Atticus Got a New Band

Julie K. Grisham

Mississippi State University

College of Veterinary Medicine

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Advisor:

Elizabeth Swanson, DVM, MS, DACVS-SA

Introduction/ Pathophysiology

A portosystemic shunt (PSS) is an abnormal vessel that directs portal blood away from the liver, allowing unprocessed nutrients, toxins, and bacteria absorbed from the intestines, stomach, and spleen to flow into the systemic circulation without having been processed, detoxified, or excreted in bile by the hepatic parenchyma. Liver hypoplasia develops because pancreatic and intestinal enzymes, nutrients, and portal vein oxygen bypass their hepatic target via the shunt. Though commonly manifesting in cats less than 2 years old, signs of PSSs also present in older patients.[9,10,12,15,20] Most PSSs occur in domestic short hair cats, but Persians, Himalayans, and Siamese are represented more than other purebreds. An unusual proportion of cats with copper eye coloration have PSSs.[4,9,10,15,19] Signs of PSSs can be intermittent and variable. The most common are neurological because PSSs cause a predisposition to hepatic encephalopathy (HE). Neurologic signs of HE in cats include seizures, ptyalism, personality changes, blindness, lethargy, ataxia, circling, unresponsiveness, muscle tremors, head pressing, and/or running into things.[4,8,9,15] Signs generally worsen after a meal as there are more substances available for portal absorption. When the liver is unable to filter toxins nor receive materials for liver-derived factor synthesis, the brain will develop HE over time.[9,15] Ammonia is the culprit most noted, but build-up of other substances such as mercaptans or short-chain fatty acids can exacerbate HE development alone or synergistically. HE development can occur due to excessive activation of gamma-aminobutyric acid receptors as GABA and other benzodiazepine-like chemicals build-up when absorbed from the gi tract. Also, excess amino acid, methionine, and aromatic amino acids phenylalanine, tryptophan, and tyrosine in the cerebrospinal fluid may alter the activities of inhibitory or normally weak neurotransmitters, causing them to be factors in HE development.[4,10,15]

Other indications of PSSs can be stunted growth due to decreased useable nutrient and enzyme availability; gastrointestinal issues such as diarrhea, ptyalism, nausea, vomiting, and anorexia; prolonged anesthesia recovery time; unexplained pyrexia; and such urinary signs as dysuria, hematuria, polyuria, polydipsia, recurrent cystitis, and development of ammonia urate urolithiasis.[4,8,9,15]

Differential diagnoses causing similar signs to PSSs include portal vein agenesis, portal vein thrombosis, primary portal vein hypoplasia (aka hepatic microvascular hypoplasia), arterioportal fistula, liver disease, chronic cholangitis, cancers of the liver or bile ducts, and any malfunction that blocks liver ducts or vessels or causes chronic hepatic degeneration.[3,9,10,11,16] Epilepsy, hydrocephalus, or severe hypoglycemia can cause signs that are similar to those of HE.[10,15] Other differentials for hyperammonemia are arginine-deficient diet, cobalamin (B12) deficiency, hepatic disease, urea cycle dysfunction, excessive ammonia load, or kidney disease.[1]

PSSs occur as either intrahepatic or extrahepatic varieties. Extrahepatic PSSs (EPSSs) are more common in cats and small dogs. When embryonic vitelline and cardinal veins do not involute properly, these anomalies can occur. An EPSS is usually a single divergent vessel which flows from the portal system into the systemic circulation, bypassing the liver.[3,4,10,15] Connections from portal to systemic circulation in mammals normally do not exist.[3]

EPSSs can also form due to congenital absence of the portal vein which occurs when normal involution of embryonic vitelline veins and their anastomoses with the liver sinusoids are defective. The portal circulation must be shunted elsewhere, so the body creates an EPSS. In the case of portal vein agenesis, surgical correction of the PSS should not occur, and medical treatment is the only option. A similar situation may cause portal vein hypoplasia and a resulting EPSS. In the case of hypoplasia, surgery is usually highly recommended. Rare cranial vena cava

hypertension can also cause EPSSs, and chronic caudal vena cava blockage can cause cavoportal collaterals to open allowing blood return to the right atrium.[3] It is hypothesized that, as there are few valves in the portal system, shunts may form due to a hepatofugal pressure gradient within the portal/splanchnic venous system.[23]

