Introduction

Extrahepatic portosystemic vascular anomalies (PSVA) in small breed dogs, originally described in the 1970s, have received notorious attention in the veterinary literature. We estimate that this congenital malformation comprises approximately 0.6 to 2.0% of a specialty hospital patient population. However, microvascular dysplasia (MVD), a genetically related hepatic vascular disorder is far more common; 15 to 30:1 compared to the prevalence of PSVA in affected kindreds based on investigations in an expansive genotyping initiative. MVD occurs as a single entity or coexists with PSVA. Unfortunately, discovery of high serum bile acid concentrations in dogs with MVD often leads to expensive and invasive diagnostic assessments for PSVA in pet dogs. Dogs affected only with MVD are typically asymptomatic and their hepatic vascular abnormalities non-progressive. The majority of dogs affected only with MVD do not need medical treatments as assigned for dogs with symptomatic PSVA and have a normal life expectancy. Many MVD affected dogs are discovered on the basis of high serum bile acid concentrations revealed upon screening kindreds for PSVA or serendipitously at the time of non-related illnesses. Misconceptions regarding management of MVD has caused confusion among clinicians, breeders of commonly affected small pure breed dogs, and pet dog owners.

Genetic Studies

Our research group has been working on a large genotyping project aimed at identifying the genetic cause of PSVA and MVD. The trait appears to be autosomal dominant with incomplete penetrance (modifier genes involved?) Data substantiate that PSVA/MVD has been perpetuated through the innocent selection of asymptomatic MVD dogs as foundation breeding stock. Prior publications addressing the genetic basis of PSVA have widely under-estimated trait incidence in Cairn Terriers owing to the failure to acknowledge a relationship between PSVA and MVD as well as the use of ammonia rather than total serum bile acids (SBA) for phenotype designation. Ammonia determinations do not identify dogs with MVD and the test is simply unreliable in practical application. Our studies substantiate a wide variation in PSVA/MVD prevalence among dog breeds and among kindreds within a breed; data describe prevalence rates ranging from 30% to > 80% in afflicted kindreds. Studies in one of terrier breed with an initial prevalence of 32% has shown vacillation of prevalence as high as 50% with kindred expansion (more breeding, new combinations of parents, importation of new unrelated founders from other countries), substantiating a breed-wide rather than a kindred-limited disorder. Clinical observations suggest that PSVA may be a lethal trait in full expression or penetrance explaining, in part, the lower number of dogs with PSVA compared to MVD. In some breeds and kindreds, the high frequency of the trait seemingly has lead to embryonic deaths (fetal resorption) and small litter sizes.

Histological Features

The normal liver receives blood from both the portal vein and hepatic artery; these circulations are regulated independently. Portal flow, normally provides 60-70% of hepatic blood flow. The liver has no inherent ability to control portal blood flow and the portal vein lacks valves. Rather, portal flow is regulated by resistance vessels in splanchnic viscera (pre-hepatic) with net circulation determined by their net outflow. The liver indirectly influences portal perfusion by regulating hepatic arterial flow (hepatic artery buffer response, HABR). The HABR is mediated by adenosine wash out, i.e. in the circumstance of low portal blood flow, less adenosine is washed out leading to hepatic arterial dilation and increased high pressure arterial flow. Thus, following acute interruption of portal vein perfusion, the HABR maintains hepatic blood flow. While the hepatic artery provides approximately 20-30% of total hepatic blood flow in health, in the presence of portal hypoperfusion, flow increases up to 4 fold. Recent evidence confirms that arteriolar flow also compensates for chronic portal hypoperfusion. In the dog, hepatic outflow also is adjusted by throttling musculature surrounding hepatic venules.

The histological features of PSVA have been frequently described and largely reflect portal hypoperfusion. Typical microscopic changes include: increased hepatic arteriole (small arteries) cross sections, obvious small non-perfused vessels (lymphatics) within the adventitia of the portal triad, small, juvenile or under-developed portal triads (very small structures) randomly located in the hepatic parenchyma, hepatic lobular atrophy, an increased number of small binucleated hepatocytes, prominent hepatic venule throttling musculature (hypertrophied) that appears variably contracted, and in some dogs, multifocal lipogranulomas and lipogranulomas perivascular to the hepatic venule. Hepatic venules inappropriately located adjacent to or within portal triads are apparent in some dogs with MVD.
These likely enable direct intrahepatic shunting. Variable lipogranulomatous and inflammatory (non-suppurative, may involve eosinophils) zone 3 lesions impose a veno-occlusive effect in some dogs. Dogs with this lesion are significantly at risk for poor response to surgical shunt attenuation (formation of acquired shunts, abdominal effusion, post-operative death). In general, microscopic abnormalities associated are so similar in PSVA and MVD that the disorders CANNOT be differentiated. Arteriolar duplication is the most common lesion; these reflects cross sections of tortuous or coiled arterioles (response or increased flow and pressure) and perhaps arteriolar “twigs”. Experimental work (rodents with chronic [6 week] portal vein attenuation) documenting a three-fold increase in hepatic arteriolar blood flow demonstrated similar tortuous, clustered, disorganized arterioles. It remains unclear if this is a remodeling response (hypertrophy, expansion) involving pre-existent arterioles or de novo angiogenesis. In this model, arterioles develop connections with more than a single acinus and branches directly drain into sinusoids as well as terminal hepatic venules. The latter communications establish conduits of intrahepatic shunting.

