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Hyperammonemia Case in an Iceland Pony

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Summary: A 22 years old castrated male Iceland pony was presented at the Clinic of Vienna Veterinary University due to vague colic symptoms. The blood examination indeed revealed hyperammonemia (Ammonia: 136 µmol/L, normal value for healthy horses: <20 µmol/L). The patient received intravenous fluids aimed at flushing out toxic metabolites. Furthermore, lactulose was given per nasogastric tube. After this therapy, there was short-term improvement for some hours, but the animals again developed serious odd behavior. He was very ataxic and injured itself. Based on the bad prognosis, the owner took the decision to have the mare euthanized. Necropsy revealed cachexia, severe ascites; the liver seemed smaller, felt dense and had an irregular surface. Histopathology showed fibrotic degeneration and necrosis of the hepacytes, a generalized accumulation of fat, medium degree of edema and in all liver lobes. The diagnosis confirmed hepatocites encephalopathy caused by hepatic cirrhosis.

Key words: Colic, horse, hyperammonemia

Bir İzlanda Ponisinde Hiperamonyemi Olgusu

Özet: 22 yaşında kısırlaştırılmış erkek bir İzlanda midillisi belirsiz bir sancı şikayeti ile Viyana Veteriner Üniversitesi Kliniği'ne getirildi. Kan örneklerinin incelenmesinde atta hiperamonyemi (Amonyak: 136 µmol/L, sağlıklı atlarda: <20 µmol/L) tespit edildi. Hastaya toksik metabolitlerin dışarı atılmasını sağlamak amacıyla intravenöz sıvı ve devamında nazogastrik tüp ile laktuloz verildi. Bu tedaviden sonra, hayvanda kısa süreli düzelme oldu, fakat daha sonra tekrar ciddi davranış bozuklukları şekillendi. Hayvanda ataksi ve kendi kendini yaralama belirtlileri gözlendi. Prognozun iyi olmamasından dolayı sahibi ikna edilerek at ötenazi edildi. Nekropside, kaşeksi, şiddetli asites ve karaciğerin küçük ve düzensiz bir yüzeye sahip olduğu görüldü. Histopatolojik muayenede, intersitisyumda nekrotik hücreli fibröz bir dejenerasyon, kolestazis, orta dereceli hücresel ödem ve tüm karaciğer loblarında genel bir yağ birikimi gözlemlendi. Teşhis hepatik siroz kaynaklı hepatik ensefalopati olarak doğrulandı.

Anahtar kelimeler: At, hiperamonyakemi, kolik

Introduction

Clinical hyperammonaemia (HA) may develop due to increased production of ammonium (NH_4^+) in the intestinal tract, increased absorption of ammonia (NH_3) due to increased intestinal permeability (both described as intestinal HA) or decreased hepatic clearance of NH_4^+. The latter has been documented in equine cases of hepatic failure and HA is frequently encountered in horses with hepatic encephalopathy (7,10,12). Clinically, neurological signs associated with markedly increased blood NH_4^+ concentrations have also been observed in severe colitis cases and surgical colic patients (4).

Case

The presented patient was a castrated male Icelandic pony; 22 years old, 404 kg. General behavior: highly apathetic, responded only to strong stimuli (gastric probe), otherwise non-responsive. The whole thoracic area was covered in sweat. The history of the patient revealed a dry hay and grass diet with a small amount of pellets but no changes in the diet prior to presentation. Teeth were last checked a year before, no medicine was administered prior to the appearance of the symptoms and no other horses manifested any symptoms. The horse

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came to the clinic due to colic pain in the past 48 hours. The animal had not defecated in the past day. Last defecation was similar to abnormal very small apples. The patient was anorexic both water and food were not eaten, urination was not observed. The pony was examined in the field, with the following results: no fever, rectal examination seemed normal, gastric lavage normal. He was treated and seemed to be better during the transportation. During examination, the animal showed odd behavior and in its stall it showed head pressing and episodes of hyperexcitation. The pony was highly ataxic. Hepatic encephalopathy was suspected based on the signs shown. While leading the horse in a circle, the animal tripped and lost balance. The clinical examination on admission revealed an increased respiratory rate of 20 breaths/ minute (normal range=10-14 breaths/minute) and pulse rate (68 beats/min, normal range=28-40 beats/min), the internal body temperature was 35.7 °C, therefore decreased (normal values 37.5-38 °C) as well as a capillary refill time of 4 seconds. Conjunctiva and sclera were moderately icteric. Striking was also the jaundice of the conjunctiva and phases of hyper excitation with dromomania even against walls. The Pony was highly ataxic. By placing a nasogastric tube for lavage, large amounts of food could be flushed, that had a pH of 6 and a light putrid smell, which spoke for a stomach overload. In the rectal examination, we found a completely empty ampulla, a large bladder, the size of a football and singular small bowel loops in the left inguinal region. The blood examination revealed hyperammonemia (136 µmol/L, normal value for healthy horses <20 µmol/L). A slight tendency to blood acidity was found. The ammonia value improved initially on the following day, but rose again to 88 µmol /L on the second day of hospitalization. Lactate and glucose in the blood were increased. The measured creatinine, a blood value that has significance for renal function, was still within reference intervals but ALP, ALT, lactate, glucose and ammonia levels were increased significantly (Table 1).

