of phosphorus. In time, the net effects of increased activity of PTH in NSH are a normal serum concentration of ionized calcium and an unchanged serum concentration of phosphorus. This increased activity is an appropriate but maladaptive process that (if the diet is not modified) eventually progresses to fibrous osteodystrophy as a result of continuous resorption of calcium and phosphorus from bone.

CLINICAL SIGNS

Clinical signs of NSH vary. Early signs usually involve a stiff gait or shifting-limb lameness. Loss of bony support of the articular cartilage of diarthrodial joints has been implicated as a cause of lameness related to the resultant joint pain. Other reasons for lameness include microfractures of the subepiphyseal region of long bones, focal periosteal avulsion fractures, and torn or detached tendons and ligaments at the points of origin or insertion. Any of these clinically evident osteopathies may progress to spontaneous fracture of long bones.

The classic clinical sign of NSH is fibrous osteodystrophy of the bones of the skull (so-called bighead) (Figure 1). Generally, enlargement of the facial bones is more common in young than in old horses, presumably because young animals have a higher rate of metabolism in bone. As calcium is absorbed from facial bones, it is replaced by fibrous tissue in excess of the amount of bone resorbed. If the process of calcium resorption is not halted, the affected horse may have difficulty with mastication as teeth loosen and be-

Figure 1—Maxillary swelling attributed to fibrous osteodystrophy in horse 1.

Figure 2—Radiograph of the skull of horse 1, with decreased facial bone density.
come painful in the maxillae and rami of the mandible. Consequently, weight loss may develop as a result of decreased ingestion.

The spectrum of disease associated with NSH is varied and may be ill-defined. In a study of racing Thoroughbred horses in Hong Kong, vertebral compression fractures were attributed to NSH. The researchers indicated that the incidence of skeletal injuries decreased when horses received calcium supplementation at the racetrack. Although other factors may have caused this decrease, the results suggest that NSH (as diagnosed by increased urinary fractional clearance of phosphorus) may contribute to skeletal injury. Clinical signs generally develop more rapidly in young horses because of their higher rate of bone metabolism.

**DIAGNOSIS**

Diagnosis of NSH, which can be challenging, is based on clinical signs and the findings of anamnesis, radiography, clinicopathologic testing, and feed analysis. Often, clinical signs strongly suggest NSH; however, clinical signs vary and may resemble those of other skeletal disorders. Because of the perception that NSH is a disease of historic importance, diagnosis is often delayed until other causes of skeletal disease have been excluded.

The most important component of anamnesis is dietary history. Traditionally, NSH is associated with diets that contain excess phosphorus (e.g., excess wheat bran) or plants that contain substances that chelate calcium (e.g., oxalate), thereby producing an imbalance in the dietary calcium:phosphorus ratio. Because concentrates are high in phosphorus relative to calcium, horses fed a ration principally composed of concentrates may develop NSH (as was the case with horse 1, discussed later in this article). In such instances, diagnosis of NSH is readily supported by the dietary history. In other instances, more thorough questioning and testing may be necessary to identify an incriminating diet (as was the case with horse 2).

Radiography of affected areas may show a generalized decrease in bone mineralization (osteoporosis). The earliest change that is radiographically evident is believed to be decreased density of the laminae durae dentes, presumably because of their thin, discrete radiographic appearance and their rate of osseous turnover.

Decreased density of facial bones may be the next radiographic finding (Figure 2), followed by decreased density of long bones (Figure 3). Because bone density must be reduced by at least 30% before it is radiographically apparent, NSH is often advanced before radiographic findings are diagnostic.

Clinicopathologic testing for NSH involves determining the serum concentrations of calcium and phosphorus, urinary fractional clearance of phosphorus, serum concentration of PTH, and calcium:phosphorus ratio in feces. As described, the net effect of increased PTH activity is an increased serum concentration of ionized calcium while the serum concentration of phosphorus is maintained. Serum concentrations of calcium and phosphorus thus are often in the normal range when clinical signs are manifested. In our experience, a slightly increased concentration of phosphorus is the most common serologic abnormality observed in horses with NSH.

