

Doberman hepatitis

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Introduction

Doberman Pinschers, particularly bitches, demonstrate a high incidence of chronic inflammatory liver disease (Dolge and others, 1981; Thornburg and others, 1983; Andersson and others, 1991). The disease has been called chronic active hepatitis (CAH), copper-associated hepatitis, and doberman hepatitis (DH). It is thought to be genetic in origin but the pattern of inheritance has not been determined. Although the disease, and especially the clinical stage, is widely documented, the aetiology is still obscure. Affected individuals should be identified as early as possible because the prognosis is grave once clinical signs have appeared (Rothuizen, 1997).

Because the liver is involved in many functions in the body and is easily secondarily affected by non-hepatic disease, it is advisable to obtain a control blood sample before proceeding to liver biopsy (Dillon, 1985). The diagnosis of subclinical DH should always be confirmed by histological examination of a liver biopsy.

In the clinical stage, the most common initial clinical signs are polyuria and polydipsia. Other signs include apathy, reduced appetite, vomiting and weight loss. Physical examination of the clinically affected dog may reveal jaundice, bleeding disorders and ascites (Cornelius, 1989; Fiorito, 1985; Ingh van den and others, 1988). A dog with ascites always has a poor prognosis because ascites indicates that the functional capacity is markedly reduced. In the terminal stages, hepatic encephalopathy may also occur.

All the liver enzymes are increased in clinical DH. Most of the dogs have hyperbilirubinemia, but serum bilirubin concentration can be normal if the dog is receiving corticosteroids. Other biochemical findings are increased serum bile acids and decreased albumin concentrations (Ingh van den and others, 1988).

The purpose of this report is to describe biochemical and histological findings of the subclinical and clinical DH and to evaluate the most important changes when the disease progresses. The treatment of DH is also discussed.

Materials and methods

Serum activities of the liver enzymes ALT and AP were determined in blood samples from 626 clinically healthy dobermans of both sexes. In the first blood sample, 55 of these dogs had increased ALT activities compared to the normal range. A liver biopsy was obtained from 20 dobermans with an ALT concentration in two consecutive months at least three times the upper normal value. Sequential blood samples were taken from DH-positive dogs to monitor progression of hepatic disease.

Serum ALT, AP, and bilirubin values of dogs with subclinical DH were also compared with those from 22 clinically affected dobermans.

Histological lesions in the liver samples were evaluated by the scoring system devised for chronic hepatitis in humans (Knodell and others, 1981). Different parameters (parenchymal inflammation, portal inflammation, piecemeal and bridging necrosis, portal expansion, bile-duct proliferation and fibrosis) were analysed. In addition histological changes in the biopsy and in the postmortem samples obtained from the same dogs (n=10) were compared.

Results

This study consists of 18 subclinical DH-positive dobermans. The follow-up time ranged from 3.5 months to 65 months. During that time seven dogs were euthanized because of DH. A postmortem sample was obtained from five of these dogs. Eight other

dogs were euthanized for reasons other than DH with postmortem specimens being obtained from five of them. When serum ALT, AP and bilirubin values were measured in dogs with subclinical DH the following results were discovered. In the very beginning of DH, ALT elevated first and during the course of subclinical DH, ALT levels did not fall within the normal range again. In addition, ALT and AP levels stayed very high for several months or years without the dog showing any clinical signs of DH. Bilirubin values were normal in most of the dogs in the subclinical stage of the disease.

In comparing the mean value of ALT of the dogs with subclinical DH (793.67 +/- 44.15) with the mean value of ALT of dogs with clinical DH (804.22 +/- 55.32), no difference was apparent. The mean value of AP was significantly higher among the clinically affected (1836.55 +/- 248.48) than subclinical dobermans (909.15 +/- 127.20). Unlike ALT, the bilirubin levels differed significantly between the subclinical (9.79 +/- 0.69) and the clinical stage (87.80 +/- 25.26). Bilirubin was normal in subclinical DH, but when dogs exhibited clinical signs the bilirubin value increased.

The ALT level of the last blood sample before the dogs were euthanized was studied in 22 clinically affected dobermans. In none of the cases had ALT returned to the normal range.

Macroscopically, the liver looked normal in the subclinical stage of DH. This was in contrast to the appearance on the postmortem examination where the liver showed micro- or macronodular cirrhosis with hyperplastic nodules on the surface.

Histologically, the main lesions of subclinical DH were parenchymal and portal mononuclear inflammation. Most of the cells were lymphocytes, Kupffer cells and macrophages. They were situated diffusely in sinusoids or gathered in small groups in the parenchymal area. Piecemeal and bridging necrosis as well as fibrosis was minimal or absent. In the subclinical stage, there was also always increased hepatic copper content (Speeti and others, 1998).

