Portal vein hypoplasia in dogs

Hypoplasie van de vena portae bij honden

1N. Devriendt, 1M. Or, 1D. Paepe, 2E. Vandermeulen, 3M. Hesta, 4H.E.V. De Cock, 1H. de Rooster
1Department of Medicine and Clinical Biology of Small Animals, Faculty of Veterinary Medicine, Ghent University, Salisburylaan 133, 9820 Merelbeke, Belgium
2Department of Veterinary Medical Imaging and Small Animal Orthopedics, Faculty of Veterinary Medicine, Ghent University, Salisburylaan 133, 9820 Merelbeke, Belgium
3Department of Nutrition, Genetics and Ethology, Faculty of Veterinary Medicine, Ghent University, Salisburylaan 133, 9820 Merelbeke, Belgium
4Medvet, Veterinary Pathology Services, Emiel Vloorstraat 9, 2020 Antwerp, Belgium
Nausikaa.Devriendt@UGent.be

ABSTRACT

Portal vein hypoplasia (PVH) is a congenital disorder, in which microscopic intrahepatic shunts are present, causing blood to bypass the liver sinusoids. As the clinical presentation and the laboratory findings are similar to those in dogs with an extrahepatic portosystemic shunt (EHPSS), differentiation between both disorders is based on the confirmation of a macroscopic shunt by diagnostic imaging techniques. This review highlights the major aspects of PVH, including the differentiation from EHPSSs, and the challenges to diagnose both disorders in dogs with concurrent PVH and EHPSS.

INTRODUCTION

Portal vein hypoplasia (PVH), also known as primary PVH without portal hypertension, microvascular hepatic dysplasia or hepatoportal microvascular dysplasia (Schmerhorn et al., 1996; Cullen et al., 2006; Berent and Weisse, 2010), is a congenital disorder, in which microscopic intrahepatic portovenous shunts are present, causing blood to bypass the liver sinusoids (Schmerhorn et al., 1996; Allen et al., 1999). Microscopic shunting may occur isolated or may coexist with a macroscopic portosystemic shunt (PSS) (Schmerhorn et al., 1996; Allen et al., 1999; Landon et al., 2008).

Portosystemic shunts can be divided in intra- and extrahepatic PSSs. Extrahepatic PSSs (EHPSS) usually occur in small pure bred dogs, whereas intrahepatic PSSs are more common in large breed dogs. Congenital PSSs typically consist of one shunting vessel, in contrast to acquired PSSs that typically consist of multiple shunting vessels (Broome et al., 2004; Berent and Weisse, 2007). Dogs with PVH, PSS or the combination of both disorders have a similar clinicopathological presentation (Phillips et al., 1996; Allen et al., 1999; Devriendt et al., 2014), although the clinical presentation in dogs with solely PVH is generally milder or even subclinical (Schmerhorn et al., 1996; Center, 2009), which makes it challenging to differentiate both diseases, especially if both are present in the same dog (Phillips et al., 1996; Allen et al., 1999; Devriendt et al., 2014). Therefore, it is likely that PVH is underdiagnosed. The prevalence of PVH in dogs is suggested to be twice to 30 times higher than the prevalence of PSSs (Schmerhorn et al., 1996; Center, 2009). It is stated that approximately 58% of dogs with PVH...
have a concurrent congenital PSS (Richter, 2003). Others suggest that approximately 10% of dogs with a congenital PSS have additional PVH (van Straten et al., 2005). Although the type of PSS associated with PVH is often not clearly mentioned in the literature, it can be assumed that it is mostly an EHPSS, as PVH is typically seen in breeds that are predisposed for EHPSSs. In the hospital of the department of Medicine and Clinical Biology of Small Animals of the Faculty of Veterinary Medicine (UGhent), dogs with the combination of an EHPSS and PVH are only exceptionally diagnosed. Nevertheless, the diagnosis may be missed, especially as liver biopsies are not routinely taken after attenuation of the EHPSS.

**SIGNALMENT AND CLINICAL PRESENTATION**

The same small dog breeds, such as Cairn terriers and Yorkshire terriers that are prone to EHPSS, are also predisposed to PVH (Christiansen et al., 2000). According to a retrospective study of Christiansen et al. (2000), 70% of the dogs with PVH are females. However, in a study of Allen et al. (1999) no sex predisposition could be determined. The average age of dogs with PVH alone at presentation is three years (Allen et al., 1999; Christiansen et al., 2000), which is generally higher than the mean age at diagnosis for dogs with EHPSSs (Phillips et al., 1996; Christiansen et al., 2000), presumably due to less severe clinical signs. Although dogs with EHPSSs are usually presented before the age of two, it cannot be ruled out in older patients (Mertens et al., 2010).