Because serum concentrations of calcium and phosphorus may be normal, it may be necessary to evaluate the urinary fractional clearance of phosphorus, which is considered to be a sensitive indicator of NSH. In
a horse, this value can be calculated by determining the concentrations of creatinine and phosphorus in samples of urine and serum simultaneously collected. The urinary fractional clearance of phosphorus is determined as follows:

\[
\frac{\text{Urinary phosphate concentration}}{\text{Serum phosphate concentration}} \times \frac{\text{Serum creatinine concentration}}{\text{Urinary creatinine concentration}} \times 100
\]

The reference range for urinary fractional clearance of phosphorus is 0% to 0.5%. In patients with NSH, the value exceeds 0.5%. Because calcium may precipitate in equine urine as calcium carbonate and calcium oxalate, use of the fractional excretion of calcium is controversial as a diagnostic aid in the workup of these patients.\(^{2,6,17}\)

Determination of serum concentration of PTH is an important test for diagnosing NSH. Two assays have been validated for use in detecting serum PTH concentration in horses: the radioimmunoassay for the C-terminal portion of the molecule\(^{18}\) and the two-site immunoradiometric assay for the intact hormone. The intact molecule is composed of 84 amino acids and has a short serum half-life. It is readily cleaved to the inactive C-terminal fragment, the inactive mid-molecule fragment, and the active N-terminal fragment. Because the intact molecule is biologically active and has a shorter half-life than the C-terminal fragment, the immunoradiometric assay is considered to be a more accurate indicator of recent hormone release from the parathyroid gland.\(^{19-22}\) Samples can be tested for intact PTH at the Animal Health Diagnostic Laboratory, College of Veterinary Medicine, Michigan State University, East Lansing, MI 48909. The reference range for normal equine PTH is 0.25 to 2.0 pmol/L. The concentration of PTH is increased in horses with NSH despite a normal serum concentration of calcium.

Hays and pasture grasses that contain oxalate may cause NSH as a result of chelating calcium in the gastrointestinal tract; the fecal calcium:phosphorus ratio may be elevated when such forage is consumed. A fecal calcium:phosphorus ratio of greater than 2.35:1 is considered to be elevated.\(^{24}\) It may be difficult to find a laboratory that provides such analysis.

**MANAGEMENT**

Treatment of NSH in horses is empirical and directed toward limiting exercise and supplying the horse with a ration that has an adequate calcium:phosphorus ratio so that inappropriate secretion of PTH is abated. The National Research Council provides recommendations for calcium:phosphorus ratios for horses based on age and physiologic status.\(^{23}\) For example, the calcium requirement of exercising horses is greater than that of idle horses.\(^{24}\)

For horses with NSH, we generally recommend feeding a ration that contains a calcium:phosphorus ratio of at least 4:1.\(^{25}\) This dietary goal can be accomplished in various ways. Feeding a diet composed principally of alfalfa hay often is effective for nutritional management of NSH because alfalfa has a high calcium:phosphorus ratio (approximately 6:1).\(^{2,5}\)

Calcium carbonate is better than bonemeal as a calcium supplement for horses with NSH; calcium carbonate contains no phosphorus, whereas bonemeal has a high concentration of the element. Because calcium carbonate is 35% calcium, 100 g of limestone (calcium carbonate) is required daily for an unaffected yearling; if limestone is the sole source of dietary calcium, 300 to 400 g would be required for an affected yearling. Calcium carbonate is often unpalatable to horses, particularly when a large amount (greater than 50 g) is fed. We thus prefer to provide calcium by feeding alfalfa hay and adding limestone (50 g/day) to a small amount of concentrate.