Histological findings in clinical DH were typical for chronic active hepatitis. There was piecemeal and bridging necrosis, fibrosis, cholestasis, and increased hepatic copper content. In the clinical stage, most of the inflammatory cells were in the periportal and bridging necrosis areas. Although there was still parenchymal inflammation it was not as severe as in the necrotic areas.

Comparing the histopathological changes in dogs with both the biopsy and the postmortem sample, the most important changes were expansion of portal areas, increased periportal and bridging necrosis, increased fibrosis and proliferation of the bile ducts. Although parenchymal inflammation was reduced

from biopsy to postmortem samples the reduction was not statistically significant. (Note: All histological changes found in the biopsies and postmortem samples were statistically analysed) (Speeti and others, 1998).

Discussion

Doberman hepatitis can be divided into two different stages, subclinical and clinical, which differ from each other biochemically and histologically. In subclinical DH, dogs are clinically healthy although the liver enzymes, alanine aminotransferase (ALT) and alkaline phosphatase (AP) are continuously elevated (Speeti and others, 1996). The subclinical stage can further be subdivided into different phases based on the biochemical results. (Fig.1)

In the very beginning of the subclinical stage, the ALT value will rise first and stay abnormally high. AP and bilirubin values are normal and the dog has no signs of liver failure. Thus ALT is the most important liver enzyme in DH. The inflammatory reaction seems to affect hepatocytes first and because ALT is a cytoplasmatic enzyme this suggest that cell membrane permeability may be altered enough to allow ALT to leak from liver cells into the blood stream. Therefore, if a clinically healthy doberman has a normal ALT but an abnormal AP value, the increased AP is unlikely to be due to DH.

In the second phase of the subclinical stage, both ALT and AP are increased. Bilirubin is still normal and the dog is asymptomatic. The dog can stay in this phase for several months or years. This is the phase where the dog is usually diagnosed to have a subclinical DH. In the third phase, ALT, AP and bilirubin values are all abnormal, but the dog is still without clinical signs. However, this is the phase where the dog has a high possibility to cross the line into the clinical stage.

Among ALT, AP and bilirubin values, bilirubin is the best indicator of a decline in condition during the subclinical stage (Speeti and others, 1996). As long as the bilirubin level of a subclinical DH-dog is in the normal range the condition of the dog should be considered to be stable. On the other hand if the dog exhibits clinical signs although the bilirubin value is normal, these signs are unlikely to be due to DH.

In many cases of advanced liver failure in dogs, most of the hepatocytes are damaged and ALT activity can be decreased to the normal range. Based on our findings, ALT value does not return to the normal range in the end stage of DH. Thus it is unlikely that clinical signs in a doberman with a normal ALT value are due to DH.

