# Portosystemic shunts in dogs and cats: definition, epidemiology and clinical signs of congenital portosystemic shunts

*Portosystemische shunts bij honden en katten: definitie, epidemiologie en klinische symptomen van congenitale portosystemische shunts*

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## ABSTRACT

**Congenital portosystemic shunts (CPSS) are hepatic vascular anomalies which can affect any breed of dog or cat. Extrahepatic CPSS are most commonly observed in cats and small dogs, whereas intrahepatic CPSS are more likely to affect large breed dogs. A hereditary basis has been observed in some dog breeds. Affected animals are usually presented at young age with a variety of neurological, gastrointestinal, urinary or other signs. Signs of hepatic encephalopathy often predominate. The pathogenesis of this condition is not yet completely understood and is probably multifactorial. The underlying cause is probably the influence on the brain of one or more toxins which normally speaking should be detoxified by the liver. Ptyalism is a very common sign in cats with CPSS.**

## SAMENVATTING

Congenitale portosystemische shunts (CPSS) zijn hepatische bloedvatafwijkingen die bij elk honden- of kattenras kunnen voorkomen. Extrahepatische CPSS komen vooral voor bij kleine honden en katten, terwijl intrahepatische CPSS vooral grote hondenrassen aantasten. Voor sommige hondenrassen is een erfelijke basis vastgesteld. Aangetaste dieren worden meestal op jonge leeftijd aangeboden met variërende neurologische, gastro-intestinale, urinaire of andere klachten. Symptomen te wijten aan hepatische encefalopathie nemen dikwijls de overhand. De pathogenese van dit syndroom is tot nu toe nog niet volledig gekend en is vermoedelijk multifactorieel. De onderliggende oorzaak is vermoedelijk de invloed op de hersenen van één of meerdere toxinen die normaal gezien door de lever ontgiftigd zouden moeten worden. Katten met CPSS vertonen zeer vaak ptyalisme.

## INTRODUCTION

This report is the first of a series in which portosystemic shunts in dogs and cats are reviewed. The definition and classification of extrahepatic and intrahepatic shunts are summarized. The current knowledge on epidemiological factors is described in detail to give practitioners an increased awareness of possible CPSS in predisposed animals. Afterwards, an overview of the most commonly observed clinical signs is given. Much attention is given to the pathogenesis of hepatic encephalopathy, because this is the subject of serious debate.

## DEFINITION AND CLASSIFICATION

A portosystemic shunt is defined as any vascular communication linking the portal vein directly to the systemic circulation, thus allowing substances in portal blood derived from the intestinal tract to bypass the liver and thus not undergo hepatic metabolism (De Rycke *et al.,* 1995; Winkler *et al.,* 2003). Portosystemic shunting is thought to be congenital if a single or occasionally double anomalous vein is present without concurrent portal hypertension. Congenital portosystemic shunts (CPSS) may be intrahepatic or extrahepatic. Portosystemic shunting is considered to

be acquired when multiple collateral vessels form to compensate for sustained hepatic or prehepatic portal hypertension (De Rycke *et al.,* 1995). These vascular channels exist normally as non-functional fetal communications between the portal and systemic veins and become functional in order to prevent fatal portal hypertension (Martin, 1993).

In the remainder of this article only congenital portosystemic shunts will be discussed.

Extrahepatic shunts are most frequent in cats and dogs and may arise from any part of the portal system. Most commonly, they originate from the main portal vein trunk, gastro-splenic or gastro-duodenal branches. Extrahepatic shunts usually drain into the posterior caval vein or the (hemi)azygos vein, but they can also empty into the hepatic veins, renal vein, phrenicoabdominal vein, internal thoracic vein or the thoracic posterior caval vein (Martin, 1993; van den Ingh *et al.,* 1995; Tillson and Winkler, 2002; Santilli and Gerboni, 2003). Although most extrahepatic CPSS are single vascular anomalies, multiple (mostly double) CPSS are occasionally diagnosed in dogs but seldom in cats (Johnson *et al.,* 1987; Birchard and Sherding, 1992; Meyer *et al.,* 1999; Winkler *et al.,* 2003).