Intrahepatic PSSs (IPSSs) generally occur due to persistence of fetal vasculature or an error as the embryo develops. As the feline portal vein enters the liver, it branches into three divisions: Right, central, and left. An IPSS is generally classed according to the division in which it is located: 1) Right, the right lateral and caudate lobes; 2) central, the right medial and quadrate lobes; or 3) left, the left medial and left caudate lobes. It has not been determined how right and central divisional shunts occur, but the most common form in dogs and cats, the left divisional,[15] has been proven to usually occur due to failure of the ductus venosus to close after birth.[3,4,8,9,10,15] The ductus venosus in the embryo, carries oxygenated umbilical blood past the liver to the heart. When it fails to close properly, blood shunts from the portal vein to the patent ductus venosus, into an ampulla where left hepatic and left phrenic venous blood empties, and, then, into the caudal vena cava.[21] IPSSs mostly affect large dogs, but they have also occurred in cats and small dogs.[3,4,10,15]

PSSs are also classed as congenital or acquired. Congenital portosystemic shunts (CPSSs) are usually singular, vesicular anomalies and extrahepatic. In a study and systemic review of 49 cats using computed tomography angiography, intraoperative mesenteric portovenography, and gross intraoperative observation, 92% of feline extrahepatic, CPSSs were left gastrophrenic, left gastrocaval, or splenocaval.[23] Left gastroazygous and colocaval were also represented.[22,23] Reports vary as to which shunt is the most common, but those originating from the left gastric vein predominate in cats.[8,9,15,22,23] Less often, other mesenteric branches are involved.[3]

Most acquired PSSs (APSS) are multiple and due to portal hypertension from chronic liver disease, primary portal vein hypoplasia or agenesis, arterio-portal fistula, or portal vein obstruction as with a portal thrombus.[3,10,11,15] Others can be sequelae to full or partial attenuation of a PSS without intraoperatively testing resultant pressure within associated vessels and hepatic parenchyma. PSS's cause underdeveloped intrahepatic vasculature, so the vessels are unable to accommodate the sudden increase in blood flow. In all cases, portal hypertension causes recanalization of vestigial embryonic connections, resulting in multiple APSSs.[3,8,10,12,15,16,19]

History and Presentation

Atticus, a 7-year-old, male, neutered, red and white Persian with copper-colored eyes, showed signs of illness in early April, 2018 when his owner noticed he was exhibiting ptyalism. A veterinary appointment was made immediately, but physical exam revealed no abnormal findings. On April 12, 2018, Atticus' owner reported a 40-minute episode of ataxia, non-responsiveness, stumbling over things, and walking about as if lost. Over the following weeks, Atticus also developed PU/PD and neurologic episodes increased in frequency. Atticus would eventually lay down and become responsive again. After the initial episode, Atticus was taken to his referring veterinarian who noted lethargy and difficulty standing. An ultrasound showed an enlarged spleen. Cytology of the spleen ruled out lymphoma. Atticus' food was changed to renal hydrolyzed protein, and he was given weekly B12. Blood chemistries in May, June, and July consistently revealed decreased BUN of 11, 13, and 13 mg/dL (14.0-36.0), respectively. On June 21st, urinalysis reported turbid urine with 1+ proteinuria and all other values within normal limits. Atticus improved with the food change and weekly B12, but neurologic episodes of circling and disorientation still occurred during the night. Pre- and post-prandial bile acid tests on June 21st were significantly elevated at 122.0 umol/L (<13.0) and 112.0 umol/L (<30.0),

respectively. Suspicious of hepatic encephalopathy (HE), Atticus' veterinarian placed him on lactulose and metronidazole, but he was unable to be medicated at home. On July 19th, complete blood count (CBC) showed a mild increase in red blood cell (RBC) count of 10.1 M/uL (5.9-9.9) and a decrease in MCV (microcytosis) of 35 fL (37.0-61.0) and a decrease in MCH (hypochromia) of 10.8 pg (11.0-21.0). A pre-prandial bile acid test indicated very high bile acids of 131.5 umol/L. Atticus' last noted neurologic episode occurred on July 30, 2018.