Surgical wedge and laparoscopic liver biopsies collected from multiple liver lobes in dogs with MVD and PSVA confirm that microscopic lesions are inconsistent among liver lobes. The caudate lobe notoriously has the most normal architecture in affected dogs (receives first portal vein branch) and often is adequately perfused in dogs with MVD and in some dogs with PSVA. Thus, needle biopsy and single liver lobe biopsies can miss lesions in MVD affected dogs. This circumstance likely influenced outcome in a study comparing total serum and HPLC measured bile acids in Maltese dogs. Portovenograms, colorectal scintigraphy, and MRI contrast studies in dogs with MVD corroborate histologic evidence that liver lobes have variable portal perfusion. It is probable that variable liver lobe perfusion in MVD affected dogs explains apparent “portal streamlining” recognized by scintigraphy is dogs suspected of having PSVA. Considered collectively, histologic and imaging features corroborate that MVD and PSVA represent complex disorders of hepatic angiogenesis / vasculogenesis and that there are a spectrum of severities. Because dogs with surgically created portosystemic shunts develop histologic features identical with those in PSVA, liver biopsy cannot confirm portal hypoplasia (lack of portal vein development) without knowledge of patient signalment. Rather, the lesion is appropriately termed portal hypoperfusion.

Clinical Signs
Study of large kindreds of dogs as well as a large clinical population of unrelated purebred dogs with PSVA and dogs with MVD has clarified typical presentations. MVD is clearly more common than PSVA and most MVD dogs do not demonstrate ANY clinical signs. While PSVA affected dogs represent the most severe vascular malformations and usually manifest clinical signs, we estimate that approximately 15-20% of these are asymptomatic, reflecting variation in shunting (smaller shunting = lack of clinical signs). Dogs with portoazygous shunts are generally least symptomatic and often present as adults with ammonium biurate calculi or are serendipitously diagnosed. Generally, dogs discovered with PSVA later in life are relatively asymptomatic and usually have a good response to PSVA ligation (see below). Clinical signs associated with symptomatic PSVA in dogs are well described and variably include: meal related neuroencephalopathic signs or somnolence, nausea or vomiting, diarrhea or constipation, polyuria and polydipsia, intermittant fever, ptyalism, maniacal or aggressive behavior, seizures, coma, signs attributable to ammonium biurate urolithiasis (ureteral, cystic, urethral locations) and chronic urinary tract infections. Symptomatic PSVA dogs have increased susceptibility to infections owing to reduced function of hepatic mononuclear phagocytes (Kupffer cells). Minor bite wounds, tick bites, subcutaneous infections, lacerations, and even vaccinations may lead to illness requiring hospitalization (fluid therapy, antimicrobials). Severity of clinical signs in symptomatic PSVA dogs is widely variable and is largely modified by feeding an appropriately formulated diet. Seemingly, relative risk for seizures in PSVA dogs (author’s hospital) exceeds that of dogs with other organ system disorders.

