

Serum Hepatitis in a Horse

by
Laurie Howarth*
Dr. Mike Shires†

SUMMARY

A case of serum hepatitis in a horse was diagnosed on the basis of clinical signs, clinical pathology findings, necropsy report and history. Tetanus antitoxin was given 197 days prior to illness. Clinical signs were depression, icterus, anorexia, incoordination, static gut, and hemoglobinuria.

They progressed to severe depression with increased respiration and heart rate, muscle tremors and tetany of the limbs. The horse failed to improve with treatment and was euthanized. The most significant clinical pathology findings included elevations of the following: PCV, total bilirubin, direct bilirubin, indirect bilirubin, serum glutamic oxaloacetic transaminase (SGOT), lactic dehydrogenase (LDH) and creatinine phosphokinase (CPK). Histological lesions consisted primarily of severe liver necrosis.

INTRODUCTION

In 1918 Sir Arnold Theiler described a disease seen in South Africa called acute staggers or Malziekte. It was a disease in which the prominent histopathological lesion was liver atrophy; in addition it was thought to be connected in some way to immunization of horses against African horsesickness with serum and virus. Theiler did report some cases of staggers in non-immunized horses, but it was present to a much higher degree in inoculated horses. The disease most consistently appeared between the 62nd and 78th day after immunization.⁹

Since Theiler's time this disease has been referred to as Theiler's disease, serum hepatitis, post vaccinal hepatitis,

*L. Howarth is a fourth year student in the College of Veterinary Medicine, Iowa State University.

†Dr. Shires is an Associate Professor in Veterinary Clinical Sciences at Iowa State University.

and acute yellow atrophy. To date, serum hepatitis has been reported in several countries including the United States after immunization with many different equine origin products: anti-encephalomyelitis serum, anthrax antiserum, pregnant mare serum, antibacterial serum of equine origin, tetanus antitoxin,⁷ and equine viral rhinopneumonitis vaccine prepared from fetal tissues.⁵

Equine serum hepatitis is an acute disease in which the primary problem is severe liver necrosis. The cause is yet undetermined, but the most popular theory is that it is caused by a virus similar to the one that causes serum hepatitis in man. Attempts to reproduce the disease with equine-origin serums, tissue suspensions, and blood from affected animals have given poor results. Spontaneous cases recorded in horses not given equine serum have occurred, but such horses were in close contact to serum treated horses. In these instances there may have been a possible insect vector.⁵

CASE REPORT

On the morning of October 2, 1975, a 15 year old standardbred mare was found in the pasture lying down near the fence. There were many abrasions on various parts of the horse's body, particularly on her head, neck and front legs. The farm hands who found her assumed that she had been caught in the fence. The veterinarian was called and arrived at the farm at 9:00 a.m. He found the mare to be depressed, incoordinated, and ataxic. The horse's temperature was 100.4; heart and respiration rates were normal. The mucous membranes were congested and slightly icteric. The tentative diagnosis at this time was encephalitis. A blood sample was withdrawn and treatment consisted of 20 mg dexamethasone^a intramuscularly and 5 grams chloramphenicol intravenously.^b

At 11:30 a.m. the veterinarian returned to the farm finding the horse down and unable to stand. The rest of the horse's condition had not changed since 9:00 a.m. No treatment was given at this time.

At this point the case was turned over to another veterinarian in the practice that usually did the veterinary work for this particular farm. He was much more familiar with the management of the farm and its past problems. The mares were kept outside on pasture during most of the year; the majority of the brood mares were being kept in the same field. Another mare from this same pasture had been found dead on

the morning of August 11, 1975. The post mortem examination revealed lesions of liver atrophy and hepatitis that were consistent with serum hepatitis. This mare died 54 days before the second mare became ill.

The hematology and blood chemistry results were available at 3:00 p.m. The hematologic examination revealed an increased PCV and a slight leukocytosis (Table 1). Since the horse had not been eating or drinking, the cause of the increased PCV was most likely dehydration. The laboratory made note that the plasma was extremely icteric.

TABLE 1—Hematology*

Factor	Case	Normal
Packed Cell Volume	58%	32-52
Hemoglobin	21.7 gm%	11-19
White blood cells	15,400/cm	8-11,000
Segmented neutrophils	77%	50-60
Lymphocytes**	23%	30-40

*Plasma was reported to be extremely icteric.