Canine and feline intrahepatic portocaval shunts may be classified as left-, central- or right-divisional. Left divisional shunts are most common and are compatible with a patent ductus venosus. The ductus venosus is a normal fetal connection between the portal vein and the posterior caval vein which normally closes shortly after birth. The oxygenated umbilical blood streams directly into the posterior caval vein through this ductus venosus, bypassing the sinusoidal vascular bed of the liver (Martin, 1993; van den Ingh *et al.,* 1995; Lamb and White, 1998; White *et al.,* 1998; Tillson and Winkler, 2002). The pathogenesis of central- and right-divisional intrahepatic shunts is not known (Lamb and White, 1998; White *et al.,* 1998).

In normal circumstances, the liver receives blood from two vessels: the hepatic artery and the portal vein. The portal vein drains the splanchnic viscera and contributes approximately two-thirds of the total hepatic blood flow. Hepatic tissue oxygenation is provided by both circulatory beds (Martin, 1993; Center, 1996b; Tillson and Winkler, 2002). The portal blood delivers toxins and nutrients absorbed from the intestines, as well as intestinal and pancreatic hormones and intestinal bacteria. Normally, toxins are cleared from the hepatic circulation when they pass through the liver and certain hormones (such as insulin, insulin-like growth factor, hepatocyte growth factor and glucagon) are trophic to the liver. Maintenance of the mass and function of the hepatic parenchyma is largely determined by hepatic perfusion, particularly by the quantity and quality of the portal blood. When portal blood circumvents the liver, the liver fails to develop normally and noxious substances are delivered to the systemic circulation. This results in hepatic hypoplasia, progressive liver atrophy and hepatic encephalopathy (Martin, 1993; van den Ingh *et al.,* 1995).

## EPIDEMIOLOGY

Congenital portosystemic shunts are seen more frequently in dogs than in cats (Table 1; Levy *et al.,* 1995; Center, 1996b).

**Table 1. Overview of epidemiological features of CPSS in dogs and cats (references, see text).**

| | **Dog** | **Cat** |
|---|---|---|
| **Prevalence** | 0.02-0.6% | 0.02-0.1% |
| **Breed predisposition** | | |
| 1. In general | North America: Havanese dog, Yorkshire Terrier, Maltese, Dandie Dinmont Terrier, Pug, Skye Terrier and Miniature Schnauzer<br><br>Australia: Maltese, Silky Terrier, Australian Cattle Dog, Bichon Frisé, Shih Tzu, Miniature Schnauzer, Border Collie, Jack Russell Terrier and Irish Wolfhound | Domestic shorthair cats, some purebred cats (Persian, Siamese, Himalayan, Burmese) |
| 2. Extrahepatic | Small purebred dogs | |
| 3. Intrahepatic | Large purebred dogs | |
| • Left divisional | Irish Wolfhound | |
| • Central divisional | Old English Sheepdog, Retriever | |
| • Right divisional | Australian Cattle Dog | |
| **Age at presentation** | 75% under 2 years | majority less than 1 year |
| **Sex predilection** | no | no |

## Breed predisposition

In dogs, CPSS more commonly affect purebred dogs than mixed-breed dogs (Lamb, 1996; Wolschrijn *et al.,* 2000; Tobias and Rohrbach, 2003; Hunt, 2004; Mehl *et al.,* 2005). Although CPSS may occur in virtually any breed of dog, the breed predisposition varies with geographical location, probably due to environmental or genetic characteristics of the regional population (Tobias and Rohrbach, 2003; Hunt *et al.,* 2000; Hunt, 2004). The most commonly affected breeds in North America and Australia are presented in Table 1 (Tobias and Rohrbach, 2003; Tisdall *et al.,* 1994; Hunt, 2004).

Intrahepatic shunts are more likely to affect large breed dogs whereas extrahepatic shunts are more likely to affect small breed dogs (Bostwick and Twedt, 1995; Smith *et al.,* 1995; Lamb, 1996; Wolschrijn *et al.,* 2000; Tobias *et al.,* 2003; Winkler *et al.,* 2003; Hunt, 2004). Bostwick and Twedt (1995) stated that a large breed dog has a 90% chance of having an intrahepatic shunt, whereas a small breed dog has a 93% chance of having an extrahepatic shunt. Even within the intrahepatic shunts there seems to be a breed predilection, which is shown in Table 1 (Tisdall *et al.,* 1994; Meyer *et al.,* 1995; Lamb and White, 1998; Kerr and van Doorn, 1999).

