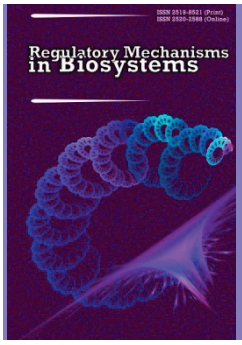

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Hepatic encephalopathy in dogs

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Malfunctioning of the neutralizing function of the liver leads to the buildup of toxins in the body, which negatively impacts the central nervous system. The objective of our study was examining dogs that had typical concurrent symptoms of dysfunctions of the liver and central nervous system. We studied two groups of dogs – the control (clinically healthy) and experimental (sick dogs with symptoms of disorders of the liver and brain). Each of the groups consisted of 10 animals: four Yorkshire Terriers, two Maltese dogs, two Russian Toy dogs, one English Cocker Spaniel, and one mixed-breed dog. The animals were examined clinically, underwent ultrasound diagnostics, and had their blood collected for labororary analyses. Clinically, in all the sick dogs, we identified the typical symptoms of liver lesions – pain in the liver region, increase in its area, and also malfunctioning of the central nervous system manifesting in soporous state, ataxis, and spasms. In blood plasma of all the sick dogs, we observed significant increase in the concentration of ammonia. High ammonia content in blood of dogs indicates an impaired neutralizing function of the liver. At the same time, it is the main endotoxin that affects the central nervous system, promoting the development of liver encephalopathy. The level of hyperammonemia was closely associated with the severity of the course of pathology. In blood serum of the dogs with signs of liver encephalopathy, the content of bile acids increased 4.5-fold and total bilirubin increased 31%, while albumin decreased 15%. In the blood of 60% of the patients, the level of Na^+ was low. In serum of blood from the patients, the activities of AST, ALT, and AP were increased. The ultrasound studies of the liver revealed increased echostructure and impaired hemodynamics, which, when co-occurring with high activity of indicator enzymes, indicate damage to liver cells. During severe liver encephalopathy, the dogs were found to have leukocytosis, neutrophilia, and lymphocytopenia, and also decline in the content of hemoglobin, number of erythrocytes, and hematocrit value. The next stage of our research will focus on the role of portosystemic shunts in the development of hepatic encephalopathy in dogs.

Keywords: dogs; liver lesion; brain lesion; ammonia; metabolism; ultrasound diagnostics.

Introduction

Liver diseases of various etiologies are often observed in dogs, depending on their age, sex, and breed (Rothuizen, 2009; Assawarachan et al., 2023; Kashliak & Vlizlo, 2023). During pathology of the liver, its main functions are impaired, in particular, neutralizing exo- and endotoxins. Hepatic cells take part in detoxification of bacterial toxins, mycotoxins, phytotoxins, various toxins of organic and synthetic origins, and also endotoxins formed during breakdown of food in the gastrointestinal tract (Besa et al., 2012). Only a minimum amount of toxins enters the general blood circulation, because the neutralizing function of the liver is quite stable and even during a liver failure can be sustained at the physiological level (Gow, 2017). Neutralization of exo- and endotoxins in the liver malfunctions in cases of significant damage to hepatocytes or the development of shunting. At the same time, toxins infiltrate the blood and concentrate in the bodies of sick animals, thus involving the central nervous system in the pathological process (Wang et al., 2017; Kabaria et al., 2021; Lynch, 2023). Such sick animals are diagnosed with lesions of the liver and brain. This pathology was described as hepatic encephalopathy (hepatogenic encephalopathy, hepatocerebral syndrome) (Gluud et al., 2016; Hadjihambi et al., 2019).