Dogs with PSS, dogs with PVH and dogs with a combination of both disorders may suffer from neurological, gastrointestinal and urinary signs (Watson, 1997; Allen et al., 1999; Christiansen et al., 2000). A retrospective study of Christiansen et al. (2000) showed that neurological signs (ranging from lethargy to hepatic encephalopathy) are the most common presenting signs. Anorexia, vomiting and diarrhea are the most common gastrointestinal signs, and urinary signs are usually associated with urolithiasis (Phillips et al., 1996; Allen et al., 1999; Christiansen et al., 2000). In dogs with PVH, the severity of the clinical signs is variable and related to the amount of affected liver lobes (Christiansen et al., 2000). The clinical significance of PVH is not always clear, as it often remains subclinical (Schemerhorn et al., 1996; Center, 2009). Nevertheless, even if asymptomatic, the knowledge of the presence of PVH is clinically useful when administering drugs that have a hepatic first pass metabolism (Center, 2009).

**DIAGNOSIS**

To date, the presence of PVH cannot be demonstrated in dogs that also have a patent EHPSS. However, it is important to consider the presence of PVH in any dog with an EHPSS, especially in dogs that have persistent clinical symptoms or laboratory abnormalities after surgical attenuation of a macroscopic shunt.

**Laboratory findings**

Abnormalities on blood analysis are generally mild and non-specific in dogs with PVH (Allen et al., 1999). Unlike dogs with EHPSSs, dogs with PVH usually do not have microcytosis (Allen et al., 1999). Generally, serum albumin levels are normal to slightly decreased in dogs with PVH and liver enzymes might be normal to increased, depending on the severity of the disease. Hepatic function tests are suggestive of the presence of a liver disease, but none of them are specific. Although preprandial serum bile acids are often normal to mildly increased, postprandial serum bile acids are usually mildly to moderately increased in dogs with isolated PVH (Phillips et al., 1996) in contrast to the high pre- and postprandial bile acid levels encountered in most EHPSS dogs (Broome et al., 2004). Protein C, a vitamin K-dependent anticoagulant, which is synthesized in the liver, may be measured in plasma. Protein C activity reflects the hepatic-portal perfusion (Toulza et al., 2006; Center, 2009). Most of the dogs with PVH have a normal plasma protein C activity (≥70%), whereas dogs with an EHPSS tend to have a lower protein C activity (<70%). Sensitivity and specificity are 92.8% and 76%, respectively (Toulza et al., 2006). Currently, no commercial assay kit is available, and samples can only be analyzed in the United States. Recently, it has been suggested that rectal ammonia tolerance testing could possibly differentiate PVH from EHPSSs, as dogs with isolated PVH generally demonstrate normal ammonia clearance despite elevated pre- and postprandial bile acids (O’Leary et al., 2014). In this test, a fasting blood sample is taken and, after evacuating the rectum, an ammoniumchloride solution is administered rectally into the descending colon. A second blood sample is collected after 30 minutes and the blood samples should be analyzed within three hours (Tisdall et al., 1995).

**Diagnostic imaging**

Ultrasonography is regarded to be the best non-invasive method for assessing the internal liver structure, including portal and hepatic vascular supply. It is widely available and relatively cheap (d’Anjou, 2007), with a sensitivity for detecting PSSs using Doppler of 95% and a specificity up to 98% (Lamb, 1996). However, an experienced operator is needed and it is a time consuming investigation (Watson, 1997; d’Anjou et al., 2004). Unless a macroscopic shunting vessel can be visualized, ultrasonographic differentiation between dogs with EHPSSs and dogs with PVH is very difficult and findings are subtle (d’Anjou, 2007). The absence of caudal vena cava
turbulence and enlargement, a normal diameter of the portal vein (defined by portal vein/aorta ratio) and a portal mean flow velocity within normal limits combined with a history suggestive of the presence of a PSS, may suggest the presence of PVH (d’Anjou, 2007).

Nuclear scintigraphy is a functional imaging technique, in which the tracer $^{99m}$Tc-pertechnetate is injected with ultrasound guidance into the splenic parenchyma. The tracer is absorbed in the splenic vein, and in normal dogs, radioactivity in the liver is seen before it arrives in the heart. In dogs with a PSS to the contrary, radioactivity is first seen in the heart, before it arrives in the liver (Daniel and Berry, 2006). The shunt fraction provides an estimated percentage of portal blood bypassing the liver. In normal dogs, it should be less than $2.6 \pm 1.3\%$ if a transsplenic scintigraphy is performed (Cole et al., 2005). In dogs with an EHPSS, the shunt fraction is usually $>84\%$ (Daniel and Berry, 2006) (Figure 1). In dogs with PVH, the radionuclide is distributed throughout the liver parenchyma, yet bypassing the hepatic sinusoids, giving the impression of a normal liver perfusion (Morandi et al., 2005; Daniel and Berry, 2006) (Figure 2). Unlike liver function tests, scintigraphy is not influenced by other conditions associated with liver dysfunction and is thus a very sensitive test to diagnose EHPSSs (Landon et al., 2008).

