IndyVet
Emergency & Specialty Hospital
Where care comes first.

AAHA ACCREDITED
The Standard of Veterinary Excellence

CASE STUDY
APRIL 2012

Signalment:
3 year old, male Sheltie – 52#

History:
The patient had a seizure four months prior to presentation characterized as a brief grand-mal seizure. One month later the patient had cluster grand-mal seizures lasting about 30-45 seconds. The referring veterinarian started the patient on 60mg (2mg/kg) of phenobarbital by mouth twice daily. The seizures were poorly controlled with the patient continuing to have seizures every one to two weeks for the next two months. Potassium bromide was added at 300mg by mouth twice daily (10mg/kg) and a fasted CBC, biochemical profile, T4, phenobarbital, and bromide evaluation was checked by the referring veterinarian two weeks after starting the bromide (Table 1).

The patient was subsequently started on a low fat, high fiber diet. The patient remained seizure free for three weeks after starting bromide therapy prior to breaking with cluster seizures again, lasting 1-2 minutes every 1-2 hours. The potassium bromide was increased to 400mg (15mg/kg PO) twice daily and 5mg of diazepam had been given IV every 4-6 hours to control seizures for 12 hours prior to referral for a neurological evaluation and seizure management.

Laboratory Data

Table 1

	RDVM Results	IVR Results	
Super Chem	October 25	November 4	
Test	Results	Results	Reference Range/Units
AST (SGOT)	47 IU/L	26 IU/L	15-66 IU/L
ALT (SGPT)	46 IU/L	63 IU/L	12-118 IU/L
Total Bilirubin	**0.9 mg/dL (HIGH)**	0.1 mg/dL	0.1-0.3 mg/dL
Alkaline Phosphatase	61 IU/L	64 IU/L	5-131 IU/L
GGT	4 IU/L	5 IU/L	1-12 IU/L
Total Protein	6.6 g/dL	6.8 g/dL	5.0-7.4 g/dL
Albumin	3.6 g/dL	3.6 g/dL	2.7-4.4 g/dL
Globlin	3.0 g/dL	3.2 g/dL	1.6-3.6 g/dL
A/G Ratio	1.2	1.1	0.8-2.0
Cholesterol	**370 mg/dL (HIGH)**	**359 mg/dl (HIGH)**	92-324 mg/dL
BUN	17 mg/dL	14 mg/dL	6-25 mg/dL
Creatinine	0.8 mg/dL	0.7 mg/dL	0.5-1.6 mg/dL
BUN/ Creatinine Ratio	21	20	4-27
Phosphorus	4.0 mg/dL	4.8 mg/dL	2.5-6.0 mg/dL
Calcium	10.9 mg/dL	**11.7 mg/dL (HIGH)**	8.9-11.4 mg/dL
Glucose	82 mg/dL	114 mg/dL	70-138 mg/dL
Amylase	702 IU/L	560 IU/L	290-1125 IU/L
Lipase	307 IU/L	328 IU/L	77-695 IU/L
Sodium	145 mEq/L	150 mEq/L	139-154 mEq/L
Potassium	4.4 mEq/L	4.6 mEq/L	3.6-5.5 mEq/L
Na/K Ratio	33	33	27-38
Chloride	**125 mEq/L (HIGH)**	119 mEq/L	102-120 mEq/L
CPK	426 IU/L	66 IU/L	59-895 IU/L
Triglyceride	**1229 mg/dL (HIGH)**	**710 mg/dL (HIGH)**	29-291 mg/dL
Magnesium	**2.7 mEq/L (HIGH)**	**2.6 mEq/L (HIGH)**	1.5-2.5 mEq/L

Physical Examination:

Physical examination revealed a patient with a body condition score of 5/5 weighing 52 lbs. Temperature (100.6°F), pulse (120), and respiration (20) were considered normal for a mildly nervous patient. The remainder of the physical exam was unremarkable. A re-check CBC, serum biochemical profile, thyroid profile (Table 1), neurological examination, CSF Tap (Table 2) and brain imaging were ordered. An MRI was suggested as the optimal imaging modality, but due to costs, a pre and post contrast CT evaluation was performed. (Figure 1)

Complete Neurological Examination:

A full cranial nerve and peripheral nerve examination was performed which showed only mild proprioceptive deficits to the rear limbs. All integrative reflexes were normal.

