“Bella’s Beast of a Liver”

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Introduction

Portosystemic shunts (PSS) are vascular anomalies that redirect blood from the portal vein to systemic circulation, bypassing the hepatic sinusoids and liver parenchyma.[1,2] Portosystemic shunts, like other hepatic vascular anomalies, result in poor hepatic development, decreased protein metabolism and production, reduced toxin clearance and drug metabolism, reticuloendothelial dysfunction, altered metabolism of fat, and if severe, liver failure.[1] Portosystemic shunts can either be congenital or acquired. The two subtypes of congenital portosystemic shunts include intrahepatic shunts, which are more commonly seen in larger breed dogs, and extrahepatic shunts, which are more commonly seen in smaller breeds.[1,2,7] Genetic associations have been observed in Irish Wolfhound, Havanese, Yorkshire Terrier, Cairn Terrier, Pugs, and Maltese breeds.[2,3,5,7]

The most common organ systems affected by portosystemic shunts are the central nervous system, the gastrointestinal system, and the urinary system.[1,6,7] Most dogs with a single congenital PSS present with signs of chronic or acute illness at a very young age.[1] Clinical signs are influenced by shunt type, anatomy, nutrition, and concurrent diseases, causing presentation to be highly variable.[2] Hepatic encephalopathy is the cause of most of the clinical signs and results in abnormal behavior including lethargy, unresponsiveness, head pressing, seizures, circling, and blindness.[1,6] Gastrointestinal signs include vomiting, diarrhea, anorexia, and gastrointestinal bleeding.[1,2,6,7] Urinary tract disease is more common in older dogs and presents as hematuria, stranguria, pollakiuria, or urinary obstruction due to the formation of ammonium urate calculi.[1,6,7]

Diagnosis is based on signalment, clinical signs, clinicopathologic findings, and diagnostic imaging. Computed tomographic angiography is the gold standard for diagnosing

portosystemic shunts in humans and is an imperative tool for surgical planning in dogs.[1,4,7] Medical and surgical management both play an important role in the treatment of portosystemic shunts. Medical management is recommended before any anesthetic event, but graduated attenuation of the shunt vessel with surgery is the treatment of choice for singular PSS. The following case report represents an example of a congenital extrahepatic portosystemic shunt, and how an early diagnosis followed by surgical intervention can lead to a great outcome. This case report will review in greater detail the clinical signs, diagnostics, pathophysiology, and treatment of extrahepatic portosystemic shunts, as well as the outcome of the patient, Bella, who was seen by the Small Animal Surgery Service at Mississippi State University, College of Veterinary Medicine.

History and Presentation

Bella is an approximately 14-week-old female intact Yorkshire Terrier puppy that presented to the MSU CVM Emergency Service on March 28th, 2021, for a suspected portosystemic shunt. She had been having hepatic encephalopathy episodes for a week and a half. The episodes occurred after eating and lasted for a few hours. They consisted of Bella swaying her head back and forth, looking extremely dazed, and head pressing. The owners noted that Bella had never been a playful, active puppy and that she vocalized an excessive amount, especially throughout the night.

On presentation, Bella was bright, alert, and responsive. She weighed 0.9 kilograms and had a body condition score of 3/9. Vital parameters included a temperature of 101.9° F, a heart rate of 180 beats per minute, and a respiratory rate of 36 breaths per minute. Cardiopulmonary auscultation was within normal limits and no murmurs, arrythmias, crackles, or wheezes were appreciated. At that time, Bella was not presenting any clinical signs of hepatic encephalopathy.

No free fluid was appreciated with an aFAST (abdominal focused assessment with sonography in trauma) scan. She was continued on lactulose that was previously prescribed by her referring veterinarian, and was started on levetiracetam, amoxicillin, and acepromazine. That night, Bella was given acepromazine and butorphanol due to hyperactivity and constantly barking in her kennel. The next morning, she was transferred to the Small Animal Surgery Service.