**Several atypical lymphocytes were seen.

The blood chemistry results were of much diagnostic value (Table 2). The most significant findings were extremely high SGOT, CPK, LDH, and indirect bilirubin; all indicative of a liver malfunction. At this point, the second veterinarian changed the diagnosis to hepatitis and returned to the farm to institute further treatment.

TABLE 2—Blood Chemistry

Factor	Case	Normal
Sodium	142 mg/L	146-152
Potassium	3.65 mg/L	2.7-3.5
Chloride	92 mg/L	98-106
BUN	5.9 mg%	10-25
Total protein	8.45 gm%	6.5-8.0
Albumin	4.22 gm%	2-4
Globulin	4.23 gm%	2-4
A/G ratio	1.0:1.0	.5-1.5
Total bilirubin	20.8 mg%	.2-3.5
Direct bilirubin	1/3-1/3 mg%	0-0.1
Indirect bilirubin	17.5 mg%	.2-3.4
SGOT	4,460 R.F. Units	50-400
CPK	135.1 I.U.	2.4-23.4
LDH	830 I.U.	41-104

By 4:30 p.m. when the second veterinarian arrived at the farm the mare had been hauled from the pasture to a small barn. The patient was prostrate and extremely depressed. The horse's limbs were tetanic and there were tremors of the shoulder and hip muscles. From these initial observations one would suspect tetanus, but examination of the eyes revealed no spasm of the third eyelid. The pupils did not respond to a light shone into the eyes. The pulse was weak and the heart rate about 120 beats per minute. Respirations were shallow, short and very rapid. The mucous membranes were muddy-congested and severely icteric. Rectal temperature was 97.6°. Upon auscultation of the abdomen one could detect no sounds of intestinal movement. Hard, dry feces were found by rectal examination. The farm hands reported having seen the mare urinate dark reddish brown urine early in the afternoon. The horse had not eaten or drunk anything all day.

Fluid therapy was begun after insertion of an intravenous catheter in the jugular vein. One liter of a 5% dextrose solution containing electrolytes, amino acids and Vitamin B complex^c was rapidly administered. This was immediately followed by 250 ml of a sodium bicarbonate solution (1 mg NaHCO₃ per ml). Shortly after the bicarbonate was given the muscle tremors stopped and the limbs of the horse became relaxed. It was assumed that the tremors and tetanic limbs were due to acidosis.

Before administering additional fluids, the veterinarian gave 100 mg of prednisolone sodium succinate^d intravenously and 5 grams chloramphenicol^e intravenously. Vitamin B₁₂ was given at a dosage of 10,000 micrograms intramuscularly. Fluid therapy was continued with one liter of Ringer's solution. A warm water and soap enema was given to soften the fecal material. Instructions were left with the farm hands to remain with the mare and to keep the fluids running. They were left with five liters of the dextrose solution and five liters of lactated Ringer's solution. Instructions were to alternate solutions and to give them as fast as they would flow. Before the veterinarian left the

patient's pupillary reflex had returned, the heart rate slowed down to about 80 beats per minute, body temperature was 99° and the mare was up on her sternum.

At 9:30 p.m. the veterinarian returned to the farm. By this time eleven liters of fluids had been given. The mare had made many attempts at standing but would fall down and try again later. Blood was taken for a check on the packed cell volume and the veterinarian returned to the clinic to obtain more fluids. The PCV was 62%. After arriving on the farm with additional fluids, the veterinarian was informed of the decision of the horse's owner to euthanize the horse. The mare's condition was deteriorating: pulse was weakening, heart and respiration rates were increasing, and the body temperature was falling. The case was terminated by euthanizing the mare.

NECROPSY FINDINGS

Macroscopic Lesions: The liver was atrophied—only about two thirds normal size. The color of the liver was light yellowish brown instead of the normal dark bluish brown. The only other abnormality involved the large colon and cecum: the contents were very compacted and balled up within the bands on the intestines; there were loose contents between these "balls." The small colon contained fecal balls which were very hard and covered with mucous.

Microscopic Lesions: There was diffuse degeneration and necrosis of the hepatocytes. The few remaining hepatocytes around the portal triad were engorged with fat and vacuolated. Fatty infiltration occurred around the portal triad, and the sinusoidal areas were infiltrated with histiocytes, lymphocytes, and plasma cells. No lesions in the central nervous system were seen.