Table 1. Laboratory data from a 22-year-old pony with ataxia, depression, and fever.

Analyse	Result	Reference Range
Hematology		
PCV (%)	42	30-45
Blood gas(venous)		
pH	7.340	7.32-7.44
pCO_2 (mmHg)	38	38-46
Clinical Chemistry		
BUN (mg/dl)	11	7-25
Creatinin (mg/dl)	1.90	<2.0
Glucose (mg/dl)	**178**	65-110
TP (g/dl)	7.5	5.7-8.0
Albumine (g/dl)	2.2	2.2-3.7
Globuline (g/dl)	**5.3**	2.7-5.0
Total Bilirubin (mg/dl)	**6.3**	0.5-2.3
Amylase (U/l)	<5	5-15
ALP (U/l)	**736**	50-170
ALT (U/l)	**30**	5-20
Lactate (mmol/l)	**11.97**	0.5-2.0
Ammonia (µmol/l)	**136**	**<20**
Ca^{++} (mg/dl)	14	11.5-14.2
Phosphorus (mg/dl)	2.7	1.9-4.3
Na^{+} (mmol/l)	**124**	126-157
K^{+} (mmol/l)	3.9	3.5-4.5
Cl^{-} (mmol/l)	100	98-107
HCO3 (mmol/l)	20.3	20-28
Beb (mmol/l)	**-5.5**	-2.5 - +2.5
Beecf (mmol/l)	**-5.5**	-2.5 - +2.5

In the box, the horse showed symptoms of dromomania towards the right, dragged his toes, seemed to be hypermetric, also hitting his head on the watering and feeding system. While leading the horse in a circle, the tail was pulled towards the left he was easily misbalanced and crossed his legs- when the tail was pulled to the right, the horse showed slightly more resistance.

Neurological testing revealed a hyper salivating, thirsty yet unable to drink, apathetic animal, with low swallowing reflexes, hanging head and a tendency to support his head on the wall.

Ultrasound examined showed the stomach distended up to the 13th intercostal space, with large amounts of free anechogenic free fluid. The colon had hypomotility and a very thickened. In the inguinal area, we could identify small intestinal loops with hypomotility and thickened walls, the liver was hypoechogenic. The abdominal cavity revealed a large quantity of abdominal fluid, which was odorless, yellow, normoproteic (1.6 g/dL (normal values<2.5), specific gravity 1025 (normally <1020), diagnosed as an ascites transsudate.

Based on these findings, the diagnosis of hepatic encephalopathy could be made. The horse received infusions to support the fluid and electrolyte balance and to "dilute" and flush out toxic metabolites (Buscopan-compositum - Injektionsloesung fuer Tiere i.v Finadyne 50 mg/mL - Injektionsloesung fuer Rinder, Pferde und Schweine 9 mL i.v, paraffinum liquidum PHE 10 L Kanister 1.5 L, Cimetidin 500 g pulver 2 measuring cups, lactulose "MIP" 650 mg/mL - Loesung zum Einnehmen 700 mL).

During the hospital stay, the state of the pony deteriorated despite intensive therapy and a short-term improvement of consciousness after treatment with magnesium sulfate 2.4% 1000 mL, 100 mL i.v, DMSO, reinst M16743 1000 mL 400 mL i.v, vanavit B-Komplex - 30 mL i.v, NaCl 0.9 % 500 mL 1 bottle, LAEVOLAC - Lactulose - Concentrate 1340 g oral suspension 1 packet). He showed more organ dysfunction especially the cardiovascular system with a very high-frequency heart rate (constantly> 120 beats/ min) and edemaformation. The patient had hypothermia, multiple edemas, sinus tachycardia and jaundice. His some values were as follows: 36.8 ºC temperature, Pulse 88 beats per minute, CRT: 2 seconds. The laboratory results before euthanasia showed: Ammonia: 88.00 µmol/L, Glucose: 193.00 mg/dL,

Due to the rapid deterioration of clinical symptoms despite supportive therapy, the owner decided for euthanasia.