Bella's signalment, history, and clinical presentation strongly suggested a congenital portosystemic shunt. One study stated that the odds ratio for PSS in Yorkshire terriers was 35.9 times greater than for all other dog breeds.[10] Dogs usually present with a wide variety of clinical signs due to decreased liver function and include stunted growth, poor muscle development, and abnormal behaviors such as disorientation, circling, head pressing, or seizures.[1] Clinical signs may be mild or even absent in animals with congenital PSS. Some patients are diagnosed after their first surgery (such as a spay or neuter) because the decreased drug clearance by the liver causes a slower recovery period after anesthesia.[13]

Diagnostic Approach and Considerations

Bella's referring veterinarian performed most of the lab work necessary for a presumptive PSS diagnosis on March 24th, 2021. Her CBC was unremarkable, though she was very mildly anemic and mildly thrombocytopenic. Microcytosis with or without normochromic, nonregenerative anemia has been associated with 60-72% of dogs with PSS and is thought to be a result from defective iron-transport, decreased iron concentrations, decreased iron-binding capacity, or increased hepatic iron storage in Kupffer cells.[1] Bella's serum chemistry revealed a mild hypoalbuminemia, moderately elevated liver enzymes, and glucose level on the low end of the normal range. Serum chemistry abnormalities typically result from decreased hepatic synthesis and include decreased blood urea nitrogen, hypoalbuminemia, hypoglycemia,

hypocholesterolemia, and elevated liver enzymes.[1,2] Serum bile acid concentrations are commonly increased due to poor liver function, and pre- and post- prandial measurements are considered the test of choice for PSS.[1,7,13] In animals with PSS, reabsorbed bile acids are shunted into systemic circulation, causing persistent increased levels.[13] Bella's serum bile acids were severely elevated, further supporting her diagnosis.

After transferring to the MSU-CVM Small Animal Surgery Service, Bella had a few more diagnostics performed to better prepare for surgical attenuation of her shunt. Her coagulation profile and urinalysis were within normal limits. A coagulation panel was warranted because coagulation factors are synthesized by the liver and altered hepatic function can lead to decreased coagulation factors and therefore clotting issues. A urinalysis was performed to ensure Bella's urinary system had not been affected. In PSS dogs, the increased amount of ammonia has been linked to the formation of ammonium urate calculi.[1,6,7] An abdominal CT with contrast confirmed our diagnosis and further revealed her PSS to be single, extrahepatic, and portocaval. Preoperative imaging greatly improves surgical intervention by reducing surgery times and by allowing accurate assessment of complex shunts.[3] Bella's PSS was described as a short, anomalous, tortuous vessel arising from the left lateral aspect of the portal vein that coursed dorsally to insert on the left lateral aspect of the caudal vena cava.

Pathophysiology

The roles of the liver include carbohydrate and protein metabolism, regulation of glucose levels, clearance of toxic metabolites, modification of immune function, storage of vitamins and minerals, and production of albumin, coagulation factors, and bile.[1] The anatomy and physiology of the liver is unique due to its role in connecting portal circulation with systemic circulation. The liver receives its blood supply, and therefore oxygen supply, by two vessels: the portal vein

and the hepatic artery. Contributors to the portal vein include the cranial and caudal mesenteric veins, the splenic vein, the gastroduodenal vein, and the left gastric vein.[1,2] Although the portal vein contains venous blood, it supplies 75-80% of afferent blood volume and 50% of oxygen to the liver.[1,2] The remainder of the blood and oxygen supply is from the hepatic artery and its branches.[1,2] Blood from the portal vein and hepatic arteries mix within the hepatic sinusoids before collecting in central veins.[1,2] The central veins merge and form hepatic veins that drain into the abdominal portion of the caudal vena cava.[1] In a healthy liver, neurotoxic substances absorbed from the gastrointestinal tract are filtered out through the portal system.[1,2,7]

During embryological development, the venous system of the abdominal cavity is derived from the umbilical, vitelline, and cardinal veins.[1,2] The portal vein originates from the umbilical and vitelline veins, whereas the non-portal venous vasculature is derived from the cardinal venous system.[2] In a normal dog, the only residual communication between the embryonic cardinal and vitelline systems are the junctions of the prehepatic and intrahepatic segments of the caudal vena cava.[1,2] However, developmental errors can produce abnormal, functional connections between the cardinal and vitelline systems, resulting in congenital extrahepatic portocaval and portoazygos shunts.[1] With blood being diverted from the liver during development, the liver remains underdeveloped which leads to the myriad of clinical signs associated with PSS.

