The Veterinary Journal 211 (2016) 14–20

Contents lists available at ScienceDirect

The Veterinary Journal

journal homepage: www.elsevier.com/locate/tvjl

Review

Canine congenital portosystemic shunts: Disconnections dissected

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ARTICLE INFO

Article history:
Accepted 29 September 2015

Keywords:
Canine portosystemic shunt
Congenital
Genetics
Aetiology

ABSTRACT

Canine congenital portosystemic shunts (CPSS) are vascular anomalies that connect the portal vein with the systemic circulation, therefore bypassing the hepatic parenchyma. Portosystemic shunts exist in two different subtypes: extrahepatic and intrahepatic. This congenital disorder is also described in mice, cat, sheep and man. Research has been focused on pathophysiology, diagnostics and treatment of CPSS and this has resulted in increased knowledge, although the aetiology of the disease remains unclear. This review focuses on the aetiology and genetic basis of both intra- and extrahepatic shunts.

Introduction

Canine congenital portosystemic shunts (CPSS) are hereditary disorders that have a severe impact on the wellbeing of the affected dog (van den Ingh et al., 1995), although the genetic background has not been elucidated. The two different subtypes of CPSS, intrahepatic and extrahepatic, show a different epidemiology (van den Ingh et al., 1995). Intrahepatic portosystemic shunts (IHPSS) are almost exclusively diagnosed in large-sized pure-bred dogs (Hunt, 2004), whereas extrahepatic portosystemic shunts (EHPSS) occur mainly in small dog breeds (Tobias and Rohrbach, 2003; Van den Bossche et al., 2012; Fukushima et al., 2014), suggesting a hereditary basis.

For both IHPSS and EHPSS, a genetic association has been observed in the Irish Wolfhound (van Steenbeek et al., 2009) as well as in the Yorkshire terrier (Tobias, 2003), Cairn terrier (van Straten et al., 2005) and Maltese (O'Leary et al., 2014) breeds. Although both shunt types result in the same pathophysiology (as a result of nearly complete bypass of the liver by portal blood flow), a different aetiology is suspected based on the developmental processes involved and the timeframe in which the different subtypes of CPSS arise (van Steenbeek et al., 2012). This hypothesis is supported by the suggested different modes of inheritance of the two shunt subtypes (Tobias, 2003; van Straten et al., 2005; van Steenbeek et al., 2009; O'Leary et al., 2014) and has been of fundamental significance in functional studies (van Steenbeek et al., 2013b). Genetic studies will in time confirm the different backgrounds for the two disorders.

Hepatic vascular anatomy and function

The anatomical structure of the liver is unique due to its role in connecting the portal circulation with the systemic circulation (van den Ingh et al., 1995). The vascular network of the liver comprises portal veins, hepatic arteries, and hepatic veins. The portal blood flow contains blood originating from the entire gastrointestinal tract, spleen and pancreas, including the cranial and caudal mesenteric veins, the splenic vein, the gastroduodenal vein, and the left gastric vein as the major contributors of the portal vein (van den Ingh et al., 1995). The portal blood flow perfuses the liver through the liver sinusoids before entering the hepatic veins and contributes to 60–70% of the total hepatic blood flow (Cullen et al., 2006). Although the portal blood is of venous origin, it delivers 50% of the hepatic oxygen supply (Payne et al., 1990; van den Ingh et al., 1995). Two or three branches of the hepatic artery supply the liver and this blood of arterial origin increases the oxygen content of sinusoidal blood (Payne et al., 1990). The total afferent hepatic blood flow is thus the result of a complicated interaction of hepatic arterial and portal venous blood flow, regulated by local and systemic factors (Payne et al., 1990; van den Ingh et al., 1995). The efferent hepatic blood flow is provided by the hepatic veins, which enter into the caudal vena cava before crossing the diaphragm (Payne et al., 1990).