Laboratory Data - Continued

Table 1 - Continued

	RDVM Results	IVR Results	
Super Chem	October 25	November 4	
Test	Results	Results	Reference Range/Units
Complete Blood Count			
WBC	6.6 103/µL	8.5 103/µL	4.0-15.5 103/µL
RBC	6.3 106/ µL	7.1 106/ µL	4.8-9.3 106/ µL
HGB	16.2 g/dL	17.3 g/dL	12.1-20.3 g/dL
HCT	37 %	49 %	36-60 %
MCV	59 %	69 fL	58-79 Fl
MCH	25.7 pg	24.3 pg	19-28 pg
MCHC	**44 g/dL (HIGH)**	35 g/dL	30-38 g/dL
Differential	**Absolute (rDVM)**	**Absolute (IVR)**	
Neutrophils	4290/µL	5950/µL	2060-10600/µL
Lymphocytes	1782/µL	2040/µL	690-4500/µL
Monocytes	462/µL	510/µL	0-840/µL
Eosinophils	66/µL	0/µL	0-1200/µL
Basophils	0/µL	0/µL	0-150/µL
Platelet Estimate	Adequate	Adequate	
Platelet Count	349 103/µL	377 103/µL	170-400 103/µL
T4	1.17 µg/dL	1.55 µg/dL	1.0-4.0 µg/dL
Phenobarbital	18.7 µg/mL		15-45 µg/mL
Bromide	**0.8 mg/mL (LOW)**		1-3 mg/mL
T3		114 ng/dL	45-150 ng/dL
Free T3		2.8 pg/mL	1.7-5.3 pg/mL
T3 Autoantibodies		1.0	<2.0
T4 Autoantibodies		1.5	<2.0
TSH		0.14 ng/mL	0-0.60 mg/mL
Thyroglobulin Autoantibodies		13 %	<20%

Table 2		
CSF Tap	November 4	
Tests	Results	Reference Range/Units
Color	Clear; Colorless	
Specific Gravity	1.005	
WBC (CSF)	1 UL	0-10 UL
RBC (CSF)	2.2 UL	0-10 UL
Protein (CSF)	30 mg/dL	15-35 mg/dL
Glucose	76 mg/dL	
Cytology:	The cytospin smear of the submitted cerebrospinal fluid contained only rare small lymphocytes and few monocytoid cells. An extremely rare erythrocyte was present. A few free nuclei were also observed. No significant inflammatory cell infiltrates were identified. Infectious agents and neoplastic cells were not observed. **MICROPSCOPIC FINDINGS:** Normal cerebrospinal fluid; canine	

CT Scan Findings:

Axial images of the brain pre and post contrast showed no corresponding evidence for pathology to account for the historical feature of seizures. Conclusion: Normal brain.

Additional Diagnostics:

Due to overt hyperlipidemia of the submitted serum sample, multiple PCV & TS samples were taken and checked at 6 hour intervals while the patient was fasted. All samples showed severe chylomicronemia with the gross appearance of whole milk. Following refrigeration a small mildly turbid area of plasma would form at the base of the microhematocrit tube. Due to the findings of persistent fasted hyperlipidemia, a lipoprotein electrophoresis was performed (Table 3).