Depending on etiology, in dogs and humans, there are three types of development of hepatic encephalopathy: type A occurs during acute liver failure; type B is related to congenital portosystemic shunts; type C develops in cases of liver cirrhosis and portal hypertension, when acquired portosystemic shunts form (Kraun et al., 2014; Lidbury et al., 2015; Swaminathan et al., 2018). During the pathogenesis of hepatic encephalopathy, the key role is believed to be played by ammonia (Vlizlo, 1999; Tivers et al., 2014; Bellafante et al., 2024). It forms in the gastrointestinal tract during catabolism of proteins. Considering that dogs are carnivores, the diet of which is based on high content of proteins, the ammonia formation in them is especially active. However, in the liver of healthy animals, it is detoxified, allowing only a small amount to circulate in blood. When the neutralizing function of hepatocytes is impaired, ammonia accumulates in the body (Caporali et al., 2015; Lidbury et al., 2016). The significance of ammonia in the development of hepatic encephalopathy is explained by the fact that it is an endotoxin, which causes pathological impact on the brain (Lima et al., 2019). In the central nervous system, ammonia leads to dysfunction of astrocytes and development of oxidative stress, leading to edema of the brain and intracranial hypertension (Romero-Gómez et al., 2015; Levitt & Levitt, 2018).

Hepatogenic encephalopathy in dogs is diagnosed in complex based on a thoroughly collected anamnesis, along with clinical, laboratory, and instrumental methods of research (Assawarachan et al., 2020). In most cases, hepatic encephalopathy in dogs is only evident after the emergence of clinical signs. Patients experience ataxia, move in circles, suffer spasms, tremor, paresis, stupor, which can lead to coma, and even death (Krishnarao & Gordon, 2020; Rose et al., 2020; Konstantinidis et al., 2023). The prognosis for such dogs is unfavorable, because the treatment efficacy is low (Mullins et al., 2022). Considering this fact, it is important to search for methods of diagnosing hepatic encephalopathy at the subclinical stage of pathology development. Important laboratory parameters in cases of this condition are the content of metabolites of protein catabolism in the blood of patients – ammonium and urea (Lawrence & Steiner, 2017). Ammonia concentration in the blood is an informative marker of hepatic encephalopathy (Tivers et al., 2014; Lima et al., 2019). Nonetheless, there

is a report that individual dogs suffering hepatocerebral syndrome had the ammonia content in blood at the level of physiological values (Gow, 2017). The objectives of the study were to examine dogs with the symptoms of lesions of the liver and central nervous system, conducting ultrasound studies of the internal organs, performing laboratory analysis of blood, and measuring the parameters that can be informative in cases of hepatic encephalopathy.

Materials and methods

All the procedures with the animals were performed according to the European Convention for the Protection of Vertebrate Animals used for Experimental and other Scientific Purposes (Strasbourg, 1986) and the General Ethical Principles of Experiments on Animals, adopted by the First National Congress of Bioethics (Kyiv, 2001). The experiments were conducted with adherence to the principles of humanity, provided in the Guideline of the European Community (Directive 2010/63/EU, 2010).

The studies were conducted at the veterinary clinic Merlion in the city of Lviv. The material for the studies was 10 clinically healthy dogs and 10 sick ones, diagnosed with the symptoms characteristic of the hepatic encephalopathy. The clinically healthy dogs were selected in relation to the sick ones according to the analogue principle, taking into account breed and age. Each group contained four Yorkshire Terriers, two Maltese dogs, two Russian Toy dogs, one English Cocker Spaniel, and one mixed-breed dog. When an animal was admitted to the clinic, the anamnesis was gathered and clinical examination was performed, and also blood samples for laboratory analyses were collected. On a hematological analyzer Mindray BC-30 Vet (Japan), we measured the content of hemoglobin, hematocrit, and the numbers of erythrocytes, leukocytes, and platelets. To generate a leukogram, we prepared and stained blood smears and counted cells under a microscope.

Using a biochemical analyzer Mindray BS-240 (Japan), we studied the blood serum for the contents of total bilirubin, total bile acids, total protein, albumin, and urea, and the activities of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphotase (AP). The concentration of ammonia in blood plasma was measured on a biochemical analyzer Fuji DRI-CHEM NX500 (Japan). Using an analyzer OPTI CCA-TS2 (USA), we studied the content of electrolytes (Na^+, K^+, Cl^-, Ca^{++}) and pH of blood in blood serum. To perform sonography of the internal organs, we used an ultrasound apparatus Easote mylab x5 (Italy) with a 3.5–7.5 MHz sensor frequency. During the procedure, the animals were placed in the dorsal recumbency position. The sensor was placed in the region of xiphoid process and with pendulum-like movements we identified the localization and boundaries of the liver margins, the condition of parenchyma, blood vessels, bile ducts, and bladder, and also other internal organs.