He was referred to the MSU CVM Internal Medicine Service on August 01, 2018. At presentation, Atticus was bright, alert, responsive, and somewhat fractious. His physical exam (PE) and vital parameters were within normal limits; no neurologic deficits were apparent. He weighed 4.25 kg (9.4 pounds) with a body condition score of 4/9. A right, corneal scar was present due to an ocular ulcer at 6 months of age which required surgery and a conjunctival flap to aid healing. Atticus was transferred to the Department of Surgery on August 3, 2018 where PE revealed a Grade 1 heart murmur, but his heartbeats were strong, steady and synchronized with his pulse. He had stenotic nares which are normal in bradycephalic cat breeds such as Persians.

Diagnostic Approach/Considerations

On August 1, 2018 a CBC, chemistry panel, coagulation profile, and urinalysis via cystocentesis were submitted. CBC indicated a mild increase in RBCs of 12.2 M/uL (4.5-10.0) with mild microcytosis of 35.3 fL (40.0-55.0) and moderate hypochromia of 10.7 pg (13.0-17.0). Hematocrit, PCV, and hemoglobin were all within normal limits. Dogs with PSSs often have nonregenerative anemia with microcytosis. About 25-50% of cats with CPSSs are microcytotic, but most do not get anemia.[10,15] Though hypochromia can cause microcytosis,[10] Atticus' increased RBC count apparently kept the hematocrit, PCV, and hemoglobin within normal

limits. In a study of 42 cats, surgical attenuation of CPSSs was proven to significantly decrease microcytosis as well as to increase hematocrit in cats with low hematocrit pre-operatively.[18]

Blood chemistry revealed a moderate increase in alkaline phosphatase (ALP) of 48 U/L (10.0-42.0). A small increase in ALP is significant in cats since the half-life of feline ALP is 6 hours as compared to dogs which is approximately 66 hours.[17] Cats with CPSSs often have a normal or moderately increased ALP. Decreased bile flow, signals ALP production in canalicular membranes. ALP can also increase due to hypoxia causing cellular damage and subsequent enzyme leakage from canalicular membranes.[15,17]

Atticus' cholesterol was markedly low at 12 mg/dl (95-200) which commonly occurs in PSS cases[17] as the liver is the body's main source of cholesterol synthesis. Osmolality was mildly low at 289 mOsm/kg (295-320) likely reflecting decreased liver production of albumen and other proteins or loss due to ascites caused by portal hypertension.[10,15]

Atticus' BUN was 13 mg/dL (10.0-40.0), which is within normal limits at MSU CVM, but, indicated previously, this BUN value is mildly decreased according to the reference range determined by the Antech lab in his home town of Memphis, Tennessee (14.0-36.0). BUN is decreased in 61-100% of feline patients with CPSSs. Ammonia is absorbed from the intestines, mainly the colon, and is normally metabolized to urea in the liver. Since PSSs divert portal blood away from the liver, ammonia goes into the systemic circulation rather than being metabolized, causing low urea values. Polyuria/polydipsia, parenteral fluid therapy, and reduced protein diets can also cause lower urea levels.[10,15]

Atticus had a mildly prolonged prothrombin time (PT) of 11.9 sec (5.0-10.0) and normal partial thromboplastin time (PTT) of 12.7 sec (15.0-25.0). Because the liver makes most major

clotting factors, a prolonged PT or PTT indicates hepatocyte dysfunction.[17] Atticus' prolonged PT indicates decreased extrinsic and/or common pathway factors. Factor VII is the likely culprit since it has the shortest half-life of the major coagulation factors. A study of 42 cats, reported that those with CPSSs are likely to have prolonged coagulation profiles, yet do not tend to have increased clinical bleeding risk.[10,18]

Cystocentesis was performed for urinalysis. Urine was slightly hazy with a specific gravity of 1.016 (1.015-1.065),[24] proteinuria of 1+ (normal=0), and alkalotic pH of 8.0 (6.0-6.5). His previous urinalysis in Memphis on June 21st reported a specific gravity of 1.036 and pH of 7. In non-primate mammals, purines are metabolized to uric acid and then to allantoin by hepatic uricase. Cats with PSSs have an increased concentration of insoluble uric acid in systemic circulation and urine. Urinary oversaturation of ammonia and uric acid predisposes cats (and dogs) to ammonium urate uroliths. Normal cats are much more prone to struvite uroliths which dissolve in acidic urine; ammonium urate is more soluble in alkaline urine. Only about 10% of all cats ever get ammonium urate uroliths,[2,6,15] so a PSS should be ruled out when a cat has an ammonium urate stone.

