Liver failure attributable to pyrrolizidine alkaloid toxicosis and associated with inspiratory dyspnea in ponies: Three cases (1982-1988)

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Summary: *Of 41 equids referred to a veterinary teaching hospital in the Pacific northwest because of dyspnea and inspiratory noise, 3 ponies were diagnosed as having liver failure, most likely attributable to pyrroliziding alkaloid toxicosis. Dyspnea appeared to be caused by laryngeal and/or pharyngeal paralysis. It is proposed that this paralysis was a manifestation of hepatic encephalopathy. Although these clinical signs are not common for pyrrolizidine toxicosis, practitioners should be aware of the possibility so that misdiagnosis of other causes of inspiratory dyspnea may not be made.*

Inspiratory dyspnea associated with hepatic failure has been seen or reported in ponies in the Pacific northwest during the past 6 years. Inspiratory dyspnea is usually caused by some obstruction of the upper airways. Dyspnea is a subjective clinical sign of disease, but can be confirmed by careful observation. Horses or ponies with dyspnea usually have flared nostrils and obvious exaggerated muscular effort in breathing. One phase of breathing, either inspiration or expiration, may be of longer duration than the other, and sometimes abnormal sounds can be heard.

In the Pacific northwest, pyrrolizidine alkaloid toxicosis, attributable to consumption of the *Senecio* species of plants, is the most common cause of hepatic failure in horses and ponies. Hepatic failure in horses is usually manifested by jaundice, weight loss, and behavioral changes attributable to hepatic encephalopathy.[1,2] However, about 10% of the equids with *Senecio* toxicosis referred to our teaching hospital were first examined because they had difficulty in breathing.

To the author's knowledge, specific cases of hepatic failure associated with dyspnea have not been reported in the veterinary literature, although some clinicians have mentioned dyspnea as being associated with hepatic disease.[3] Dyspnea related to hepatic failure could easily be misdiagnosed as some form of upper airway obstruction, especially if the veterinarian is not aware of the possible association. Three cases of hepatic failure are described in ponies for which veterinary assistance was solicited because of the ponies' difficulty in breathing.

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Criteria for Selection of Cases

Thirty equids referred to the Veterinary Teaching Hospital at Oregon State University, between 1982 and 1988, had diagnosis of *Senecio* toxicosis. Equids were of either gender and various breeds, and age ranged between 6 months and >21 years. In addition to physical examination, serum biochemical values were determined, and percutaneous liver biopsy was performed on each equid. Three ponies that had signs typical of this syndrome involving inspiratory dyspnea were evaluated in more detail. Postmortem examination was performed on 2 of the 3 ponies. Prevalence of other clinical signs of *Senecio* toxicosis cases were tabulated by use of a computerized medical records retrieval program.[a]

Results

A small percentage of the total cases of *Senecio* toxicosis in this area are referred to the veterinary teaching hospital. Most are diagnosed in the field by practicing veterinarians on the basis of history, clinical signs of disease, liver enzyme activities, and histopathologic findings of liver biopsy specimens.[b]

The prevalence of clinical signs of disease in more than one referred case of liver failure is seen in Table 1. Depression, jaundice, weight loss, anorexia, and behavioral changes were the most frequently observed clinical signs that might point to liver disease. Serum γ-glutamyltransferase activity was high in each equid in which it was measured, as was serum total bile acids concentration. Three equids, all ponies, were referred because of dyspnea and inspiratory noise, heard loudest near the throat region.

Most (76%) of the 41 equids referred to this

[a]Eicker S. University of Wisconsin, Madison, Wis: Copyrighted program, 1989.

[b]Diagnosis records, Veterinary Diagnostic Laboratory, Corvallis, Ore.