These reports show that breed has a significant effect on shunt anatomy in dogs. Furthermore, unusual or inoperable shunts more likely occur in breeds that are not predisposed for CPSS. A possible explanation may be that predisposed breeds suffer from programmed genetic defects, whereas in non-predisposed breeds shunt development is more often a result of random errors in embryogenesis (Hunt, 2004).

Because certain breeds appear to be at increased risk for CPSS and because breed clearly influences shunt anatomy, a genetic predisposition is hypothesized (Tisdall *et al.,* 1994; Tobias and Rohrbach, 2003; van Straten *et al.,* 2005). CPSS is identified as hereditary in Yorkshire Terriers, Irish Wolfhounds and Cairn Terriers but the exact mechanism of inheritance has yet to be elucidated (Meyer *et al.,* 1995; Tobias, 2003; van Straten *et al.,* 2005). In Yorkshire Terriers, it has been determined that the mode of inheritance is not sex-linked, simple autosomal dominant or simple autosomal recessive. It has been suggested that incomplete penetrance, variable gene expressivity or multifactorial components can be involved (Tobias, 2003). In Cairn Terriers an autosomal mode of inheritance has been defined that is probably polygenic or monogenic, with variable expression comparable to hepatoportal microvascular dysplasia (HMD). It is not clear whether there is a genetic relationship between CPSS and HMD (Schermerhorn *et al.,* 1996; van Straten *et al.,* 2005). By screening Irish Wolfhound pups in 2 studies, an incidence of 2.1% in the Netherlands and 3.4% in the United Kingdom for intrahepatic shunts, all left-divisional, has been determined, which suggests a hereditary basis for this type of CPSS in this breed (Meyer *et al.,* 1995; Kerr and van Doorn, 1999). Environmental factors may also influence the development of CPSS, but until now no other risk factors other than heredity have been clearly defined (Tobias and Rohrbach, 2003).

Portosystemic shunts are diagnosed rarely in cats, and the domestic shorthaired cats are the most commonly affected breed group (Table 1; Scavelli *et al.,* 1986; Holt *et al.,* 1995; Levy *et al.,* 1995; Lamb *et al.,* 1996; Wolschrijn *et al.,* 2000; Havig and Tobias, 2002; Kyles *et al.,* 2002; Tillson and Winkler, 2002). The most commonly reported shunt in cats is the single, extrahepatic portocaval shunt (Scavelli *et al.,* 1986; Rothuizen *et al.,* 1982; Blaxter *et al.,* 1988; Birchard and Sherding, 1992; Wolschrijn *et al.,* 2000; Havig and Tobias, 2002; Kyles *et al.,* 2002). Almost 10% of the shunts in cats are located intrahepatically (Levy *et al.,* 1995; Tillson and Winkler, 2002).

## Age at presentation

Most dogs and cats are presented with clinical signs at a young age (Table 1), but occasionally animals (mainly dogs) are presented at an older age. Many patients with CPSS, especially cats, already have a long or even a life-long history of illness (Rothuizen *et al.,* 1982; Scavelli *et al.,* 1986; Johnson *et al.,* 1987; Blaxter *et al.,* 1988; Birchard and Sherding, 1992; Lawrence *et al.,* 1992; Smith *et al.,* 1995; Bostwick and Twedt, 1995; Levy *et al.,* 1995; Hunt and Hughes, 1999; Wolschrijn *et al.,* 2000; Havig and Tobias, 2002; Kyles *et al.,* 2002; Tillson and Winkler, 2002; Winkler *et al.,* 2003). The type of shunt can influence the age of onset and the severity of the clinical abnormalities. Several reports have demonstrated that dogs with intrahepatic shunts tend to be younger at the time of diagnosis than those with extrahepatic shunts, probably due to a larger anomalous vessel in the case of intrahepatic CPSS (Komtebedde *et al.,* 1991; Martin, 1993; Lamb, 1996). By contrast, dogs with an extrahepatic portoazygos shunt may be presented at older ages (Rothuizen *et al.,* 1982; Martin, 1993; Mehl *et al.,* 2005). However, Smith et al. (1995) could not show a correlation between shunt location and the age at surgery.