Atticus' thoracic radiographs revealed a mildly enlarged cardiac silhouette and a mild bronchial pulmonary pattern. Abdominal radiographs showed bilateral, mild enlargement of the kidneys; animals with PSSs often have mild enlargement of the kidneys as well as microhepatica, though the latter is less often seen in cats than dogs.[10]

Ultrasound showed bilaterally enlarged kidneys and some urinary bladder debris. The heterogenous liver had numerous hyperechoic patches, and the portal vessels were not easily seen throughout the hepatic parenchyma. A small amount of free fluid was seen near the spleen.

Computed tomography revealed an apparent extrahepatic shunt, though the exact type and location was not discernable.

Treatment and management

PSSs can be treated medically or surgically. The primary purpose of medical management is to ameliorate or resolve signs when possible, depending on the severity of individual cases, but medical management cannot correct a PSS.[9] Sometimes signs are better only temporarily. One study showed slight, positive correlation between the length of medical treatment prior to surgery and the extent of intrahepatic perfusion seen via intraoperative, post-occlusion portovenograms.[8] Medical management includes antibiotics such as metronidazole to kill ammonia-producing bacteria in the gut; reduced-protein diets to decrease protein byproducts; diets with branch-chain amino acids rather than aromatic amino acids; lactulose to help trap ammonia (reducing its absorption) and to acidify the colon (reducing alkalosis); and antiseizure medications such as levetiracetam or phenobarbitone.[8,10]

Studies show a positive, long-term outcome associated with surgical attenuation, thus surgery is the recommended treatment for CPSSs. Eventual, complete attenuation has the best post-operative results long-term.[10,16] Existing electrolyte, acid-base, hypoglycemic, and hydration imbalances should be corrected before surgery, and appropriate antibiotics are recommended perioperatively. Anti-seizure medications are also recommended perioperatively for cats since the feline patient has an increased likelihood for post-surgical seizures and other neurological signs.[10]

Currently, the three main surgical techniques are ligation with a silk or prolene[16] suture or attenuation with cellophane banding or ameroid constrictor. Temporary shunt occlusion should

be performed intraoperatively for portal hypertension assessment to determine if complete attenuation is an option. Shunt over-attenuation causes dangerous portal pressure increases post-operatively. Not all cats can receive full PSS occlusion at first. The degree of attenuation that produces the safest portal pressure should be implemented.[8,12,16] Cats which must receive partial attenuation are more likely to re-develop hepatic clinical signs than those which can safely receive full PSS ligation, so patient post-operative monitoring is critical.[7] Currently, new hybrid surgical techniques are being developed for IPSS attenuation using a stent and fluoroscopic guidance to insert a coil device into the shunt. Post-operative ultrasonography is used to monitor blood flow. The procedure was successful in two cases reported in 2018, but long-term evaluation is not yet available.[19]

Intraoperative arterial or central venous pressure should not decrease during temporary occlusion, nor should heart rate significantly increase. Portal hypertension assessment can be done objectively by measuring portal pressure using a water manometer with catheter placement in a mesenteric vessel. Normal feline portal pressure is 3-13mmHg (0-14.0cmH_2O), and pressure during the temporary occlusion should never exceed 15.0-18.0mmHg (20.0-23.0cmH_2O).[16] Intraoperative mesenteric portovenography (IMP) is strongly recommended to monitor changes in hepatic vasculature during temporary shunt occlusion. [8,12,14.16] Studies prove that when IMP indicates poorly developed intrahepatic portal vasculature, post-operative neurologic complications will increase significantly. Similarly, dogs which tolerate first surgery complete attenuation usually show no pre-operative signs of HE and have greater hepatic blood flow pre-operatively.[8,12,14]

Subjective assessment of excess portal hypertension is also reliable and is accomplished by careful observation for pancreatic and intestinal cyanosis, jejunal vessel pulsation, and intestinal hypermotility, as all of these are indicative of excessive portal pressure.[16]