Magnetic resonance angiography and computed tomography angiography are both imaging techniques available to scan hepatic vascular anatomy. Microvascular anomalies in dogs with PVH are considered too small to be adequately visualized by these imaging techniques (Seguin et al., 1999; Zwingenberger et al., 2005), but no studies have been done in dogs to investigate this in detail.

**Histopathology**

As complete hepatic lobules are essential to evaluate the internal liver structure microscopically, surgical biopsies are preferred over percutaneous needle or Tru Cut liver biopsies (Phillips et al., 1996). In dogs with EHPSSs, all liver lobes seem to be affected regardless of the location of the shunting vessel (Schermernhorn et al., 1996; Baade et al., 2006). Contrarily, not all liver lobes are necessarily affected in dogs with PVH (Schermernhorn et al., 1996; Center, 2009). To diagnose PVH, biopsies of at least three different liver lobes should be taken (Baade et al., 2006). The caudate lobe should preferably not be biopsied, since this lobe is frequently not involved in the disease (Center, 2009).

In contrast to dogs with an EHPSS, which have a functional hypoplasia of the portal veins, dogs with PVH have a morphological hypoplasia of the portal vessels. Portal vessels in EHPSS dogs normalize following successful attenuation of the shunt, whereas portal vessels of dogs with PVH are unresponsive to an increase in portal blood flow (Satzmari et al., 2004a; Szatmari et al., 2004b). However, it is very difficult to differentiate between functional and morphological hypoplasia histologically (Satzmari et al., 2004a; Landon et al., 2008). In addition to portal vein hypoplasia, the following histopathological fea-

Figure 1. Preoperative transsplenic scintigraphic scan of a five-year-old Yorkshire terrier with a shunt fraction of 99%. The top left image is a composite image with the regions of interest (ROI): ROI 1 (red) = cardiac area, ROI 2 (yellow) = hepatic area, ROI 3 (blue) = background correction. The bottom left image is a time-activity curve, which demonstrates the arrival of the activity in the heart, bypassing the liver. The image on the right is composed of selected frames. The pathway of the activity is suggestive of a portoazygos shunt.

Figure 2. Transsplenic scintigraphic scan of the same Yorkshire terrier six months after surgical attenuation of the shunt. The top left image is a composite image with the regions of interest (ROI): ROI 1 (red) = cardiac area, ROI 2 (yellow) = hepatic area, ROI 3 (blue) = background correction. The bottom left image is a time-activity curve, which demonstrates the arrival of the activity in the liver before it enters the cardiac region, indicating the absence of a portosystemic shunt. The image on the right is composed of selected frames. The calculated residual shunt fraction is 0.88%. In this dog, PVH was diagnosed based on histopathology (see Figure 4).
tures in dogs with EHPSSs are described: arteriolar and ductular proliferation, mild to moderate fibrosis, hepatocellular atrophy and presence of lipogranulomas (Baade et al., 2006; Landon et al., 2008) (Figure 3). Dogs with PVH have similar histopathological features as those described in EHPSS dogs (Figure 4). In addition, the liver of PVH dogs shows central venous muscular hypertrophy and an abnormal orientation of the central veins with respect to the portal triads (Schermerhorn et al., 1996; Landon et al., 2008). According to Philips et al. (1996), dogs with PVH have portal and periportal veins that are significantly more dilated than in dogs with an EHPSS. Because of the lower degree of shunting in dogs with PVH relative to EHPSS dogs, their histopathological changes are often less prominent and inconsistent (Schermerhorn et al., 1996). Nevertheless, solely based on histopathology of the liver, it is impossible to differentiate between dogs affected with an EHPSS and/or PVH (Phillips et al., 1996; Baade et al., 2006; Landon et al., 2008; Center, 2009). It is worthy to note that liver biopsies may confirm the presence of PVH if an EHPSS is excluded or successfully treated.