DISCUSSION

The early misdiagnosis of this case as encephalitis is a common occurrence with serum hepatitis. Any type of hepatic insufficiency is often confused with Western Equine Encephalomyelitis. With serum hepatitis the central nervous system signs are quite variable during the course of the

disease; a horse seen early may present an entirely different set of signs later that same day. Most commonly there is anorexia and depression of varying degrees which may turn to a comatose state in the terminal stages. Ataxia, compulsive aimless walking, tripping over objects and bumping head into surroundings inflicting wounds upon itself are also commonly seen. Another sign that may occur is hyper-tonicity of the lip and facial muscles which is similar to that seen with Yellow Star Thistle poisoning. Not only does one consider viral encephalomyelitis and Yellow Star Thistle poisoning but also Rabies, wobbler syndrome and encephalomalacia (moldy corn poisoning).

The CNS signs are most often attributed to nitrogenous metabolites; the bacterial action on proteins in the intestines produces ammonia which is absorbed into the portal circulation. In the normal liver this ammonia is converted to urea, but with impaired liver function a large amount of ammonia enters the general circulation and eventually reaches the brain. The toxic reaction of ammonia on the brain most likely causes all the central nervous signs seen with serum hepatitis. Because of the nonfunctional liver the amino acids in the fluids given for rehydrating the case just discussed were contraindicated.

The presence of icterus is a very helpful diagnostic sign, although marked clinical icterus such as seen with the case previously mentioned is not always present. Horses tend to be prone to icterus; it can be seen with obstructive colic, leptospirosis, viral arteritis, equine infectious anemia, and hemolytic streptococcal septicemia,³ as well as a host of liver problems.

To determine whether or not the icterus is due to liver damage, tests can be run that help determine liver function. The time for Bromasulfonphthalein dye excretion (BSP) can be determined; with a nonfunctional liver, retention of the dye is elevated. The level of serum enzymes such as glutamic oxaloacetic transaminase (SGOT) may be measured. Although it is not specific for liver function, it is definitely an aid in differentiating liver disease from Rabies or encephalomyelitis. Sorbitol dehydrogenase is present in liver cells and has much

promise for detecting liver necrosis in the horse when it begins to be routinely used. The Van den Bergh test which evaluates bilirubin metabolism is quite diagnostic. In intrahepatic disease viable hepatocytes continue to conjugate bilirubin but the capacity for conjugation is greatly reduced allowing free bilirubin to escape in the blood and tissues. Any conjugated bilirubin escapes from the bile canaliculi to the blood during liver degeneration and necrosis and it is easily excreted into the urine. This explains why there was such an extreme rise in this horse's indirect (unconjugated) bilirubin levels with only a moderate rise indirect (conjugated) bilirubin.¹

The rest of the blood chemistry (Table 2) is also compatible with the diagnosis of serum hepatitis. The low BUN is commonly seen with hepatic failure. The elevated total protein along with the high PCV indicate dehydration. If this had been a case of chronic hepatitis one could expect a hypoproteinemia. The increased levels of CPK are due to skeletal muscle damage which occurred when the mare struggled and walked into objects and repeatedly fell. LDH increases are indicative of necrosis of any tissue; in this case liver and skeletal muscle.

The histological examination of the liver can be used to help differentiate the cause of the hepatic degeneration. If the disease was an acute toxic hepatitis there would not be a liberal infiltration of inflammatory cells, primarily lymphocytes and neutrophils, into portal areas and any remaining parenchyma. This case was found to have cellular infiltration within the sinusoidal areas.

This horse was given a tetanus anti-toxin inoculation on March 18, 1975 when her previous Caslick's operation was opened up to allow for foaling. This was 197 days before the mare was found ill, which does not fall within the 27-165 day period most common as an incubation period. This mare was pastured with the mare that had died August 11, 1975, 59 days earlier. In either type of exposure, if the disease is caused by a virus the long incubation periods are comparable to that of human serum hepatitis. In humans it is believed that carriers exist and blood from them is the

main infective source. This carrier state may pass from mother to child in utero. There are rare occurrences of contact cases where wives of soldiers with serum hepatitis have become ill with the disease. It is a disease not unfamiliar to narcotic addicts who use improperly sterilized syringes and needles.