## Sex predisposition

Although older reports suspected a slight male predisposition in cats (Birchard and Sherding, 1992; Levy *et al.,* 1995), nowadays, a sex predisposition is not described either in cats or dogs (Table 1; Rothuizen *et al.,* 1982; Holt *et al.,* 1995; White *et al.,* 1996; Murphy *et al.,* 2001; Havig and Tobias, 2002; Kyles *et al.,* 2002; Tillson and Winkler, 2002; Mehl *et al.,* 2005). There may be an association with golden- or copper-colored irises and congenital cardiac murmurs in cats with CPSS (Figure 1; Scavelli *et al.,* 1986; Levy *et al.,* 1995; Havig and Tobias, 2002; Kyles *et al.,* 2002; Tillson and Winkler, 2002). A high rate of cryptorchidism is also reported in cats with CPSS (Levy *et al.,* 1995; Tillson and Winkler, 2002) and in two canine studies (Johnson *et al.,* 1987; Watson and Herrtage, 1998).

## CLINICAL SIGNS

The clinical signs of CPSS are very variable and are in general a combination of neurological, gastrointestinal and urinary signs.

### Dogs

*Central nervous system signs*

Central nervous system (CNS) signs usually predominate with CPSS, which is the most common cause of hepatic encephalopathy in young dogs and cats (Rothuizen *et al.,* 1982; Blaxter *et al.,* 1988; Martin, 1993; Lawrence *et al.,* 1992; Holt *et al.,* 1995; Murphy *et al.,* 2001; Mehl *et al.,* 2005). The key diagnostic features of hepatic encephalopathy are intermittent and, in most cases, reversible clinical signs (Rothuizen *et al.,* 1982; Tyler, 1990a; Maddison, 1992; Aronson *et al.,* 1997). These signs can vary in intensity from day to day, and they often show a progressive severity and range, from depression and lethargy to behavioral changes, seizures, coma and death. Sometimes signs present in relationship with feeding or medication (Tyler, 1990a; Martin, 1993). Possible presentations of hepatic encephalopathy in dogs are head pressing, staring, disorientation, circling, ataxia, dementia, apparent blindness, unusual behavior, vocalization, ptyalism, seizures and dullness (Rothuizen *et al.,* 1982; Johnson *et al.,* 1987; Tyler, 1990a; Holt *et al.,* 1995; Aronson *et al.,* 1997; Winkler *et al.,* 2003; Mehl *et al.,* 2005).