Feeding a diet with a high calcium:phosphorus ratio should be continued at least until radiographic findings are normal and clinical signs have resolved. In our experience, this generally takes 6 months to 1 year. The urinary fractional clearance of phosphorus and the serum concentration of PTH often return to normal ranges within days of the initiation of dietary management. In some cases, lameness may resolve within several weeks; in other cases, lameness does not resolve.\(^{4,21}\)

Often, maxillary swelling partially regresses but does not completely resolve.\(^{2,3,24}\) It has been suggested that radiographic abnormalities resolve before full recovery and that dietary management should be continued for at least 1 year.\(^{2,1}\)

**PREVENTION**

The disease can be readily prevented by ensuring that horses consume a diet that has an appropriate calcium:phosphorus ratio. Ensuring a proper ratio is particularly important in young, growing horses; the recommended dietary calcium:phosphorus ratio for a growing yearling is 1.8:1.\(^{25}\) In addition to dietary management, confinement or restricted exercise may be required to prevent pathologic fractures of osteoporotic bone.\(^{2,1}\)
CASE STUDIES
Recently, two horses with NSH were diagnosed at our clinic. A discussion of these cases illustrates the principles presented in this article.

Horse 1
An 88-kg, 3-year-old miniature horse stallion was admitted to the Veterinary Teaching Hospital at Texas A&M University for evaluation of intermittent hindlimb lameness and suspected ataxia lasting approximately 1 year. Radiography of the pelvic limbs and pelvis performed by the referring veterinarian demonstrated no abnormalities. Before referral, the patient was treated with intramuscular polysulfated glycosaminoglycan (six 500-mg doses given every 5 days), flunixin meglumine (dosage unknown), and ketoprofen (dosage unknown).

The stallion’s diet consisted of an unspecified amount of concentrates with vitamin and mineral supplements and a few handfuls of coastal hay fed twice daily. Although a ration analysis was not performed, such a diet would be expected to supply an excess of phosphorus in relation to calcium.

At the time of admission, abnormalities noted during physical examination included bilaterally enlarged, firm maxillary bones that were not painful to digital palpation. The horse exhibited a stilted gait and had mild effusion in the left and right femoral patellar joints. Lameness of the left hindlimb (which did not bear weight during a trot) was evident. Neurologic examination demonstrated no abnormalities.

Radiography of both stifles demonstrated severe accentuation of the trabecular pattern of all bones, indicating osteoporosis. In addition, a fragment of bone was evident immediately proximal to the base of the right patella. Radiographic studies of the maxillary sinuses, mandible, left radius, and ulna also demonstrated generalized osteoporosis. Abdominal and thoracic radiography did not reveal opacities or abnormal radiographic patterns that indicated neoplasia.

A complete blood count demonstrated hyperfibrinogenemia (800 mg/dl; reference range, 100 to 400 mg/dl) of undetermined origin. A serum biochemical profile revealed an elevated serum concentration of phosphorus (4.0 mg/dl; reference range, 1.7 to 3.9 mg/dl) and a decreased serum concentration of calcium (9.9 mg/dl; reference range, 11.0 to 13.0 mg/dl). The serum PTH concentration (C-terminal portion, determined by radioimmunoassay) was elevated (10.9 ng/ml; reference range, 0.32 to 0.92 ng/ml).

Diagnosis of NSH was made on the basis of anamnesis and physical and clinicopathologic findings. The patient’s diet was changed over a period of 2 weeks to 0.7 kg of alfalfa and 0.25 kg of an incomplete pelleted feed, fed twice daily. The goal was to provide a ration with an adequate amount of calories and protein and a calcium:phosphorus ratio of 3:1 to 4:1.

By day 15 of hospitalization, the lameness was nearly inapparent. By day 21, the serum PTH (C-terminal fragment) concentration had decreased to within the reference range (0.7 ng/dl) and radiography of the skull and stifles demonstrated increased bone density com-
pared with radiographic findings obtained at the time of admission (Figure 4).

At the time of discharge, the stallion was not lame but maxillary swelling remained. Within 1 year after discharge, the owner reported that the maxillary swelling had slowly resolved and that the stallion had returned to the show ring.