Table 1—Clinical signs of pyrrolizidine alkaloid toxicosis in thirty horses with liver failure

Sign	Number	Frequency percentage
Depression	14/30	46
Weight loss	10/30	33
Anorexia	9/30	30
Jaundice	7/30	23
Tachycardia	5/30	16
Behavioral change	5/30	16
Ataxia	4/30	13
Dyspnea	3/30	10
Skin lesion	3/30	10

hospital because of dyspnea and inspiratory stertor were diagnosed as having some form of upper airway obstruction. However, 7% of these were diagnosed as having liver disease, most probably attributable to *Senecio* toxicosis. Table 2 gives the frequency of various diagnoses in cases involving dyspnea and inspiratory noise.

A 20-year-old Pony of America gelding (No. 1) was referred because of difficulty in breathing and large abdomen. The breathing problem was acute, was observed abut 24 hours prior to admission, and was the reason for seeking veterinary assistance. The owner thought the breathing problem might be attributable to eating too much clover hay.

The pony was depressed and had difficulty moving or staying on its feet. Sometimes it staggered while it was standing. The shape of the abdomen was normal, but slight distention was evident. The pulse and respiratory rate were 120 breaths and 60 beats/min, respectively. The pony was slightly dehydrated (5 to 6%). The mucous membranes were somewhat icteric, and had capillary refill time of 3 seconds. Pupillary reflex time was greater than normal. Stertorous inspiratory sounds were heard and were loudest in the throat region. In addition, breathing was labored, the nostrils were flared, and exaggerated movement of the thorax and abdomen was seen with each breath. Flaccid paralysis of the tongue was noticed. Thoracic auscultation detected only referred upper airway sounds.

Fiberoptic endoscopy of the pharynx and larynx revealed petechiae on the arytenoid cartilages and epiglottis, with little movement of the larynx. The epiglottis was flaccid. Tracheostomy was performed and oxygen was administered through the tracheostomy tube; the urinary bladder was catheterized and 3.5 L of urine was removed. After these procedures, the pony appeared to be more comfortable. Percutaneous liver biopsy was performed, and the tissue was submitted for histologic examination.

Periportal fibrosis, bile duct duplication, and hepatocyte necrosis were evident on frozen liver sections. The pony was euthanatized at the owner's request, and necropsy was performed.

The only gross changes noticed on postmortem examination were in the liver, which was small, tan, and firm. Histologically, the liver tissue had marked portal fibrosis, bile ductule duplication, large hepatocytes, and dilatation of centrilobular sinusoids. All these changes were consistent with pyrrolizidine alkaloid toxicosis. Examination of sections of the brain revealed only mild edema of myelinated tracts, consistent with hepatic encephalopathy.

*Table 2—Frequency of diagnosis in forty-one equids referred because of dyspnea and inspiratory stertor**

Diagnosis	Number	Frequency percentage
Laryngeal hemiplegia	5/41	12
Pharyngitis	7/41	12
Arytenoiditis	4/41	9
Entrapment of epiglottis	3/41	7
Sinusitis	2/41	4
Guttural pouch empyema	2/41	4
Elongated soft palate	1/41	2
Displaced soft palate	1/41	2
Other upper airway obstruction	6/41	15
Pulmonary or lower airway disease	19/41	46
Liver failure, probably *Senecio* poisoning	2/41	7

*13% had lower airway or pulmonary disease concurrent with or secondary to upper airway problems.

A 14-year-old Shetland Pony mare (No. 2) was referred because of difficulty breathing of several weeks' duration. The pony had lost weight, but was still in fair condition. Rectal temperature was 37.6 C, pulse was 76 beats/min, and respiratory rate was 88 breaths/min. Inspiration and expiration were associated with exaggerated effort. Some stertorous sounds were heard on inspiration. Thoracic auscultation revealed diminished lung sounds caudoventrally. This pony had several episodes of syncope, but arterial Pa_{O2} (80.7 mm of Hg) was not greatly diminished after the episodes. Oral administration of aminophylline, 12 mg/kg of body weight, did not noticeably improve respiratory distress.