Common clinicopathologic features of PSVA include a borderline non-regenerative anemia, low MCV, target cells, low BUN, low creatinine, low cholesterol, and slightly low albumin concentrations, normal to variable increases in liver enzymes (mild to modest), low normal glucose concentration (except for ill young toy breed dogs: e.g. Yorkshire Terriers, Maltese that may have symptomatic hypoglycemia), and ammonium biurate crystalluria (minimally examine 3 urine specimens before dog is place on a protein restricted diet) High serum bile acid concentration are typically found unless enteric malabsorption co-exists. Bile acid quantification should be done using paired samples (pre-meal and 2-hours post meal). I no longer demand a 12-hour fasted sample as this may delay sample collection. The point of this test is to assess the ability to extract bile acids form the portal circulation after a provoked endogenous bile acid challenge (abnormal: any value ≥ 25 uM/L). Use of a fasting SBA “normal range” should be discarded as 15-20% of dogs tested with paired samples will demonstrate a higher pre-meal than post-meal bile acid concentration attributable to physiologic variables influencing the test. Blood samples for
quantification of SBA should be free of hemolysis and the laboratory should remove clarify lipemia before testing. Collection of SBA samples into lithium heparin tubes, removing the needle and vacutainer stopper before gently placing blood in the tube (avoids hemolysis), will allow immediate sample preparation for laboratory submission (avoid waiting for clot retraction). Blood ammonia concentrations continue to remain controversial in the diagnosis of PSVA because environmental contaminants can generate false positive tests values, the test has low reproducibility, and is inconvenient because of ammonia lability (transport samples on melting ice, cannot be mailed). Finding ammonium biurate crystalluria is however is nearly pathognomonic for PSVA when coupled with patient signalment, clinicopathologic and imaging findings. The recently validated Protein C test is useful for predicting the degree of shunting and in monitoring patient response to surgical shunt attenuation. Values ≤ 70% are useful for differentiating PSVA from MVD (most MVD dogs have Protein C > 70%). This cutoff prioritizes pursuit of expensive ultrasound and colorectal imaging studies in dogs with high SBA.

**Treatment**

**Surgical PSVA Attenuation:** Current textbook dogma predicts that all dogs with PSVA have a shortened life span if they are not provided surgical shunt attenuation. This is clearly not true. We have diagnosed dogs with PSVA as old as 13 yrs and have medically managed asymptomatic and symptomatic dogs effectively with dietary therapy for years. Surprisingly, even dogs with extrahepatic portal atresia can be effectively managed with strict dietary control (the author maintains 3 such dogs in her home-3 years to date using a prescription diet formulated for dogs with hepatic insufficiency without additional lactulose or metronidazole). The best surgical method of PSVA attenuation remains controversial among surgeons. Ameroid constrictors can considerably reduce surgical table time but present a hazard for dogs that cannot tolerate complete shunt attenuation. Selecting a “large” ameroid to avoid complete shunt attenuation is a strategy used by some surgeons. Early use of ameroid constrictors in some Yorkshire Terriers developed acquired portosystemic shunts as some dogs are unable to accommodate complete shunt occlusion (severe intrahepatic hypoplasia-MVD). At present, there is no evidence that slow PSVA occlusion allows hepatic vasculature accommodation to increased (forced) portal flow. Physiologic mechanisms consistent with this hypothesis are undefined in the experimental literature. We and others approximate that 15 to 20% of the dogs presenting for PSVA cannot accommodate even partial PSVA occlusion. The best review of ameroid constrictor performance described findings in 168 dogs (7.1% mortality, 10% postoperative complications: seizures, hemoperitoneum, acute ascites, sudden death [thrombi]; 58/162 dogs had a portoazygous shunt [less symptomatic and more amenable to attenuation]). Authors reported 86/108 (80%) dogs with excellent outcome (no treatments or hemoperitoneum, acute ascites, sudden death [thrombi]; 58/162 dogs had a portoazygous shunt [less symptomatic and more amenable to attenuation]).

**Postoperative Management:** Postoperative complications include: the return of clinical signs of hepatic insufficiency, worsening hepatic insufficiency without additional medical or dietary treatments, or progression of chronic gastrointestinal signs. Protein C < 70% are predictive for poor postoperative outcome. Response to surgical PSVA attenuation is judged on the basis of clinical signs, normalization of routine clinicopathologic tests, resolution of ammonium biurate crystalluria, and decline of SBA concentrations. However, many dogs retain abnormally increased SBA values which may reflect: continued small flow shunting, failure of shunt ligation, presence of two PSVA (only 1 ligated), ligation of a wrong vessel, acquired portosystemic shunts, or concurrent MVD. Prospective comparison of pre- and post-surgical Protein C activity suggests that this parameter better substantiates improved portovenous circulation despite continued high serum bile acid concentrations. Dogs with poor surgical outcome fail to increase Protein C activity > 70%. Dogs with Protein C activity > 70% before surgery are minimally symptomatic and can be fully ligated with excellent outcome. Observations suggest that
Protein C activity > 70% reflects relatively low grade portosystemic shunting for which dietary therapy alone may be effective.