**Horse 2**

A 280-kg, 1-year-old Thoroughbred filly was admitted to the Veterinary Teaching Hospital at Texas A&M University with a 3- to 4-month history of dyspnea and bilateral swelling of the maxillary region (Figure 1). Before admission, the filly had been treated every 12 hours with an oral combination of trimethoprim-sulfamethoxazole (20 mg/kg) and phenylbutazone (3 mg/kg) for approximately 1 month. The diet consisted of 1.7 kg of a commercial sweet feed and 1.7 kg of oats (divided and fed twice daily), unspecified vitamin supplements, free-choice coastal hay, and access to a Bermuda grass pasture.

At the time of admission, the respiratory rate of the patient was 40 breaths/min. Bilateral, mucopurulent nasal discharge was present. The maxillary bones were bilaterally enlarged, firm, and nonpainful. Referred inspiratory sounds from the nasal passages made thoracic auscultation difficult, but neither crackles nor wheezes were detected.

Thoracic radiography demonstrated increased opacity in the caudal ventral lung field with a peribronchial pattern that was deemed to be consistent with pneumonia. Skull radiography revealed increased opacity in the region of the maxillary sinuses (maxillary sinusitis) and a generalized decrease in bone density. Radiography of the left carpus and left tarsus demonstrated an increased trabecular pattern of the long bones, indicating generalized osteoporosis (Figure 3).

A complete blood count demonstrated leukocytosis (white blood cell count of 22.8 × 10^9/L; reference range, 5.4 to 14.3 × 10^9/L) attributed to mature neutrophilia (19.8 × 10^9/L; reference range, 2.2 to 8.6 × 10^9/L) as well as hyperfibrinogenemia (900 mg/dL). Serum and urine biochemical profiles revealed that the fractional excretion of phosphorus was increased (16.65%; normal, less than 0.5%) and that the serum PTH (intact molecule) was elevated (33.0 pmol/L; reference range, 0.25 to 2.0 pmol/L).

Cytologic findings from a transtracheal aspirate, obtained at the time of admission, demonstrated septic suppurative inflammation. Streptococcus zoopneumoniae was isolated from the aspirate. The pneumonia and maxillary sinusitis were treated with intravenous potassium penicillin (22.0 × 10^5 IU/kg every 6 hours) and gentamicin (6.6 mg/kg/day). Physical examination and radiography of the thorax and maxillary sinuses indicated that the pneumonia and sinusitis clinically resolved within 2 weeks.

In light of the physical examination and the clinicopathologic presentation, the feeding regimen was investigated further. The client revealed that although the filly was offered free-choice hay, she was consuming less than one flake (approximately 2.3 kg) per day. An analysis of the feed samples obtained from the client indicated that the ration had a calcium:phosphorus ratio of 0.57:1. During hospitalization, the filly was maintained on a diet restricted to alfalfa (approximately 5 kg every 12 hours) because alfalfa has a high calcium:phosphorus ratio. A serum biochemical analysis on day 15 of hospitalization demonstrated a serum concentration of PTH (intact molecule) at the upper limit (2.0 pmol/L) of the normal range.

When the patient was discharged, the owner was instructed to (1) continue feeding alfalfa hay (5 kg every 12 hours); (2) gradually reintroduce concentrates (1 kg of commercial sweet feed every 12 hours); and (3) add oral calcium carbonate to the feeding regimen (50 g every 12 hours) to provide the minimum daily calcium requirement for a growing Thoroughbred yearling. Six months later, the owner reported that the filly was breathing normally and training acceptably and that the maxillary swelling had decreased dramatically.

**CONCLUSION**

The diagnosis of NSH is based on the findings of physical examination, anamnesis, clinicopathologic testing, and radiography. Definitive diagnosis can be made by verifying excessive serum concentrations of intact PTH in conjunction with low or normal ionized calcium, low or normal total calcium, and/or elevated phosphorus. The urinary fractional clearance of phosphorus is a sensitive indicator of NSH and is elevated if the condition is present.

As demonstrated by the cases described here, physical examination often does not reveal clinical signs specific for NSH. The two horses we examined were referred for other diseases—hindlimb lameness (horse 1) and suspected sinusitis (horse 2). Because clinical signs of NSH can be variable and are nonspecific, it is difficult to base a diagnosis on clinical findings alone.