Thoracic radiography revealed ventral densities, consolidation, and diffuse interstitial pattern in the dorsal portion of the lung field. Blind percutaneous liver biopsy was performed, and histologic examination of the specimen revealed marked fibrosis in the periportal and centrilobular areas, with bridging between some areas. Some large hepatocytes were noticed, as well as greater than normal numbers of mononuclear inflammatory cells and macrophages. Stellate macrophages (Kupffer cells) contained considerable amounts of hemosiderin. This pony also was euthanatized at the owner's request, and complete postmortem examination was performed.

The most relevant postmortem findings were in the lungs and liver. The lungs were diffusely congested and were wet on cut surface; excess amount of tracheal froth was apparent. Histologic examination of the lungs revealed severe vascular congestion, and most alveoli were flooded with proteinaceous fluid (pulmonary edema). Some alveolar septa also contained hemosiderophage. The liver was firm and dark red. Histologically hepatic

Table 3—Abnormal serum biochemical data in three ponies (No. 1-3) with hepatic failure and dyspnea

Variable	No. 1	No. 2	No. 3	Normal values
BUN (mg/dl)	12	9	12	12 to 30
Serum total protein (g/dl)	9.6	7.5	6.8	5 to 7.9
Albumin (g/dl)	3.7	3.0	2.8	2.5 to 3.5
Bilirubin (mg/dl)	ND	1.5	4.6	0.4 to 2
ALP (IU/L)	255	246	275	73 to 194
GGT (IU/L)	499	525	378	8 to 30
AST (IU/L)	ND	768	643	150 to 270
Bile acids (μmol)	38.8	ND	97.2	<11.8

ALP = alkaline phosphatase; GGT = γ-glutamyltransferase; AST = aspartate transferase; ND = not determined.

changes were the same as those found in the biopsy specimen.

A 16-year-old Pony of America mare (No. 3) was referred because of severe episodes of labored breathing that had started a week earlier. Difficult breathing was associated with loud noises heard near the head and throat. Placement of a tube in the trachea had allowed the pony to breathe freely.

At referral, the pony was extremely depressed and almost nonresponsive to manipulation. Rectal temperature was 38.2 C, and heart rate was 108 beats/min. While the tracheal tube was in place, respiration was without extreme effort and the rate was 20 breaths/min. The pony would walk continuously, sometimes in circles, and head pressing was evident. When the tongue was extended, the pony did not attempt to replace it. The mucous membranes of the mouth were dry, injected, and had a bluish cast.

Endoscopy revealed mild amound of laryngeal edema, and the laryngeal cartilages hung near the midline, with little movement. Neurologic disease was suspected, and a CBC and serum biochemical analysis were performed to determine whether hepatic encephalopathy was a possibility. Because γ-glutamyltransferase, aspartate tranaminase, alkaline phosphatase, and serum bile acid values were high (Table 3), liver biopsy was performed. While waiting for the results, the pony was administered fluids containing 1 g of dimethyl sulfoxide/kg and 200 mg of flunixin meglumine, IV. Within 1 to 2 hours, the pony seemed more alert, ate some grain, and drank water.

Histologic examination of the liver biopsy specimen revealed dense bands of connective tissue extending across the specimen at several sites. The hepatocytes were packed into small groups, and some of them were binucleate or had extensive foamy cytoplasm. Large hepatocytes with large nuclei were also evident, as were foci of necrosis. The changes were assumed by the pathologist to be chronic and irreversible, and probably attributable to pyrrolizidine alkaloid toxicosis. The pony was euthanatized, but necropsy was not performed.

Discussion

Because of the high prevalence of hepatic disease attributable to *Senecio* toxicosis in this area, only a small percentage of the total cases is referred to a teaching hospital. Some local veterinary practitioners have identified ponies, and sometimes horses, with severe inspiratory dyspnea without apparent anatomic cause. When liver enzyme activities and bile acid concentrations are determined in these cases, they are sometimes high. Examination of liver biopsy specimens from these cases often reveals pathologic changes consistent with pyrrolizidine alkaloid toxicosis[b] or, at least, confirms hepatic damage.