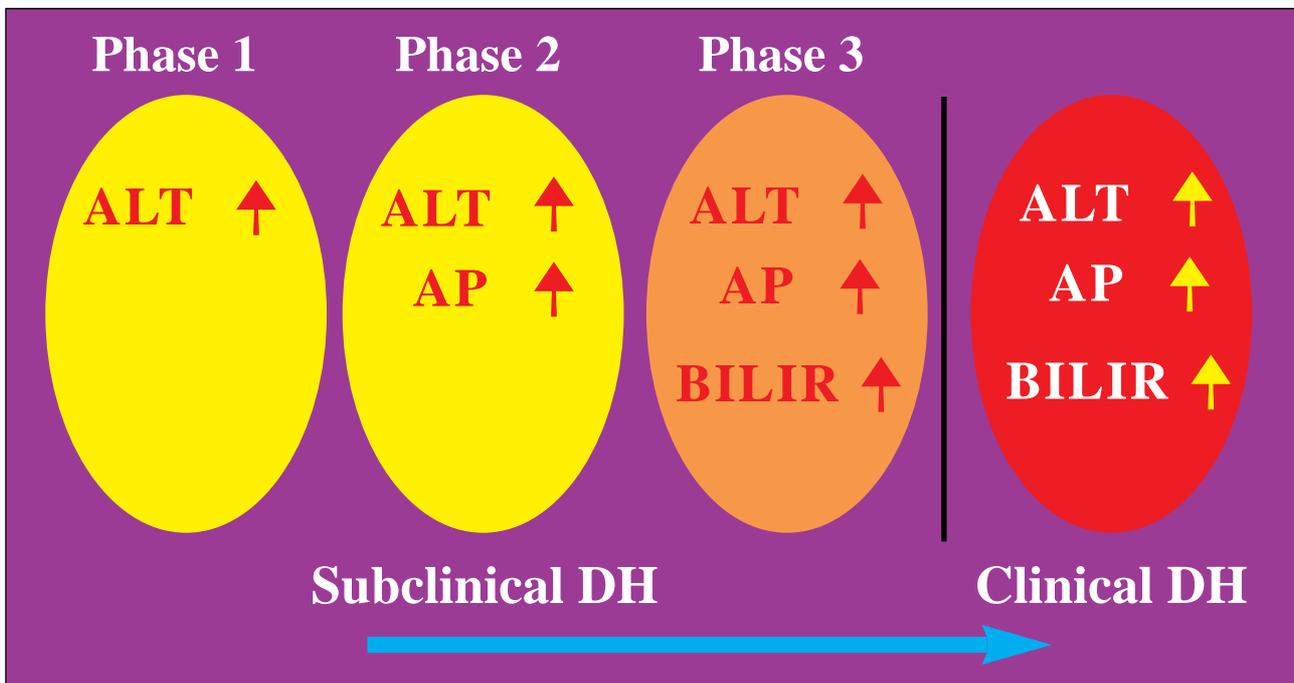


Figure 1 - Progression of doberman hepatitis based on biochemical findings.

Based on our studies, doberman hepatitis is a progressive disease. During the follow-up time almost 40% of the subclinical DH-dogs developed clinical signs of liver failure and were euthanized because of doberman hepatitis. When a doberman is diagnosed as having subclinical DH based on the biochemical results, histological lesions and increased hepatic copper content, it will have this disease for the rest of its life. Although the prognosis cannot be predicted by a liver biopsy it is good to be aware of subclinical DH. It is important to be able to tell the owner of the dog that even the dog is suffering from doberman hepatitis, the disease at the moment is in the subclinical stage and the dog may live for several years. The dog may even die for a reason other than DH.

At this moment, no medication has been shown to stop the progression of DH.

DH most probably has a genetic background and environmental factors such as stress are likely to affect the rate of progression of the disease. When a dog is diagnosed during the subclinical stage, our task is to eliminate all possible stress factors from its life in order to keep it in the subclinical stage. These stress factors may be as follows: 1) Pregnancy. Several females have developed clinical signs of DH soon after whelping. 2) Medication. If a DH-positive dog needs medication it should not be harmful for the liver. 3) Anaesthesia. Unnecessary anaesthesia should be avoided. 4) Copper in the diet. Because there is increased hepatic copper content in the liver in the subclinical stage, the diet should be low in copper, as recommended for bedlington terriers with copper toxicosis (Twedt, 1997).

The prognosis for clinical DH is grave. However, if the diagnosis is made in the subclinical stage we know what kind of disease we are dealing with. When the dog later develops clinical signs and these signs are determined to be due to DH based on ALT, AP and especially bilirubin values, appropriate medication can be started at once. In the opinion of the authors, by starting corticosteroid treatment at the very beginning of the clinical stage we can prolong survival time. On the other hand, by anaesthetizing the dog to obtain a liver biopsy in the clinical stage we can enhance the progression of the disease.

In the clinical stage, the main goal of treatment is to reduce hepatic inflammation. Prednisolone is the most widely used anti-inflammatory drug for DH. The initial dose of prednisolone is 1-2 mg/kg/day and should be gradually tapered to the maintenance level (Twedt, 1998). D-penicillamin (10-15 mg/kg bid) is used to reduce liver copper content. At the moment its benefit for DH is controversial. Bile acid concentrations are elevated in DH and the cytotoxic bile acids will cause damage to the hepatocytes. Urcoexychoic acid is a synthetic bile acid, which is recommended for cholestatic liver diseases. It changes the toxic bile acids to forms with lesser toxicity. The dose of urcoexychoic acid ranges between 4 to 15 mg/kg/day (Center, 1996). Patients with hepatic insufficiency are also often treated with B vitamins because they may be deficient. It is assumed that free radicals have an important role in initiating the cellular damage in canine chronic hepatitis. Vitamin E has antioxidant properties and

can protect the liver from oxidant damage. D-alfa tocopherol E is given at dose of 5 to 10 IU/kg/day (Twedt, 1998).

DH-positive dobermans, especially those on corticosteroid treatment for several months, are prone to develop gastritis. It is known that both acute and chronic liver disease can cause erosion of the mucosa of the stomach. The actual mechanism is not known, but it is assumed that portal hypertension causing mucosal ischaemia, and additionally hypoproteinemia may result in reduced turnover of gastric epithelial cells. Hypergastrinemia may also contribute (Guilford and others, 1996). Although corticosteroids alone rarely cause ulceration in the normal dog, they may enhance the incidence of liver failure related gastritis. Thus the use of gastric cytoprotectants are advocated when the DH-positive dog is on a corticosteroid treatment. The author's first choice is ranitidine (2mg/kg tid). If ranitidine does not work it may be changed to omeprazole (20 mg/dog/day). Spironolactone (1 mg/kg bid) or furosemide (1 mg/kg bid) is used to control ascites (Magne, 1986). The diet, home made or commercial liver diets, should be well balanced with a low copper content.