The blood parameters were statistically analyzed using Statistica 7 (StatSoft Inc., USA). The graphs were developed in Statistica 7 using the generally accepted algorithms. The article presents the mean arithmetic values and standard deviation x ± SD (mean ± standard deviation), presented in the figures. To compare the differences between the mean parameters of the clinically healthy and sick animals, we used the Tukey Test, where the differences were considered statistically significant at $P < 0.05$.

Results

According to the owners, the dogs were depressed, had low appetite or had no appetite at all. During the clinical study of the patients, with deep palpation in the right epigastric region, we identified pain in the area of the liver and increase in its size. Of the ten patients, one was observed to have icteritiousness of the mucous membranes, and in the rest they were palered. At the same time, the dogs were diagnosed with the symptoms of malfunctioning of the nervous system, with inhibited general state (stupor), disorders in the coordination of moves (ataxia), and spasms. At the same time, tactile and pain sensitivity remained.

According to the results of hematological studies, the dogs with symptoms of hepatic encephalopathy had reduced level of hemoglobin ($P < 0.05$). The number of erythrocytes and the size of hematocrit tended to decrease (Table 1). The mean number of platelets in blood of the dogs was no different from such in the clinically healthy dogs (Table 1) and only two out of ten had a low number of platelets. The number of leukocytes in blood of the sick dogs was 66% higher compared with the clinically healthy dogs (Table 1). At the same time, four out of the ten dogs were diagnosed with leukocytosis due to increase in band neutrophils.

Table 1
General blood analysis of the dogs (x ± SE, n = 10)

Groups of animals	Hemoglobin, g/L	Erythrocytes, 10^{12}/L	Hematocrit, L/L	Leukocytes, 10^9/L	Eosinophile, %	Band neutrophils, %	Segmented-nucleus neutrophils	Lympocytes, %	Monocytes, %	Platelets, 10^9/L
Clinically healthy	171.2± 2.9	7.48± 0.24	0.45± 0.012	9.15± 0.53	2.7± 0.6	2.5± 0.6	68.2± 3.1	23.6± 2.9	3.0± 0.7	290± 25
Sick	147.6± 11.0*	6.71± 0.48	0.39±0.025	15.23± 4.03	1.7± 0.4	8.0± 3.1	66.7± 3.5	19.2± 3.5	4.4± 0.8	268± 45

Note: * – $P < 0.05$ between the clinically healthy and sick animals.

In the blood plasma of the sick dogs, we found a significant increase in the ammonia concentration (122.6 ± 57.2 μmol/L; $P < 0.001$), compared with the clinically healthy ones (23.6 ± 9.5 μmol/L). Hyperammonemia was observed in all the sick dogs (Fig. 1a). It has to be noted that the severity of the disease, especially nervous disorders, depended on the ammonia content in blood. When hyperammonemia was higher, hepatic encephalopathy was more acute.

The content of bile acids in blood serum of the dogs with signs of hepatic encephalopathy (Fig. 1b) measured 56.0 ± 35.8 μmol/L, 4.5 times higher ($P < 0.001$) than in the clinically healthy dogs (13.1 ± 5.4 μmol/L).

The concentration of total bilirubin in blood (Fig. 1c) of the sick dogs was 30% higher (7.5 ± 3.3 μmol/L) than in the clinically healthy ones (5.7 ± 1.5 μmol/L). At the same time, the urea content in serum on average did not differ between the groups (5.93 ± 4.4 and 5.90 ± 2.1 mmol/L, respectively).

In blood serum of the sick dogs, we observed decline of albumin to 24.0 ± 4.5 g/L ($P < 0.05$) compared with 28.3 ± 3.5 g/L in the clinically healthy dogs (Fig. 1d). Hypoalbuminemia promoted decrease in the total protein in blood of the sick animals to 65.0 ± 7.9, against 71.0 ± 6.3 g/L in the control.