Findings in the 3 referred ponies of this report were typical of pyrrolizidine alkaloid toxicosis. Ponies 1 and 3 apparently did not have problems other than liver damage and hepatic encephalopathy. Behavioral changes and ataxia were typical. Pony 2 may have had more than one condition. Pulmonary congestion, edema, and heart failure cells were evidence of congestive heart failure, but lesions were not seen in the heart. This pony may also have had chronic airway inflammation, although it was not apparent on postmortem examination. The liver was severely damaged, which could have aggravated the other diseases.

The cause of the inspiratory dyspnea in these ponies has not been proven. Because of tongue paralysis, flaccid epiglottis, and noise from the throat area, it was assumed that some sort of laryngeal or pharyngeal paralysis existed. We also speculated that hepatic encephalopathy could cause this type of change.[3]

Other causes of inspiratory dyspnea in horses and ponies are more common. Anatomic obstruction of airflow in the upper airways occurs frequently and includes: retropharyngeal abscesses, tumors, foreign bodies, displacement of the soft palate, epiglottic entrapment, laryngeal hemiplegia, arytenoiditis, tracheal obstruction, laryngeal edema, and obstruction of the nasal cavities by neoplasia, inflammation, or foreign body.[4] These can be seen by use of endoscopy and/or detected by use of radiography. In horses, laryngeal paralysis can also develop in associaton with lead toxicosis, and other CNS diseases can cause paralysis of the pharynx or larynx.

Hepatic encephalopathy is a condition in which dysfunction of part of the brain is secondary to liver failure. The pathogenesis of this dysfunction is still debatable.[5] In most cases, blood ammonia concentration is high, but not necessarily high enough to induce all relevant clinical signs of disease. An imbalance in blood amino acid concentrations can cause similar signs of disease.[6-9] Amounts of branched-chain amino acids are decreased in proportion to amounts of aromatic amino acids. Administering branched-chain amino acids to patients with clinical signs of hepatic encephalopathy will sometimes alleviate signs of the disease, at least temporarily.[7,8] Horses with hepatic encephalopathy often have bizarre behavioral changes and, sometimes, ataxia or paresis. Head

pressing, continuous walking, depression, belligerence, and even mania have been reported.[1-3]

Other signs of liver disease in horses and ponies include jaundice and weight loss. Photodermatitis is sometimes associated with *Senecio* toxicosis.[2] The prevalence of clinical signs of disease in our ponies with liver disease probably was different from that in the total population of equids with liver failure, because many are referred only because of unusual signs of disease. Signs of *Senecio* toxicosis, such as diarrhea, ascites, and tenesmus, are seen less frequently in horses than in cattle. In cattle, diarrhea and ascites probably are a result of portal hypertension,[2] which may not be as important in horses. Tenesmus is thought to be a manifestation of hepatic encephalopathy in cattle as may be pharyngeal laryngeal paralysis in ponies.

It is not certain whether dyspnea can develop in association with any cause of liver failure in equids or just in association with pyrrolizidine alkaloid toxicosis. Controlled proof that these ponies had pyrrolizidine alkaloid toxicosis is not available, but circumstantial evidence makes that the most probable cause. Each pony had larger than normal hepatocytes, which has been called the hallmark of pyrrolizidine alkaloid toxicosis.[10] This finding also is associated with aflatoxicosis, but none of the ponies had known exposure to moldy feed. Other histopathologic changes consistent with pyrrolizidine alkaloid toxicosis were seen in these ponies, including portal fibrosis, biliary hyperplasia, necrosis of hepatocytes, and accumulation of hemosiderin in Kupffer cells.[10,11,c] *Senecia jacobaea* or *S. longibilus,* both pyrrolizidine alkaloid-containing plants, are found in many of the pastures in the Pacific northwest, especially west of the Cascade Mountains; so, many horses and ponies are exposed to it. The plants also are present in some of the local hay, where they are even more likely to be consumed and not detected. Evidence of consumption of *Senecio* sp is not usually readily apparent from the history because the mechanism of toxicosis is delayed, and clinical signs may not appear until 6 months to a year after the animal has stopped consuming the alkaloid.