Another theory is that serum hepatitis is a hypersensitivity reaction. It is known that horses sometimes have a violent local reaction to a subcutaneous or intramuscular inoculation. It may be possible that a local inflammation occurs which, if the damage is severe enough, will initiate enough inflammatory response that the irritant (an equine origin biologic) is almost completely localized. A sensitizing antigen may escape by way of the blood or a leukocyte to antibody producing cells before the irritant is completely localized. In the future when the inflammatory process breaks down, any residual sensitizing antigen is released and a hypersensitivity reaction occurs causing hepatitis. The antigen-antibody reaction could occur in the liver causing hepatocyte necrosis or it could occur elsewhere and produce toxic products which cause liver destruction.⁶

Death in most cases is likely due to hypoglycemia, increased levels of blood ammonia, dehydration, and electrolyte imbalance.⁷ If the patient can receive supportive therapy until regeneration of hepatocytes occurs there will be complete recovery without any visible lesions remaining. If the horse is going to recover, there will be improvement by the 4th to 5th day. If the case is fatal death usually occurs within 12-48 hours. Mortality rate varies from 50-90%.²

The suggested treatment regime is as follows:^{2,3,7}

1. Reduce blood ammonia levels: Empty the GI tract and withhold feed; use oral antibiotics to keep down bacterial activity; administer glutamic acid to bind ammonia forming glutamine which is metabolized in the Krebs cycle without releasing ammonia. The dosage for glutamic acid has not been established but in man 20 grams of glutamic acid are neutralized with sodium hydroxide in 80 ml of water, 500 cc of 5% dextrose is

added; it's given as a slow IV drip over a four hour period.

2. Restore blood glucose, electrolyte and water balances: Dextrose provides the body with a ready source of needed energy because the liver is not able to metabolize carbohydrates. Two liters of 10% dextrose in water should be given every six hours. If fluids can be given orally, a total of 5 gallons a day should be given. B vitamins may be of benefit if added to the fluids.
3. Protect against secondary bacterial infections by giving parenteral antibiotics.

REFERENCES

1. Duncan, J. R. and Prasse, K. W.: *A Syllabus of Veterinary Pathology*. Dept. of Vet. Path., Univ. of Georgia.
2. Fowler, M. E.: Clinical Manifestations of Primary Hepatic Insufficiency in the Horse: *J.A.V.M.A.*, 147, (1965):55-6.
3. Fowler, M.E.: The Clinical Syndrome of Liver Disease in the Horse, *Proc. Am. Ass. Equine Pract.*, (1964):113-123.
4. Harens, W. and Paul, J. R.: Infectious Hepatitis and Serum Hepatitis, *Viral and Rickettsial Diseases*, J. B. Lippincott Co., Philadelphia, Pa., (1965):965-993.
5. Hjerpe, C. A.: Serum Hepatitis in the Horse. *J.A.V.N.A.*, 144, (1964):734-740.
6. McCullum, W. H.: Comments on Serum Hepatitis in the Horse. *J.A.V.M.A.*, 155(1969):410-412.
7. Panciera, R. J.: Serum Disease (Theiler's Disease, Stageers, Secondary Disease, Liver Necrosis, Encephalosis, Acute Yellow Atrophy, Post vacinal Hepatitis), *Equine Medicine and Surgery*, 2nd ed., Amer. Vet. Publications, Santa Barbara, Calif., (1972): 275-276.
8. Smith, H. A., Jones, T. C., and Hunt, R. D.: *Veterinary Pathology*, Lea and Febiger, Philadelphia, Pa., (1972): 1240-1241.
9. Theiler, A.: Acute Liver Atrophy and Parenchymatous Hepatitis in Horses. 5th and 6th Report of the Director of Veterinary Research, Dept. of Ag, Union of South Africa (1919):7-164.

^aAzium Aqueous Suspension, Schering Corp., Kenilworth, N. J.

^bRogar-Mycine, rogar/STB, Division of BTI Products Inc., London, Ont.

^cAmbex, Elanco Products Co., Indianapolis, Indiana.

^dSolu-Delta-Cortex, The Upjohn Co., Kalamazoo, Mich.

^eRogar-Myoine, rogar/STB, Division of BTI Products Inc., London, Ont.