Dietary history can also be misleading. In the case of horse 2, the initial radiographic findings of osteoporosis prompted us to further explore the feeding history because of our suspicion of NSH. Based on the original history, the ration was apparently adequate for a yearling horse with regard to calcium and phosphorus content. Further investigation indicated that, although the
illy was offered free-choice coastal hay, she was consuming less than one flake each day. The amount and mineral content of grass consumed in the pasture were unknown. The grass may have had a high concentration of oxalate, which would have exacerbated the calcium-phosphorus imbalance. The presence of oxalate in feed can confound the results of dietary history because the ration may contain adequate amounts of calcium that are not absorbed due to chelation by the oxalate.

Treatment of horses with NSH is accomplished by dietary management and exercise restriction. Dietary management consists of feeding a ration with a calcium-phosphorus ratio of at least 4:1 for a period of 6 months to 1 year.

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REFERENCES

ARTICLE #5 REVIEW QUESTIONS
The article you have read qualifies for 1 hour of Continuing Education Credit from the Auburn University College of Veterinary Medicine. Choose only the one best answer to each of the following questions; then mark your answers on the test form inserted in The Compendium.

1. Common clinical signs in horses with NSH include
   a. shifting-limb lameness.
   b. swelling of facial bones.
c. stilited gait and swollen joints.
d. dyspnea.
e. all of the above

2. Which of the following skeletal disorders is not commonly associated with NSH?
a. osteochondrosis
b. microfractures of subepiphyseal bone
c. fibrous osteodystrophy
d. avulsion fractures

3. Which of the following are most commonly observed in horses with clinical signs of NSH?
a. hypocalcemia and hyperphosphatemia
b. hypercalcemia and hyperphosphatemia
c. normocalcemia and hyperphosphatemia
d. normocalcemia and hypophosphatemia

4. Diagnosis of NSH is facilitated by measuring:
a. total serum calcium.
b. urinary fractional clearance of calcium.
c. serum PTH.
d. serum calcitriol.

5. Which of the following grasses is not known to contain high concentrations of oxalate?
a. blue or green panic
b. Klein
c. Dallis
d. Setaria
e. buffel

6. Concerning the measurement of serum PTH in horses,
a. serial samples after infusion of calcium are required to support a diagnosis of NSH.
b. tests for equine PTH are not available.
c. the intact molecule has a longer half-life than does the C-terminal fragment.
d. it may be preferable to measure the intact molecule, which is more indicative of active secretion of PTH.

7. Often, the earliest radiographic finding associated with NSH is:
a. a generalized decrease in the density of the long bones.
b. decreased density of the laminae durne dentes.
c. decreased density of the facial bones.
d. patellar fragmentation.

8. In a yearling horse, which of the following is the recommended calcium:phosphorus ratio?
a. 0.8:1
b. 1:1
c. 1:32:1
d. 1:80:1

9. Concerning dietary management of horses with NSH,
a. bone meal is the preferred source of calcium replacement because it does not contain phosphorus.
b. limestone can be used as the sole source of calcium because it is palatable to most horses.
c. the diet must be restricted to grass or legume hays to avoid energy-associated orthopedic diseases.
d. alfalfa hay and small amounts of grain (with or without calcium supplementation) are recommended.

10. In treating patients with NSH, the clinician should remember that:
a. dietary management should be discontinued when serum PTH returns to normal.
b. dietary management and restricted exercise should be discontinued when radiography indicates that decreased bone density has resolved.
c. appropriate management should be discontinued when lameness has resolved.
d. appropriate management should be discontinued approximately 6 to 12 months after serum PTH has returned to normal.

ERRATA

"Interpreting Immunoblot Testing of Cerebrospinal Fluid for Equine Protozoal Myeloencephalitis"
by Noah D. Cohen, VMD, PhD, and Robert J. MacKay, BVSc, PhD

In Table Two of this EQUINE FORUM column, which appeared in the October 1997 issue, page 1178, the following errors were published:

- Positive predictive value = ... 90% (correct is 50%)
- Negative predictive value = ... 90% (correct is 99%)

We regret any inconvenience caused by these errors.