The serum of the sick dogs had heightened activities of amino transferases (AST, ALT). In particular, the activity of AST in blood (Fig. 2a) was 3.4 times higher (164.8 ± 34.4 U/L; $P < 0.01$) than in the clinically healthy animals (48.4 ± 15.3 U/L). The activity of ALT in serum of the sick animals rose to 215.9 ± 71.4 U/L, 5.9 times exceeding ($P < 0.05$) the parameters in the clinically healthy animals (36.5 ± 16.5 U/L, Fig. 2c). At the same time, the AP activity in the blood of the patients was 4-fold higher (197.5 ± 77.1 U/L) compared with the clinically healthy animals (45.0 ± 18.7 U/L, Fig. 2c).

The concentration of electrolytes in the blood serum varied little between the examined clinically healthy dogs and the sick dogs, but in most of the animals it was within the physiological fluctuations (Table 2). However, it has to be noted that the content of cations (Na^+, K^+, Ca^{++}) in the patients tended to decline. In six of the ten dogs with signs of hepatic encephalopathy, Na^+ ions in serum were below the lower threshold of the parameters of control dogs.

According to the ultrasound study of the liver, the clinically healthy animals had the typical anatomic configuration and distinct even margins. In the dogs suffering hepatic encephalopathy, we observed increase in the borders of the liver and smoothened and moderately expressed vascular pattern. Echogenicity of the parenchyma in them ranged moderately to significantly increased. The echostructure of the liver was characterized by non-homogeneity, some patients having significant granularity. No tumors were found in the liver and other organs of the abdominal cavity.

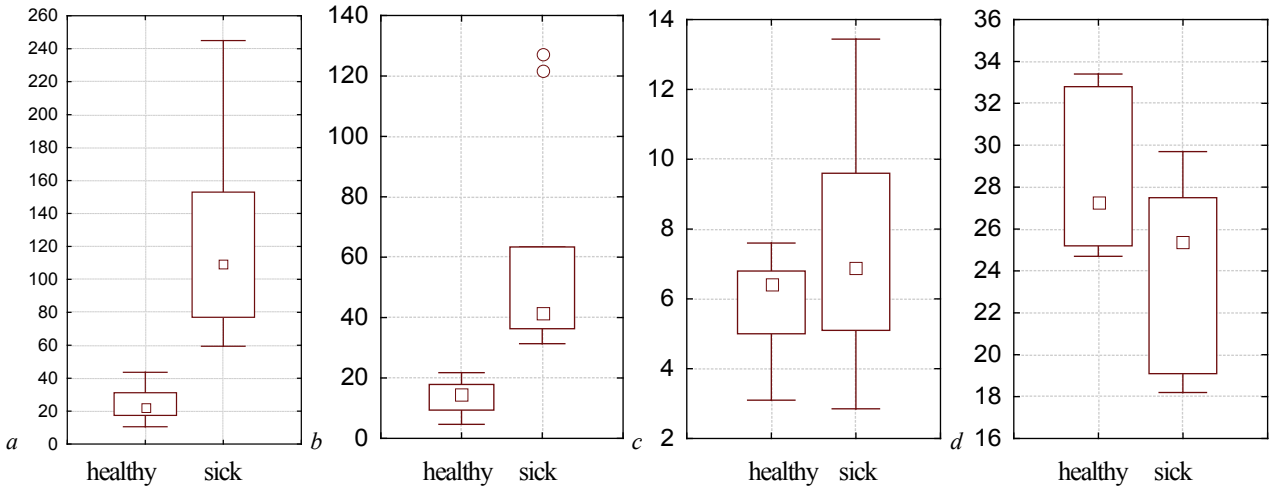

Fig. 1. Biochemical parameters of blood of the clinically healthy and sick dogs: *a* – ammonia content (μmol/L) in plasm; *b* – content of bile acids (μmol/L) in serum; *c* – content of bilirubin (μmol/L) in serum; *d* – content of albumin (g/L) in serum; abscissa axis indicates the groups of animals, ordinate axis shows the measurement units of the parameters; small square – median, upper and lower rectangle borders – 25% and 75% quartiles, vertical line – minimum and maximum values, circles – outliers; n = 10