Clinical signs and histological abnormalities

Congenital portosystemic shunts cause liver atrophy and hepatic dysfunction that lead to a diversity of progressive clinical signs. As ammonia, aromatic amino acids, absorbed bacteria and endotoxins are not subjected to hepatic metabolism, the brain is exposed to toxins and metabolites causing hepatic encephalopathy (HE) in the affected animal (Rothuizen et al., 1982). The plasma ammonia concentration, used as a diagnostic method in CPSS, has also been shown to be predictive for the presence of HE in dogs, although diagnostic errors have been reported in the literature (Tivers et al., 2014).

The interaction of ammonia with other factors, such as inflammation, as determined using the systemic inflammation response syndrome (SIRS) score, has been found to play a crucial role in the

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http://dx.doi.org/10.1016/j.tvjl.2015.09.025
1090-0233/

development of HE. In dogs with CPSS in which the signs of HE resolved after successful attenuation of the shunt, the plasma ammonia concentration decreased significantly. The SIRS score also decreased, although not significantly as it may not be a sensitive score to detect changes in inflammation.

CPSS can be diagnosed as early as 6 weeks of age, facilitating routine screening of litters (Kerr and van Doorn, 1999; van Straten et al., 2005). However, based on presentation due to clinical signs, dogs with CPSS are diagnosed at varying ages with the majority of affected dogs detected within the first year of life (Tisdall et al., 1994; Tobias and Rohrbach, 2003; Van den Bossche et al., 2012). Clinical signs are influenced by shunt type, anatomy, nutrition and concurrent diseases and therefore presentation is also highly variable (Van den Bossche et al., 2012; Kraun et al., 2014). An index of suspicion based on breed predisposition and owner and veterinarian recognition of early clinical signs aids the diagnosis.

Pathological findings in dogs with CPSS are the result of shunting of portal blood with all its contents. Macroscopic changes include liver atrophy and portal vein hypoplasia proximal to the shunt origin for EHPSS (van den Ingh et al., 1995; Cullen et al., 2006). Histological findings include enlarged portal fields by proliferation of small arterioles and biliary hyperplasia together with hypoplasia of the portal vein and mild to moderate fibrosis in the portal areas (Baade et al., 2006; Cullen et al., 2006; Parker et al., 2008). Sinusoidal dilatation in the periportal area has also been described (Cullen et al., 2006; Parker et al., 2008). In addition to parenchymal changes, including atrophy of hepatocytes and lipid infiltration, the presence of fatty cysts, lipogranulomas and lymphangiectasia has been reported (Baade et al., 2006; Cullen et al., 2006; Parker et al., 2008). Lipidosis, the accumulation of lipids in the hepatocytes, was compared in the livers of dogs with CPSS and control dogs using stereological point counting following Oil Red O staining (Hunt et al., 2013). The study confirmed that this technique can demonstrate lipidosis in livers of dogs with CPSS, even in the absence of lipogranulomas or large lipid vacuoles, which are necessary in a haematoxylin and eosin staining to achieve the diagnosis. Significantly more small lipid droplets have been observed in the liver tissue of dogs with CPSS compared to those of control dogs.

A more recent study demonstrated a strong association between lipogranulomas and age. Dogs < 12 months of age had significantly fewer lipogranulomas compared to dogs > 12 months. No relationship has been observed between steatosis and pre- or post-operative shunt fraction and effect on short-term outcome after shunt attenuation (Hunt et al., 2014). If a difference is observed in the amount of steatosis between healthy and CPSS dogs (Hunt et al., 2013) and shunt fraction is not correlated with steatosis (Hunt et al., 2014), it seems likely that steatosis could be a genetically determined factor. Extensive genomic research will be required to determine whether there is a genetic background for steatosis in shunt. Given the active role of specific lipids during liver regeneration (Delgado-Coello et al., 2011), it would be of great added value to determine which type(s) of lipids tend to accumulate.