Necropsy revealed a low body conditioning score, severe ascites, and liver seemed smaller and rougher (Figure 1A). The histopathological examination showed pseudolobule formations in liver (Figure 1B), hydropic degeneration, necrosis, and sinusoidal dilatation were detected. Interlobular areas were widened due to development of fibrosis (Figure 1C). Formation of fibrosis starting from the portal regions through the parenchyma with presence of occasional necrotic hepatocytes and mononuclear cellular infiltration was evident (Figure 1D).

The stomach had low food content, small intestine was also only lightly filled, whereas cecum and colon were tympanized and filled with gastrointestinal content. There was with a submucosal edema in the ventral parts of the colon. In the thorax, there was an accumulation of fluid, as well as light hydropericardium, right and left heart hypertrophy. The rest of the organs showed no pathological changes. The diagnosis of the pathology department was hepatic cirrhosis.

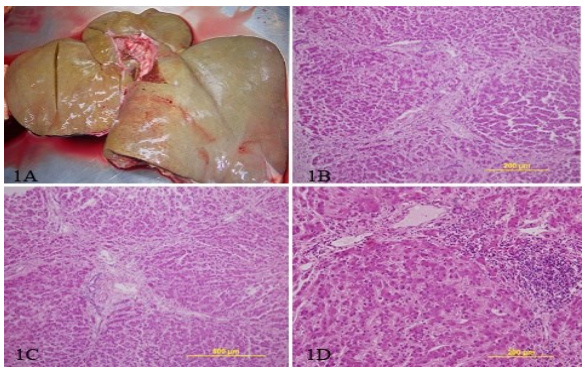

Figure 1. The macroscopic and microscopic examinations of the liver: 1A) Macroscopic view of the liver 1B) Pseudo lobe formation in liver 1C) Increased areas of connective tissue in the interlobular region of the liver 1D) Increased lymphoid cell infiltration in the portal area

Discussion and Conclusion

Although liver disease is the most commonly reported cause of hyperammonemia in horses, the laboratory data and history of colic in this case might be compatible with hyperammonemia associated with gastrointestinal disease (3,8). The case supported this hypothesis. Toxic ingestion of ammonium salts or urea supplements were unlikely in this case because other horses on the farm were not affected and hors-

es are relatively resistant to urea poisoning (11), which can be induced experimentally (6).

Main sources of ammonia are colon (through bacterial metabolism of proteins and urea) and small intestine (through bacterial degradation of glutamine). The ammonia then is delivered to the liver via the enterohepatic circulation, where it is catabolized to urea, which subsequently is excreted by the kidney (1). The main metabolic route is uptake of ammonia by periportal hepatocytes followed by urea synthesis via the urea cycle. Ammonia that escapes this pathway is converted to glutamine in perivenous hepatocytes. Hepatic transformation of ammonia into urea and subsequent excretion of urea via colon or kidneys prevent entrance of ammonia into the systemic circulation. If the hepatic metabolic capacity is exceeded, or if ammonia bypasses the liver by shunting of blood, circulating ammonia levels increase and elimination of ammonia is shifted to kidneys, brain, and skeletal muscle. Hyperammonia usually is associated with either hepatic failure (or subsequent loss of sufficient urea cycle activity to catabolize ammonia) or vascular shunting of blood around the liver (5). An inherited enzyme deficiency in the urea cycle has been reported in 2 Morgan foals and resulted in persistently increased ammonia concentrations in blood (9). Hyperammonemia also can be the result of increased absorption from the intestinal tract following ingestion of toxic levels of ammonia or urea as well as from increased bacterial breakdown of urea leading to increased production of ammonia (3,5,8,11).

Hyperammonemia contributes to hepatic encephalopathy in patients with liver failure; however, there are pathophysiologic differences between the neurologic syndrome associated with hyperammonemia caused by gastrointestinal disease, intoxication, or congenital metabolic defects, and that observed in patients with liver failure (1). Patients with liver failure have additional metabolic complications that are not described in patients with other causes of hyperammonemia (2). Increased ammonia can affect the brain via a number of different mechanisms, although there is controversy in the literature regarding the details and relative importance of various pathologic effects. Ammonia appears to impair postsynaptic inhibition, inhibit excitatory neurotransmission, and contribute to brain edema by causing cellular swelling of astrocytes (2). And this may cause brain disorders such as ataxia, incoordination. Characteristic histopathologic findings in the brains of horses reported to have hyperammonemia associated with gastrointestinal disease include predominantly grey-matter proliferation of Alzheimer type II astrocytes (5,11).

The gross and histopathologic findings in this horse confirmed that liver pathology was sufficient to explain the severe hyperammonemia.

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