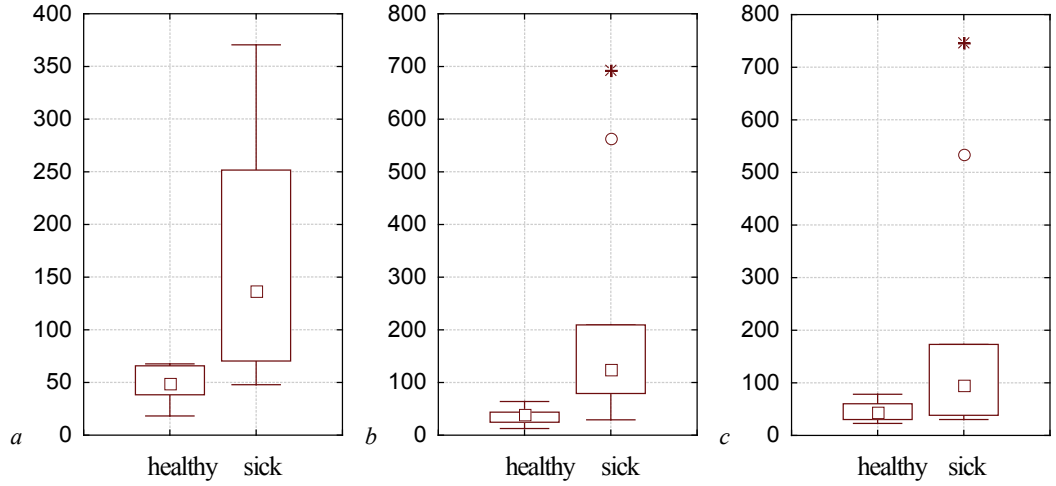

Fig. 2. Activity of enzymes in blood serum of the dogs (U/L): *a* – AST, *b* – ALT, *c* – AP abscissa axis indicates groups of animals, ordinate axis shows measurement units of the parameter; small square – median, upper and lower rectangle borders – 25% and 75% quartiles, vertical line – minimum and maximum values, circles – outliers; n = 10

Table 2

Concentration of electrolytes (mmol/L) and pH in blood serum of the dogs (x ± SE, n = 10)

Groups of dogs	Na^+	K^+	Cl^-	Ca^{++}	pH
Clinically healthy	148.0±1.2	4.8± 0.4	108.5± 3.4	1.41±0.42	7.40±0.05
Sick dogs	145.8± 3.1	4.6± 0.4	107.8 ±1.7	1.35±0.03	7.39±0.06

Discussion

The data obtained as a result of the gathering anamneses, clinical studies, laboratory blood analyses, and ultrasound examination of the sick animals indicated concurrent lesions of the liver and the central nervous system. In particular, the sick animals were found to have symptoms that are typical for pathologies of the liver (pain and increase in the size of the liver) and the central nervous system (stupor, ataxia, spasms). The clinical signs of lesions of the liver and central nervous system suggest the development of hepatic encephalopathy (Tivers et al., 2014; Lidbury et al., 2016). Most often, hepatogenic encephalopathy has been diagnosed in Yorkshire Terriers, Miniature Schnauzers, Chihuahuas, Labrador Retrievers, Poodles, Pugs, Dachshunds, Cocker Spaniels, and Pomeranian dogs (Lidbury et al., 2015; Cheon et al., 2022). In our study of 10 sick dogs, the pathology was found in Yorkshire Terriers, two Maltese dogs, two Russian Toy dogs, one English Cocker Spaniel, and one mixed-breed dog. Therefore, our data are consistent with the literature sources.

The course of the disease in the dogs varied moderate to severe. This has been indicated by other researchers as well (Ferenci, 2017). Therefore, it is important to gather a comprehensive anamnesis and to thoroughly examine the patient clinically in order to assess the complexity of the pathological process and its duration (Xenoulis et al., 2015; Jawaro et al., 2016). During insignificant changes in the clinical status of the patients, when the symptoms of damage to the central nervous system are not clearly apparent, important data are provided by laboratory blood assays. Blood analysis can reveal the severity of liver malfunctioning, in particular, in neutralizing toxins that cause harm to the brain (Hadjihambi et al., 2019; Nardelli et al., 2023). Ammonia is an endotoxin, which inflicts the most harmful damage on the central nervous system (Webster, 2017; Kawaguchi et al., 2019; European Association, 2022). We determined that ammonia analysis is a highly informative test of concurrent damages to the liver and central nervous system. Hyperammonemia was closely associated with the severity of the clinical course of hepatic encephalopathy, and also disorders in the main functions of the liver. The content of ammonia in the blood is high in cases of severe hepatitis, cirrhosis, or necrosis of the liver, indicating the presence of congenital or acquired portosystemic shunts (Chapman et al., 2013; Seller et al., 2022; Farhoodimoghadam et al., 2024).