The pathogenesis of hepatic encephalopathy is largely unknown and complex but causes the majority of the clinical signs seen in our PSS patients.[1,7] The altered liver cannot appropriately metabolize toxic substances absorbed from the digestive tract, allowing them to enter systemic circulation through the portosystemic shunt.[1] This has deleterious effects on multiple organ systems, but most importantly the central nervous system. More than 20 different

circulating compounds have been found in excess when liver function is impaired, with ammonia being the most harmful.[1] Ammonia is produced by the gastrointestinal flora and converted to urea and glutamine by the urea cycle in the liver.[1,8] Ammonia is associated with an increased release of glutamate, the major excitatory neurotransmitter of the brain. With chronicity, inhibitory factors such as GABA and endogenous benzodiazepines, which are also unregulated due to the faulty liver, surpass the excitatory stimulus, causing central nervous system depression and a coma-like state.

A link between shunt morphology and the degree of clinical illness has long been suspected, and with the increased use of computed tomography angiography more specifically characterized shunt morphologies have been described.[13,14] In particular, patients with portoazygous or portophrenic shunts developed less severe clinical signs and presented at an older age because the shunts inserted caudal to the diaphragm and cranial to the liver.[14] Portal perfusion is likely improved with these types of shunts due to the intermittent compression of the shunt by the diaphragm during respiration or by gastric distention after meals.[13,14] Dogs with portocaval shunts that insert caudal to the liver (such as with Bella's case) are more commonly to present with clinical signs because the shunt is never compressed.[14]

Treatment

Both medical and surgical management should be considered for the treatment of portosystemic shunts. Medical management controls the clinical signs associated with the shunt, but does not resolve the underlying issue of decreased hepatic perfusion.[1] Medical management includes correction of fluid, electrolyte, and glucose imbalances and prevention of hepatic encephalopathy.[7,8] All dogs should have their hepatic encephalopathy medically managed for 2-3 weeks prior to attempted shunt attenuation to make the anesthetic event easier to manage.[11]

Therapy for hepatic encephalopathy is directed at decreasing production and absorption of ammonia and includes administration or warm water enemas, oral or rectal lactulose, antibiotics to decrease urease-producing bacteria, and anticonvulsant therapy.[1,3,7,8] Lactulose shortens the transit time in the digestive tract and promotes acidification of colonic contents which entraps ammonia in the form of ammonium, reducing its absorption.[3] Antibiotics that concentrate in the gastrointestinal tract will reduce the number of bacteria responsible for ammonia production.[3,7] These include amoxicillin, neomycin, and metronidazole.[3] An antiseizure medication, such as levetiracetam is also started to help decrease the severity of post attenuation seizures in the perioperative period.[15] A protein-restricted, highly digestible diet is essential for all animals with portosystemic shunts.[7] Diets should contain a protein source of high biologic value, supply essential fatty acids, restrict components that hasten hepatic encephalopathy, and supply vitamins and minerals that promote liver function.[1,7,8] Nutraceuticals for hepatic supportive therapy have been recommended, but their effectiveness has not been well documented.[1] With proper medical management, weight and quality of life stabilize or improve greatly, but patient consideration is important.

Surgery is the treatment of choice for animals with singular congenital extrahepatic portosystemic shunts to correct blood supply and encourage regeneration of hepatic tissue.[1,7,9]. Non-encephalopathic dogs can usually tolerate complete shunt occlusion, however up to 86% of animals undergoing shunt ligation require partial attenuation.[1] Visual inspection of portal hypertension (pallor or cyanosis of intestines, increased intestinal peristalsis, cyanosis of pancreas) determines the degree of attenuation.[1] Additionally, the surgeon can measure portal and central pressures with a water barometer to determine if the shunt can be completely ligated.[13] Complete ligation is acceptable if the maximum portal pressure is between 17-24 cm

H_2O, the maximal change in portal pressure does not exceed 9-10 cm H_2O, and the maximal decrease in central venous pressure does not exceed 1 cm H_2O.[13] Gradual occlusion allows the liver to adjust to the increased vascular supply while avoiding potentially fatal portal hypertension.[1,8] Gradual attenuation is accomplished using ameroid constrictors or cellophane bands that can be placed on extrahepatic shunts (at the insertion site on the caudal vena cava or azygous vein) and many intrahepatic shunts.[1,7,8,9] Ameroid constrictors have an inner ring of casein that is surrounded by a stainless steel sheath.[1] The casein slowly swells as it absorbs body fluid causing the ring's diameter to decrease in size.[1,7,9] It also stimulates a fibrous tissue reaction that causes shunts to stricture close over 2-5 weeks.[1,7,9] Cellophane bands work similarly to ameroid constrictors by causing fibrous tissue reaction and gradual shunt occlusion.[1,7,9] They can be made from nonmedical grade cellophane that is cut into strips and gas sterilized.[1] Cellophane bands are held in place by surgical clips and excess banding is removed.[1]