Suture ligature can be used for complete or partial ligation. If partial ligation is performed, the intrahepatic vascular supply should increase enough in three months such that a second operation can usually completely occlude the shunt. Cellophane bands or ameroid constrictors are normally implemented for attenuation. Scintigraphy can be used at post-op check-ups to determine the degree of attenuation achieved over time with cellophane or ameroid constrictors.[16] Doppler ultrasound is also used as it is less invasive,[10] and computed tomography angiography is recommended as well.[5]

With cellophane banding, the body creates an immune response against the foreign object. Over an 8 week period, vascular fibrosis occurs at the site of the band, gradually occluding the shunt and allowing the body time to adjust to the changes in blood flow.[5,16] A recent case report raises concern that some cats may not develop enough inflammatory response to achieve eventual complete occlusion of the shunt, allowing recanalization to occur. Multiple types of cellophane exist, and inflammatory results could be specific to individual cats. Studies have not shown which cellophane causes the best inflammatory reaction in most cats.[5]

Ameroid constrictors are designed to gradually occlude shunts via enlargement of the constrictor's inner portion, a casein ring, as it slowly absorbs peritoneal fluid. The stainless steel outer portion of the ring does not enlarge. Problems documented with this device include slippage, lack of complete attenuation, recanalization, and thrombus formation at the constrictor causing a more acute occlusion than is optimal. There is always a chance of dysfunction for any

device.[16] Computed tomography imaging angiography (CTA) can verify that a shunt is occluding properly when partial attenuation of any type is done.[5]

Post-surgical complications in cats are primarily neurologic and include seizure, blindness, ataxia, mild tremors, lethargy, skin hypersensitivity, and abnormal behavior. Seizure or blindness are the most common post-op complications,[5,8,16] so feline patients should be on seizure watch for a minimum of 72 hours in-hospital after PSS attenuation or ligation, and owners should be warned to watch for the above signs at home indefinitely. If any neurological sign manifests, treatment should begin immediately. In a study involving 49 cats, 18 cats developed neurological, post-operative signs with most occurring within 72 hours. One cat developed signs within 96 hours, and two others developed seizures 6 months post-op after appearing to completely recover. Most of the 18 cats received post-operative serum testing which revealed normal ammonia, glucose, and electrolyte levels.[7] Anti-seizure medications, levetiracetam or phenobarbitone, should be a standard in feline post-operative treatment.[16] It is unknown why feline post-op neurological signs are common, but one proven risk factor is underdeveloped intrahepatic vasculature. Other hypotheses are: 1) Acute changes in endogenous benzodiazepine release after PSS attenuation, 2) other inhibitory and excitatory neurotransmitter imbalances,[8,16] 3) chronic metabolism abnormalities from hepatic encephalopathy, or 4) irreversible damage caused by pre-operative seizures. The first three should improve with time.[16]

Portal hypertension development can be a deadly post-operative complication.[12,16] Owners should be told to watch for signs of ascites, hemorrhagic diarrhea, abdominal pain, pyrexia, transfusion reactions, or hypovolemic shock (lethargy, confusion, tachycardia, tachypnea, unresponsiveness, lack of urination, nausea/vomiting, pale mucous membranes).[16]

A CBC, blood chemistry, and urinalysis should be done pre-operatively to identify abnormalities to be stabilized before surgery and to rule out other problems with signs similar to HE, such as electrolyte imbalances and hypoglycemia.[9] Atticus' blood chemistry showed no such imbalances; his hydrolyzed renal diet was continued, and he was given maintenance IV LRS fluids post-operatively.

On August 3, 2018, Atticus was taken to surgery for abdominal exploration, cystotomy, and shunt attenuation. Routine cystotomy was performed. After careful examination of the bladder lumen and copious flushing of the urethra, no stones were found. A piece of urinary bladder mucosa was taken for aerobic and anaerobic culture and sensitivity. The bladder wall was sutured with a simple continuous pattern using 3-0 PDS.