The pathophysiology of hepatic encephalopathy is still not completely understood. This disorder does not cause significant structural damage to the CNS (Tyler, 1990a; Maddison, 1992; Aronson *et al.,* 1997). Analyses of cerebrospinal fluid and electroencephalogram are normal or only show non-significant abnormalities consistent with metabolic encephalopathy (Tyler, 1990a; Maddison, 1992). The metabolic cause of hepatic encephalopathy is unknown and is probably multifactorial (Tyler, 1990b; Maddison, 1992; Aronson *et al.,* 1997; Holt *et al.,* 2002). Every author agrees that this condition most likely is caused by one or a combination of toxins which normally should be detoxified by the liver (Tyler, 1990b; Maddison, 1992; Aronson *et al.,* 1997; Tillson and Winkler, 2002; Winkler *et al.,* 2003). Many abnormalities are linked to the effects of ammonia on the CNS (Maddison, 1992; Holt *et al.,* 2002). Because the brain has no urea cycle, astrocytes metabolize ammonia in the brain by transamination of glutamate into glutamine via glutamine synthetase (Tyler, 1990b; Holt *et al.,* 2002; Morita *et al.,* 2004). Glutamine normally shares an antiport transport mechanism with tryptophan. As in humans, an increased concentration of glutamine, tryptophan and tryptophan metabolites is found in the cerebrospinal fluid of dogs with CPSS. These substances may contribute to the neurological abnormalities seen in hepatic encephalopathy (Holt *et al.,* 2002). Besides ammonia, some aromatic amino acids, short-chain fatty acids, mercaptans and benzodiazepine-like substances also play a role, probably due to a synergistic effect with the ammonia toxicity (Tyler, 1990a; Tyler, 1990b; Maddison, 1992; Tillson and Winkler, 2002). Aromatic amino acids may be released during catabolism of skeletal muscle caused by increased glucagon concentrations as a consequence of persistent hyperammonemia (Matushek *et al.,* 1990). The insufficient hepatic clearance results in increased concentrations of aromatic amino acids in the CNS, which might contribute to neurological signs because they are precursors of false and inhibitory neurotransmitters (Matushek *et al.,* 1990; Maddison, 1992). A possible explanation for common signs such as head pressing, ataxia, circling, dementia or coma is the inhibitory influence on the CNS of the benzodiazepine-like compounds by interaction with binding sites on the γ-aminobutyric acid (GABA)-benzodiazepine receptor complex. The role of benzodiazepine-like substances is confirmed by detection of a higher concentration of endogenous benzodiazepines in systemic and portal blood of dogs with CPSS compared to normal dogs (Aronson *et al.,* 1997). The gastrointestinal tract is suggested to be a source for these compounds because in most dogs with CPSS a higher level of endogenous benzodiazepine ligand is detected in portal blood compared to systemic blood. It is not yet known whether these gastrointestinal compounds originate from the diet, the gut flora or from endogenous modification of inactive gut precursors. This theory is supported by the generally good therapeutic response of hepatic encephalopathy to medical modification of the gut flora or intestinal absorption (Aronson *et al.,* 1997). Studies in humans showed that the "increased GABAergic tone" is not due to changes in the GABA-A receptor binding site or the functional coupling (Ahboucha and Butterworth, 2005). Several benzodiazepine-receptor antagonists have been studied for the treatment of hepatic encephalopathy. Flumazenil showed discrepant findings in experimental acute hepatic encephalopathy in rats and rabbits (Ahboucha and Butterworth, 2005). For the treatment of chronic hepatic encephalopathy, beneficial effects were observed in humans, but not in dogs (Meyer *et al.,* 1998; Ahboucha and Butterworth, 2005; Lock and Pandit, 2006). Sarmazenil ameliorated the physical effects of experimentally induced chronic hepatic encephalopathy in dogs and acute hepatic encephalopathy in rats (Meyer *et al.,* 1998; Ahboucha and Butterworth, 2005). However, no clinical studies have been performed yet, and at this point flumazenil and sarmazenil can only be administered intravenously. Therefore, further studies are necessary to substantiate the possible role of sarmazenil or flumazenil in the treatment of chronic hepatic encephalopathy. According to Meyer et al. (1998), the "increased GABAergic tone" in the pathogenesis of hepatic encephalopathy is confirmed by the positive effects of sarmazenil, but the lack of effects for flumazenil make it unlikely that endogenous benzodiazepines play an important role in this process. Several other factors may contribute to hepatic encephalopathy. High serum bile acid concentrations reversibly enhance the permeability of the blood brain barrier and thereby facilitate the entry of toxic metabolic substances into the CNS (Center *et al.,* 1985). Other metabolic abnormalities such as hypokalemia, alkalosis, hypovolemia, hypoglycemia and hypoxiacan precipitate hepatic encephalopathy (Maddison, 1992).

**Figure 1. A 4-month-old British Shorthair cat diagnosed with an extrahepatic portocaval CPSS. The wet mouth due to ptyalism and the copper colored irises are obvious.**

In metabolic alkalosis, which can be caused by vomiting, volume depletion and/or hypokalemia, ammonia is present in unionized form, which facilitates its transfer across the blood-brain barrier (Tyler, 1990a; Tyler, 1990b; Maddison, 1992; Center, 1996b). Furthermore, the level and metabolism of neurotransmitters (such as serotonin, norepinephrine or dopamine) and the densities and affinities of neurotransmitter receptors (such as GABA, glycine or diazepine receptors) can be altered in hepatic encephalopathy, although the presence of most of these changes still needs to be proven in dogs and cats (Tyler, 1990b).