Diagnostic tests useful in suspected cases of *Senecio* toxicosis are determination of serum liver enzyme activities, especially γ-glutamyltransferase and alkaline phosphatase. Some of the dehydrogenases, such as lactate dehydrogenase, sorbitol dehydrogenase, and glutamate dehydrogenase, may not retain high activity by the time clinical signs of chronic or delayed *Senecio* toxicosis are seen.[2,3,12-14] Serum total bile acid concentration also is usually high, and sulfobromophthalein clearance halflife time is increased above 3.5 minutes. Histologic examination of liver tissue obtained by biopsy is usually necessary to make a diagnosis. As with the 3 ponies of this report, results of these tests may not prove pyrrolizidine alkaloid toxicosis, but histopathologic changes will be consistent with it.

It would be easy to misdiagnose hepatic failure as an anatomic upper airway obstruction in equids with inspiratory dyspnea if the diagnostician were not aware of the possible relationship. Accurate diagnosis would prevent inappropriate surgery which, in turn, would save the owner money and the pony unneeded suffering. Subsequent cases could also be prevented by looking for the source of the pyrrolizidine alkaloid or other hepatotoxin. Although inspiratory dyspnea is not a common clinical sign of hepatic failure, liver function tests should be performed if no obvious anatomic cause of the dyspnea can be found.

[c]Pearson EG. A study of *Senecio jacobaea* toxicosis in calves and ponies. MS thesis, Oregon State University, Corvallis, 1979.

References

1. Ford EJH. Clinical aspects of ragwort poisoning in horses. *Vet Annu* 1973;14:86-88.
2. Pearson EG, Craig AM. The diagnosis of liver disease in equine and food animals. *Mod Vet Pract* 1980;61:233-237, 315-320.
3. Byers TD. Chronic liver failure in horses. *Compend Contin Educ Pract Vet* 1983;5:S423-S430.
4. Koch C. Diseases of the lungs and pharynx of the horse. *Compend Contin Educ Pract Vet* 1980;11:S73-S80.
5. Schenker S, Breem KJ, Hayompa AM. Hepatic encephalopathy: current status. *Gastroenterology* 1974;66:121-151.
6. Gulick B, Liu I, Qualls C, et al. Effect of pyrrolizidine alkaloid-induced hepatic disease on plasma amino acid patterns in the horse. *Am J Vet Res* 1980;41:1894-1898.
7. Gulick B, Rogers Q, Knight H. Plasma amino acid patterns in horses with hepatic disease, in *Proceedings.* Am Assoc Equine Pract 1978;24:517-522.
8. Gulick B, Knight H, Rogers Q. Use of plasma amino acid patterns in liver disease of the horse. *Calif Vet* 1979;33:21-23.
9. Fischer JE, Rosen HM, Ebeid AM, et al. The effect of normalization of plasma amino acids on hepatic encephalopathy in man. *Surgery* 1976;80:77-91.
10. Bull LB. The histological evidence of liver damage from pyrrolizidine alkaloids. *Aust Vet J* 1955;31:33-40.
11. Jubb KVF, Kennedy PC. *Pathology of domestic animals.* 2nd ed. New York: Academic Press Inc, 1970;2:194-261.
12. Reed S, Andrews F. The biochemical evaluation of liver function in the horse, in *Proceedings.* Am Assoc Equine Pract 1986;32:81-93.
13. Lessard P, Wilson W, Olander H, et al. Clinicopathologic study of horses surviving pyrrolizidine alkaloid *(Senecio vulgaris)* toxicosis. *Am J Vet Res* 1986;47:1776-1780.
14. Giesecke P. Serum biochemistry in horses with *Echium* poisoning. *Aust Vet J* 1986;63:90-91.