Other less common surgical techniques include placing a hydraulic occluder or using silk suture to ligate the shunt[1,13] A hydraulic occluder is a silicone and polyester cuff connected by tubing to an access port.[1,9] The cuff is secured around the shunt while the access port is inserted under the skin. After surgery, sterile saline is injected through the port to gradually inflate the cuff.[1,9] Disadvantages of the hydraulic occluder include the potential for loss of occlusion due to implant leakage, the need for additional manipulations of the implant, and the possibility of implant related complications.[9] Silk suture has been historically used to ligate shunts due to its ease of handling and knot security.[1] It is also highly reactive in tissues allowing for a fibrous reaction to further occlude the vessel.[13]

Embolization of anomalous vessels with percutaneous coils using interventional radiology is a newer technique used to occlude PSS.[12,13] With this technique, a multipurpose

catheter is inserted into the caudal vena cava and then into the PSS.[12] An auto-expandable stent is placed in the caudal vena cava next to the shunt to inhibit the coil from migrating and then a vascular catheter is used to pass through the stent and to place the coils in the shunt.[12,13] This method is thought to be less invasive than a laparotomy, but there are still some risks associated with coil migration.[12,13]

Postoperative care includes monitoring for seizures, hypothermia, hypoglycemia, hemorrhage, and signs of portal hypertension (hypovolemic shock, severe abdominal pain, abdominal distention, melena, and diarrhea).[1,7,9] Postattenuation neurologic signs (PNS) is a poorly understood and potentially devastating complication of shunt attenuation that most commonly occur within 7 days after surgery.[15] PANS include seizures, behavioral changes, tremors, twitching, and depression and are typically unrelated to hyperammonemia, hypoglycemia, or other electrolyte disturbances.[15] There is increasing evidence that prophylactic antiepileptic drugs do not prevent PANS, however they may decrease the severity.[15] Animals may require opioid analgesics and possibly minor sedation for 1 to 3 days following surgery.[1] Opioids should be used with caution since they are metabolized by the liver. Lactulose is continued for 4-6 weeks, based on clinical signs and protein restricted diets should be fed until there are signs of improved hepatic function.[1,8] Bile acids and a serum chemistry should be evaluated 2-3 months after surgery to assess liver function.[1,8] If the liver is normal, medical management can be slowly weaned.[1]

Case Outcome and Prognosis:

Bella had surgery on March 30th, 2021, for an extrahepatic portosystemic shunt attenuation using the cellophane banding technique. A sample of her liver was submitted for histopathology. There were no intra-operative complications and she recovered uneventfully in

our intensive care unit. She was kept on intravenous fluids, injectable pain medications, lactulose, amoxicillin, and levetiracetam overnight. The day after surgery, she was transitioned to oral medications and sent home to continue her recovery. Bella's liver biopsy revealed an undulant capsule, proliferation of portal arterioles, and mild fibrosis suggestive of recanalization due to hypo-oxygenation, which is common with extrahepatic shunting. However, her portal architecture was generally preserved, and we were confident that her liver would regenerate healthy tissue. As of October 15th, 2021, Bella is doing extremely well at home. Her owners reported that she is a happy, healthy dog and did not have any complications following surgery.

Prognosis is best for extrahepatic shunts and for dogs that underwent ameroid constrictor placement or cellophane banding.[1,8,9] Good to excellent outcomes were noted in 78-94% of animals undergoing extrahepatic shunt occlusion.[1]

Conclusion

There are many types of portosystemic shunts, but most patients will present similarly due to hepatic dysfunction. Early diagnosis, medical management for stabilization, and surgical intervention can lead to excellent prognoses in our portosystemic shunt patients. Development of shunts is caused by hereditary factors in many breeds, most commonly Yorkshire Terriers.[5] The genetic predisposition is not completely understood and is likely multifactorial but discouraging breeding of affected individuals is highly recommended.[5]

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