Treatment and prognosis

The treatment of choice in dogs with CPSS that is designed to achieve long-term improvement consists of surgical attenuation of the shunt vessel (Rothuizen et al., 1982; Greenhalgh et al., 2014). However, complete ligation can be fatal due to a sudden increase in portal blood flow resulting in portal hypertension and shock when hypoplasia or aplasia of the portal venous circulation cranial to the shunt is present. The technique is therefore not applicable in the majority of dogs. Gradual shunt attenuation is often implemented as an alternative, using partial ligation with silk ligatures in which the shunt is closed to the maximum tolerated level so portal pressure does not reach critical values (Winkler et al., 2003; Kummeling et al., 2004). Ameroid ring constrictor placement (Falls et al., 2013), cellophane banding (Hunt et al., 2004) and thrombogenic intravascular coils (Gonzalo-Orden et al., 2000; Weisse et al., 2014) have also been used to achieve progressive ligation. Post-operative outcomes remain variable (Winkler et al., 2003; Kummeling et al., 2004), which makes each surgical intervention a challenge. Therefore (and due to the expense of surgery) medical management provides an alternative therapy for reducing the clinical signs such as hepatic encephalopathy and urinary tract disease in dogs with CPSS (Watson and Herrtage, 1998; Winkler et al., 2003; Greenhalgh et al., 2014).

Medical therapeutics include dietary adjustments (high-quality, easily digestible low-protein diets) in combination with antimicrobials (i.e. ampicillin or metronidazole) and/or a synthetic disaccharide, like lactulose (Center, 1998; Proot et al., 2009; Greenhalgh et al., 2010, 2014). Research has been performed on the influence of soy protein isolate vs. meat-based protein source in a low-protein diet on hepatic encephalopathy (Proot et al., 2009). Both diets had a long-term positive effect on HE-scores in dogs with CPSS. Although no difference in HE-scores was observed between the two diets, the soy protein based diet reduced plasma ammonia levels and decreased prothrombin time in dogs with CPSS compared to the control diet, thereby decreasing the risk for HE and supporting liver function.

As this management approach offers purely supportive therapy to reduce the clinical signs, it does not resolve the underlying disease, neither does it reduce the frequency of ongoing clinical signs and it does not appear to have improved survival time over the long term compared to surgical treatment (Greenhalgh et al., 2014). In cases with high surgical risk, or where the owner has declined surgery, this therapy could be recommended for long-term support as an alternative to attenuation and, in addition, it may be provided in preparation for surgery or in dogs with insufficient clinical improvement after surgical attenuation (Proot et al., 2009; Greenhalgh et al., 2014).

Aetiology vs. physiology

The veins located in the abdominal cavity are derived from the umbilical, vitelline and caudal cardinal veins of the embryo. The portal vein originates from the umbilical and vitelline veins, whereas the non-portal venous drainage of the abdominal organs is derived from the cardinal venous system of the fetus. No functional vascular connections exist between the cardinal veins and the umbilical–vitelline veins. In contrast, numerous non-functional vascular portocaval and portoazygos communications are present and may become functional due to portal hypertension (Payne et al., 1990). The vitelline veins include a left and a right vitelline vein, connected by three separate anastomoses defined as cranial, middle and caudal. The ductus venosus connects the cranial anastomosis and the left umbilical vein. The ductus venosus is responsible for the flow of nutrient and oxygen rich blood derived from the placenta directly to vital organs, bypassing the liver sinusoids. In dogs this vessel is functionally closed within 2–9 days after birth, establishing the normal hepatic circulation (Lamb and Burton, 2004).

Congenital portosystemic shunts are vascular anomalies that directly connect the portal venous system with the systemic venous circulation, thereby bypassing the liver sinusoids. EHPSS represent abnormal developmental functional communications between the embryonic vitelline veins, responsible for the entire extrahepatic portal system and the cardinal venous system that contributes only to all non-portal abdominal veins (Payne et al., 1990). Distinctions have been reported between left, central and right divisional intrahepatic portosystemic shunts but the majority of the IHPSS are left divisional shunts that are classified as a patent ductus venosus, compatible with the normal embryology of the dog (White et al., 1998).