**Medical Management PSVA:** First line medical management of PSVA involves restriction of the dietary protein allowance (2.2 to 2.5 gm/kg body weight per day protein) and modifying the source of dietary protein to dairy or soy sources preferably, or while meat chicken. All red meats, fish, and eggs are avoided. Several excellent prescription diets formulated for dogs with hepatic encephalopathy have made a remarkable improvement treatment options and the success of medical therapy. For owners preferring to cook for their small dog, we provide the NAT 2 website link for dietary adjustment of a basic recipe (nat.crgq.com). Meals are fed frequently and in small portions to maximize digestion and assimilation. Providing continuous access to a dry prescription diet formulated for dogs with hepatic insufficiency and meal feeding the canned formula twice daily, has been a successful management strategy for many PSVA dogs of small breeds. Many dogs can be maintained exclusively on a strict dietary regimen without additional supplements (such as lactulose or metronidazole). However, if dietary restriction alone does not provide optimal response (recurrent hepatic encephalopathy, persistent ammonium biurate cystaltrullia) then additional medical interventions are used. The second line strategy is to incorporate lactulose to modify the enteric environment. A synthetic disaccharide that undergoes microbial fermentation in the enteric canal, lactulose derived organic acids acidify the enteric environment, cripple ureases and proteases, trap the ammonium ion, and induce a colonic catharsis. Lactulose also augments bacterial nitrogen fixation further reducing availability of ammoniagenic products in the enteric canal. Careful dosing to achieve several soft stools per day is advised; individual titration starting at a low dose (0.5 ml per 5 to 10 kg, PO, BID to TID) is titrated to effect. Dosing too high results in abdominal cramping, painful borborygmi, flatulence, and liquid diarrhea that can progress to hematochezia. Metronidazole is used if response to lactulose and diet prove insufficient; 7.5 mg/kg PO SID to BID. Side effects of metronidazole include inappetence due to dysgeusia and rarely, granulocytopenia. Clavamox can alternatively be used as an enteric modifying antimicrobial in animals intolerant of metronidazole. Neomycin is uncommonly used in the author’s hospital; as an aminoglycoside, chronic neomycin absorption in dogs with inflammatory bowel disease has produced otoxicity (2 dogs) and renal damage (1 dog). Low liver zinc concentrations are commonly found in liver tissue of PSVA dogs are thought to reflect reduced intake and increased urinary losses (surmised from human studies). We routinely increase zinc intake either through diet or as a separate supplement (zinc acetate: 1-5 mg elemental zinc per kg body weight, titrate against changes in plasma zinc concentrations) because of the importance of zinc in metalloenzymes to metabolism, including some integral to the urea cycle. Dogs presented in hepatic coma, should receive cleansing enemas (lukewarm crystalloid fluids in very small patients). Thereafter, retention enemas containing lactulose can effectively deter production/absorption of colonic toxins. Crystallloid fluid therapy, avoidance of neuroglycopenia, and broad spectrum antimicrobials are usually provided. Treatment of severe hepatic encephalopathy is beyond the scope of this discussion. Dogs with PSVA do not need treatment with ursodeoxycholic acid. These dogs have high SBA due portosystemic bile acid flux. Since most PSVA dogs lack necroinflammatory lesions they do not need s-adenosylmethionine nor other hepatoprotectants (e.g. milk thistle, phosphatidylcholine). Glutathione concentrations in dogs with PSVA confirm adequate antioxidant status in most dogs. Hepatic fibrosis is not a typical feature of PSVA in dogs.

**Medical Management of MVD:** Dogs with MVD do not require special diets for hepatic insufficiency, lactulose, antioxidants, ursodeoxycholate, or hepatoprotectants. Most MVD dogs live a full lifespan without any signs of hepatic insufficiency or hepatobiliary dysfunction. Examination of liver biopsies collected from elderly dogs diagnosed with MVD as puppies (early 1990s: Cairn Terriers, Tibetan Spaniels, Yorkshire Terriers) has verified a lack of progression of either degenerative or inflammatory lesions. Dogs with zone 3 inflammation and veno-occlusive lesions usually have concurrent inflammatory bowel disease and are treated with hypoallergenic diets (soy based home cooked ration), anti-inflammatory dexamethasone (dosed q3days), and in some, ultra-low dose aspirin (0.5 mg/kg PO SID to EOD). Metronidazole is used adjunctively to manage the bowel inflammation.

Knowledge of MVD is clinically useful when estimating dosages for drugs requiring first pass hepatic extraction. We recommend serum bile acid quantification in all puppies of pure breeds having prevalence for PSVA and MVD. Testing at is recommended at 4 to 6 months of age (paired samples, pre- & 2-hours post-meal) so that high bile acids are not discovered during assessments for non-hepatic illnesses.

**References**