Summary

This article describes biochemical and histological findings of 18 Doberman Pinschers suffering from subclinical doberman hepatitis (DH). At the time of liver biopsy, the dogs were asymptomatic although their serum alanine aminotransferase (ALT) had been continuously elevated. Dogs could stay in the subclinical stage of the disease for several months or years and during that time ALT and AP levels never fell to the normal range. Comparing serum ALT, AP and bilirubin values taken in the subclinical stage with values from 22 dogs with clinical DH, bilirubin proved to be the best indicator of the decline on the condition of subclinical stage.

The prognosis of clinical DH is grave and consequently affected dogs should be identified before they manifest signs of liver failure. Histologically the main findings in the subclinical stage of DH were parenchymal and portal mononuclear inflammation and increased hepatic copper content. In clinical DH the histological lesions were typical for chronic active hepatitis.

References

- Andersson, M. & Sevelius, E. (1991) Breed, sex and age distribution in dogs with chronic liver disease: a demographic study. *Journal of Small Animal Practice* 32, 1-5.
- Center, S.A. (1996) Chronic liver disease in the dog: Important concepts and management consideration. In: *Liver disease, Proceedings of Waltham Symposium*, Waltham Center for Pet Nutrition, Leicestershire, 20- 41.
- Cornelius, L.M. (1989) Chronic weight loss. The case of a Doberman Pinscher. *Veterinary Medicine Report* 1, 351-357.
- Dillon, R. (1985) The liver in systemic disease. An innocent bystander. In: *The Veterinary Clinics of North America, Small Animal Practice* 15, Ed. D.C. Twedt. W.B. Saunders Company, pp.97-117.
- Dolge, C.A. & Lester S (1981) Chronic active hepatitis in dogs - A review of fourteen cases. *Journal of the American Animal Hospital Association* 17, 725-730.
- Fiorito, D.A. (1985) Chronic active hepatitis in dogs - A review of fourteen cases. *Journal of the American Animal Hospital Association* 17, 725-730.
- Guilford, W.G. & Strombeck, D.R. (1996) Acute gastritis. In: *Strombeck's Small Animal Gastroenterology*, 3rd edn. Eds. W.G. Guilford, S.A. Center, D.R. Strombeck, D.A. Williams and D.J. Meyer. W.B. Saunders, Philadelphia. 261-274.
- Ingh van den, T.S.G.A.M., Rothuizen, J. & Cupery, R. (1988) Chronic active hepatitis with cirrhosis in the Doberman Pinscher. *Veterinary Quarterly* 10, 84 -89.
- Knodell, R.G., Ichak, K.G., Black, W.C., Chen, T.S., Craig, R., Kaplowitz, N., Kiernan, T.W. & Wollman, J. (1981) Formulation and application of a numerical scoring system for assessing histological activity in asymptomatic chronic active hepatitis. *Hepatology* 1, 431-435.
- Magne, M.L. & Chiapella, A.M. (1986) Medical management of canine chronic hepatitis. *Compendium on Continuing Education for the Practicing Veterinarian*, 8, 915- 921.
- Rothuizen, J. (1997) Current concepts of chronic hepatitis in dogs. *The European Journal of Comparative Gastroenterology* 2, 15-20.
- Speeti, M., Ihanola, M. & Westermarck, E. (1996) Subclinical versus clinical hepatitis in the Doberman Pinscher: evaluation of changes in blood parameters. *Journal of Small Animal Practice* 37, 465-470.
- Speeti, M., Eriksson, J., Saari, S. & Westermarck, E. (1998) Lesions of Subclinical Doberman Hepatitis. *Veterinary Pathology* 35, 361-369.
- Thornburgh, L.P., Nelson, S.L. & Kintner, L.D. (1983) Post-necrotic canine cirrhosis - 2. Diagnosis, prognosis and treatment. *Veterinary Medicine* 78, 168-173.
- Twedt, D.A. (1997) Diagnosis and management of copper associated liver disease in dogs. *The European Journal of Comparative Gastroenterology* 2, 7- 12.
- Twedt, D.C. (1998) Treatment of chronic hepatitis and management of biliary tract disorders. In: *Voorjaarsdagen congress, Special Issue of the Veterinary Quarterly*, Eds. J.K. Kirpensteijn and H.P. Meyer, Royal Netherlands Veterinary Association, Utrecht, S47 - S48.