*Other clinical signs*

Gastrointestinal signs related to hepatic dysfunction are most often non-specific (vomiting, diarrhea, melena, poor appetite). Some dogs present with signs of urinary tract disease (pollakisuria, hematuria) with or without concurrent nervous or gastrointestinal signs (Rothuizen *et al.,* 1982; Martin, 1993; Holt *et al.,* 1995; Mehl *et al.,* 2005). In rare cases, the urinary tract signs are the only abnormality. These signs are due to ammonium biurate or urate crystal or stone formation. Hepatic insufficiency impairs the conversion of ammonia to urea by urease and the conversion of uric acid to allantoin by uricase, which leads to hyperammonemia and hyperuricemia. This results in increased urinary excretion of ammonia and uric acid and consequently a predisposition for urate calculi (Johnson *et al.,* 1987; Center, 1996a; Bartges *et al.,* 1999). The reported incidences of dogs with CPSS and concurrent urinary calculi vary from 20% to more than 50% (Rothuizen *et al.,* 1982; Johnson *et al.,* 1987; Center, 1996b; Santilli and Gerboni, 2003; Winkler *et al.,* 2003).

Other clinical signs which may accompany CPSS in dogs are a thin and undersized body condition, poor growth, slow recovery from anesthesia, recurrent pyrexia, primary polydipsia and secondary polyuria (Rothuizen *et al.,* 1982; Martin, 1993; Mehl *et al.,* 2005). The reasons for the polyuria and polydipsia are not clearly understood. Possible explanations include decreased renal medullary gradient secondary to limited blood urea nitrogen (BUN) production, psychogenic polydipsia, altered function of portal vein osmoreceptors and stimulation of central thirst centers (Rothuizen *et al.,* 1982; Tillson and Winkler, 2002). The intermittent fever can be due to transient bacteremia by translocation of intestinal bacteria into the portal blood and the subsequent entering of bacteria into the systemic circulation, or to reduced hepatic or total body reticuloendothelial function. As a consequence, a CPSS should be included in the differential diagnosis for fever of unknown origin (Koblik and Hornof, 1995; Watson and Herrtage, 1998; Wess *et al.,* 2003). Patients with CPSS do not suffer from portal hypertension and do not develop ascites unless they have profound hypoalbuminemia (Mathews and Bunch, 2005).

## Cats

The most common observations in cats with a CPSS are ptyalism, seizures, ataxia, tremors and depression. Other neurological signs are intermittent or permanent blindness, mydriasis, disorientation, and behavioral changes (such as excessive vocalization, aggression, tail twitching, unusual docility and hiding) (Scavelli *et al.,* 1986; Blaxter *et al.,* 1988; Birchard and Sherding, 1992; Levy *et al.,* 1995; Havig and Tobias, 2002; Kyles *et al.,* 2002; Tillson and Winkler, 2002). In about half of the cats, the encephalopathic episodes are precipitated or exacerbated by meals (Levy *et al.,* 1995; Havig and Tobias, 2002). Beyond the neurological signs, gastrointestinal (vomiting, diarrhea, intermittent anorexia, pica, polyphagia, constipation, weight loss), respiratory (tachypnea, dyspnea, nasal discharge) and urinary (dysuria, pollakisuria, hematuria, stranguria, proteinuria) signs can also be present in cats with CPSS (Scavelli *et al.,* 1986; Levy *et al.,* 1995; Havig and Tobias, 2002; Kyles *et al.,* 2002; Tillson and Winkler, 2002). Excessive salivation or ptyalism is very common and its presence should heighten the suspicion for a CPSS (Figure 1; Scavelli *et al.,* 1986; Blaxter *et al.,* 1988; Birchard and Sherding, 1992; Havig and Tobias, 2002; Kyles *et al.,* 2002; Tillson and Winkler, 2002). However, signs which are not related to hepatic encephalopathy seem to be less common in cats than in dogs (Blaxter *et al.,* 1988). In a small proportion of feline cases (almost 10%), anesthetic complications such as prolonged recovery time, cardiac arrest, postoperative blindness or seizures develop due to the decreased functional hepatic mass. Polyuria, polydipsia and intermittent fever are infrequently observed (Levy *et al.,* 1995; Havig and Tobias, 2002; Kyles *et al.,* 2002; Tillson and Winkler, 2002; Wess *et al.,* 2003).

## CONCLUSION

A congenital portosystemic shunt is an infrequent disorder in dogs or cats, although an increased awareness is necessary in young animals with vague or intermittent signs of the nervous, gastrointestinal and/or urinary systems.

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