An abdominal exploratory procedure was begun. The liver exhibited microhepatia and had a diffuse nutmeg pattern. A 1.0 cm x 0.5 cm liver wedge biopsy was aseptically removed and placed in formalin for histopathology. Liver and bile swabs were submitted for aerobic and anaerobic culture and sensitivity. The stomach was moved cranioventrally, exposing an approximately 1.0 cm diameter portosystemic shunt located caudal to the diaphragm. Turbulent blood flow was seen coursing through it. Gentle, blunt dissection released the shunt from its underlying tissue. A cellophane band was folded into thirds, positioned under the shunt at a right angle, wrapped around the anomaly, and cut to approximately 4.0 cm in length. The band was placed just before the shunt intersected the phrenic vein. The intestines were checked and rechecked for possible hypertension, and absence of hyper-motility was verified. No pancreatic or intestinal cyanosis was observed. The cellophane band was secured with four medium ligation clips. The abdomen was thoroughly lavaged with sterile 0.9% saline solution and suctioned with a Poole suction tip. The rectus sheath was closed with a simple continuous pattern using 3-0

PDS. The subcutaneous layer was closed using a simple continuous pattern with 4-0 Monocryl. The cutaneous layer was closed with 4-0 Monocryl in an intradermal pattern. The incision was covered with a Telfa pad and Suresite occlusive bandage.

Post-operative complications of attenuation with cellophane banding include possible slippage, possibility of portal hypertension, failure of the shunt to fibrose properly in the following weeks, possibility of the band dissolving before desired attenuation is achieved, or post-operative seizures and other neurological signs. Other complications of partial attenuation CPSS surgeries were discussed previously.[5,16]

Liver biopsies are recommended during PSS attenuation surgeries.[16] The usual liver histopathology of cats with PSSs shows small to non-existent portal branches and enlarged hepatic arterioles.[10,11,12,14,15,16] This change occurs because the body attempts compensation for lack of portal blood flow by increasing blood received from the hepatic artery.[12] Liver histopathology may also show biliary tract hyperplasia, lymphatic hyperplasia, periportal fibrosis, macro- and micro-vesicular vacuolar changes (hepatocyte degeneration), lobule atrophy, and/or increased hemosiderin deposits often in the Kupffer cells,[10,11,12,15,16] though the latter is decidedly more common in dogs. Atticus' liver biopsy contained small to inapparent portal veins, numerous arterioles, increased bile ducts, dilated lymphatics, macro- and micro-vesicular swelling, lobular atrophy, and hemosiderin deposits in both the Kupffer cells and centrilobular cells. Macrovesicular vacuolar change is often noted in older cats with CPSS.[12]

The bladder mucosa sample and spleen swab yielded no aerobic or anaerobic pathogenic growth after 48 hours. The liver swab yielded no aerobic or anaerobic pathogenic growth after 72 hours.

Atticus went home on August 6, 2018 with the following medications: Buprenorphine for post-op pain, levetiracetam, lactulose, and metronidazole. Lactulose and metronidazole were to be continued until liver function tests were normal and for at least 8 weeks. Levetiracetam was to be discontinued at a gradual rate when normal liver test results were obtained. Atticus was to be kept at home in an isolated bathroom with his cone on until his incision had healed. He was to be monitored closely for any neurological signs for a week, and a recheck appointment was to be made with his primary veterinarian in Memphis for 10 days post-op. His owner was instructed to schedule blood work and ultrasound to assess Atticus' shunt in one month and, then, in the following months as determined by test results and his primary veterinarian.

Case outcome

After returning home, Atticus continually improved. Episodes of polyuria and polydipsia had disappeared by August 21, 2018. His appetite returned to normal, and there were no longer signs of HE. Interestingly, Atticus' went from being a grouch to a curious, playful, and loving companion. Blood work and bile acid tests returned to normal.

In July of 2019, the owner said that Atticus' disposition had continued to improve. For example, where he used to have nothing to do with people, he now loves human interaction. The maid's visits have become a highlight of Atticus' week as he follows her room to room while she vacuums. Atticus loves to be around guests, and he has become very playful and romps with his brother, Sam. He still shows no signs of HE. On August 17, 2019, Atticus' owner reported that a pre-prandial bile acid test had come back slightly elevated at 37 umol/L (<30); Atticus will go back for a recheck in 3 months. He is currently on no medications or special diet, but still acts like he feels great. With the owner's permission, I left a message on Atticus' primary veterinarian's email on August 26th and am hopeful to hear back from her soon.

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