Besides ammonia, important parameters for diagnosing liver lesions are the contents of albumin, bile acids, bilirubin, urea, and also the activities of alanine aminotransferase, aspartate aminotransferase, and alkaline phosphotase in the blood (Simonov & Vlizlo, 2015; Lawrence & Steiner, 2017; Zelenina et al., 2022). Therefore, we studied the blood serum of the sick dogs, finding decreased content of albumin ($P < 0.05$), which is a sign of malfunctioning of the most important activity of the liver – synthesis of protein. At the same time, the sick animals were observed to have cholemia and hyperbilirubinemia. This is explained by the fact that damage to the hepatic cells leads to disorder in the transport of bile acids and bilirubin from hepatocytes to the bile ducts, causing enhanced inflow of those metabolites into the blood (Selgas et al., 2014; Lester et al., 2016; Vlizlo et al., 2023). It is also possible that significant increase in the concentrations of bile acids and bilirubin in the blood of patients can also cause toxic impact on the nervous system.

It was reported that the contributing factors of the development of hepatic encephalopathy can be inflammatory cytokines (Odeh, 2007; Kilpatrick et al., 2014), hyponatremia, and hypokalemia (Tivers et al., 2014; Lidbury et al., 2016). This was corroborated by our data. In particular, in the blood serum of the sick dogs with severe pathology, the concentrations of Na^+ and K^+ ions were low. Hyponatremia causes brain edema, and hypokalemia enhances the renal ammoniagenesis and decreases the renal excretion of ammonia (Gow, 2017), thereby exacerbating the pathology. At the same time, in half of the patients, we found leukocytosis due to increase in neutrophils, indicating inflammatory processes in the body. Those animals also had lymphocytopenia, evidencing weakened protective powers of the body (Elhiblu et al., 2015).

Of the hematological parameters, we should note reduced content of hemoglobin in the sick dogs. In two of the ten, we found erythrocytopenia and decline in hematocrit value. Such changes in blood can indicate the onset of anemia in certain animals. This was observed during the development of pathological processes in the liver (Webster et al., 2019) and could be associated with hemorrhage in the gastrointestinal tract in hepatic encephalopathy patients (Lidbury et al., 2015).

Significant damage to the hepatic cells was suggested by stable increase in the activity of aminotransferase (AST, ALT) and AP in the blood serum of the sick dogs. This was also pointed out by other scientists (Alvarez & Whittemore, 2009; Vallarino et al., 2020). The first cells to be damaged are hepatocytes that come into contact with blood inflowing from the gastrointestinal tract, which contains a large amount of ammonia and other endotoxins (Jalan et al., 2006; Jawaro et al., 2016; Krishnarao & Gordon, 2020). At the same time, increase in the echostructure of parenchyma and disorders in hemodynamics of the organ, concurring with high activity of the indicator enzymes, confirm the damage to the hepatic cells (Assawarachan et al., 2019).

Conclusions

The liver disease in the dogs manifested in disorders of the neutralizing function of hepatocytes with accumulation of ammonia in the blood, which was harmful to the central nervous system, causing the development of hepatic encephalopathy. During this pathology, we observed the typical symptoms of liver lesion (pain and increase in the size of the liver), changes in the structure, and disruptions of the main functions of hepatocytes (neutralizing, protein-synthesizing, bile-forming, and bile-excreting), and also the typical symptoms of damage to the brain (stupor, ataxia, spasms). In cases of severe hepatic encephalopathy, the blood of the sick dogs had decreased ions of sodium, leukosis developed, and also neutrophilia, lymphocytopenia, and signs of anemia. In the future, it is important to determine the role of portosystemic shunts in the development of hepatic encephalopathy in dogs.

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