Immunohistochemistry (IH) is a technique in which antibodies are used to label proteins. In human medicine, it is used to differentiate liver diseases (Schmitt-Graff et al., 1991). Baade et al. (2006) investigated this technique in dogs with PSSs. However, the utility of IH in dogs with PVH and in dogs with the combination of a PSS and PVH is still unclear. Perisinusoidal hepatic cells are multifunctional mesenchymal cells, which are present between the sinusoids and the hepatic cells (Schmitt-Graff et al., 1991). In normal canine livers, these cells express alpha-smooth muscle actin (α-SMA) and no desmin (Baade et al., 2006). Increased expression of α-SMA and desmin are signs of cellular proliferation and transformation of perisinusoidal hepatic cells to myofibroblast-like cells (Baade et al., 2006). In inactive cells on the contrary, there is a decrease in the production of α-SMA. In dogs with PSSs and in human patients with developing liver cirrhosis, there is an increased quantity of α-SMA positive cells compared to normal livers (Baade et al., 2006). In human patients with end stage liver diseases, perisinusoidal cells are inactive causing a decrease of α-SMA (Schmitt-Graff et al., 1991). In dogs with PVH, it can be expected that perisinusoidal cells in the affected liver lobes are inactive as the microvascular shunts bypass the sinusoids, causing a decrease of α-SMA positive cells. In liver biopsies of dogs with a combination of a PSS and PVH, liver lobes affected with PVH may have a decreased amount of α-SMA, whereas other lobes may have an increased amount of α-SMA. These assumptions remain to be studied in affected dogs.

Since all currently available tests fail to diagnose PVH in the presence of a patent EHPSS, further investigations should be done to define the importance and usefulness of IH in the future. Consistent examination of pre- and postoperative liver biopsies in dogs with EHPSSs may help to investigate the improvement of liver morphology after shunt attenuation. This may also reveal if clear differences can be made in preoperative biopsies between dogs with solely an EHPSS and those with a combination of an EHPSS and PVH.

**TREATMENT**

Since there is no macroscopic shunt to attenuate in dogs with PVH, medical management is the only treatment option currently available (Christiansen et al., 2000). Medical therapy is supportive and should be tailored to the individual patient (Christiansen et al., 2000). Its aim is to control the clinical signs by reducing encephalogenic toxins and by prevent-
ing them from reaching the systemic circulation by means of drug administration or dietary modulations (Watson, 1997; Broome et al., 2004).

The majority of dogs respond well to dietary management alone. However, marked dietary modification may not be indicated in every dog with PVH. It is recommended to give a readily digestible diet with a limited to moderate amount of proteins (Watson, 1997; Christiansen et al., 2000; Berent and Weisse, 2007) and highly digestible complex carbohydrates (Bexfield and Watson, 2009). Proteins should be of high quality and, unless hepatic encephalopathy is present, excessive reduction of dietary proteins should be avoided, as protein malnutrition may contribute to hepatic degeneration and increase the need to break down body proteins (Watson, 1997). Several nutritional supplements such as vitamin E have been suggested as hepatoprotectants, but currently, no clear evidence exists regarding their efficacy (Webster and Cooper, 2009; Vandeweerd et al., 2013). Depending on the clinical symptoms and their severity, medical treatment is similar as in dogs with an EHPSS (Watson, 1997), subclinical dogs might even not require any treatment (Center, 2009). Nevertheless, drugs that have a hepatic first-pass metabolism should be avoided or, if impossible, the doses given should be adjusted (Bexfield and Watson, 2009). Follow-up examinations should be tailored to the individual dog.

PROGNOSIS

Response to treatment and prognosis are variable and depend on the number of liver lobes affected by PVH (Center, 2009). Although PVH cannot be cured and medical therapy is only supportive, dogs with PVH seem to have a better long-term prognosis than non-surgically treated dogs with a PSS (Christiansen et al., 2000). The majority of dogs with PVH have a relatively good prognosis, and may have a normal life expectancy, even without any treatment (Christiansen et al., 2000; Center, 2009). Dogs presented with neurological signs seem to have a poorer outcome (Christiansen et al., 2000). Once dogs with PVH develop symptoms, supportive treatment should be started as soon as possible, as delay may worsen the long-term prognosis (Christiansen et al., 2000).

CONCLUSION

Dogs with isolated PVH can display a variable degree of symptoms associated with hepatic dysfunction. Their clinical presentation and laboratory findings are similar, but usually less pronounced than those found in dogs with an EHPSS. Consequently, most dogs with PVH are only diagnosed when they are older. Portal vein hypoplasia has to be differentiated from an EHPSS by excluding a macroscopic anomalous vessel with medical imaging and by histological confirmation. The diagnosis of PVH in a dog with a patent EHPSS remains a diagnostic challenge as none of the available diagnostic techniques (laboratory findings, diagnostic imaging and histopathology of the liver) make it possible to diagnose both disorders at the same time. Further studies should focus on determining the actual impact of the disease and improving diagnostic methods. Generally, the prognosis in dogs with isolated PVH is good.

REFERENCES


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