Figure 1 - Pre-Contrast

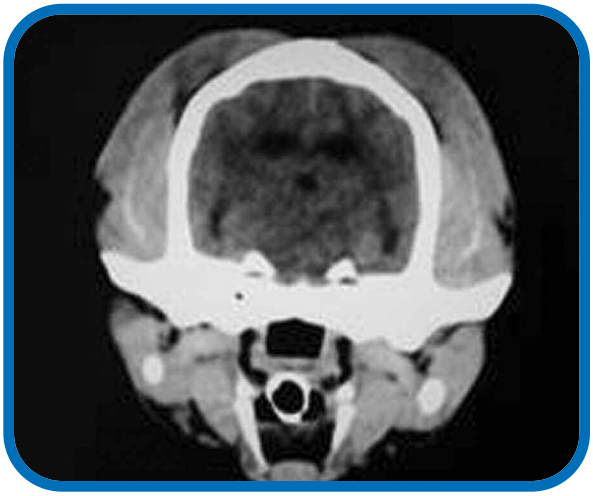

Figure 1 - Post-Contrast

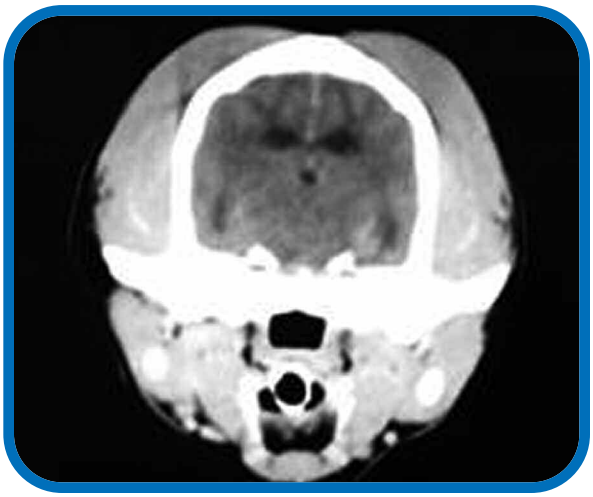

Table 3		
Hyperlipidemia Panel		
Tests	Results	Reference Range/Units
Cholesterol	359 (HIGH)	92-324 mg/dL
Triglyceride	710 (HIGH)	29-291 mg/dL
Lipoprotein Electrophoresis		
HDL-1	36.91 (LOW)	72.0-90.0
HDL-2	18.56	10.0-30.0
LDL	9.59	0.0-12.0
VLDL	25.00 (HIGH)	0.0-8.0
Chylomicrons	9.94	0.0-12.0

Treatment:

Following phlebotomy for the lipoprotein electrophoresis sample, the patient was given 200U/kg heparin IV once. Blood samples were taken at hourly intervals and checked for hypertriglyceridemia. Within two hours the serum became much improved and appeared only moderately turbid.

Figure 2 - Pre-Heparin **Figure 2 - Post-Heparin**

The patient remained on a low fat diet and was started on niacin at 100mg by mouth once daily and gemfibrozil (Lopid) at 300mg by mouth twice daily for three days and then reduced to 150 mg PO BID. Phenobarbital was increased to 3mg/kg PO BID, and potassium bromide was kept at 15mg/kg PO BID. The patient had no further seizures during the next 48 hours and was discharged into the owners care on niacin, gemfibrozil, phenobarbital, and potassium bromide with instructions to have the triglycerides, cholesterol, phenobarbital, and potassium bromide re-checked in one month.

Phone call follow up at three weeks showed the patient had suffered no further seizures and was more playful and active then he had been for six months. The clients noted that he had also been started on Soloxine by a third veterinarian to be administered at 0.4mg by mouth twice daily, based on his suggestion that the patient was hypothyroid. The patient was re-checked at one month and additional blood work was drawn for comparison to assess his lipid, hepatic, and thyroid values (Table 4).

Table 4

Super Chem	December 8	
Tests	Results	Reference Range
AST (SGOT)	26 IU/L	15-66 IU/L
ALT (SGOT)	63 IU/L	12-118 IU/L
Total Bilirubin	0.1 mg/dL	0.1-0.3 mg/dL
Alkaline Phosphatase	64 IU/L	5-131 IU/L
GGT	5 IU/L	1-12 IU/L
Total Protein	6.8 g/dL	5.0-7.4 g/dL
Albumin	6.8 g/dL	2.7-4.4 g/dL
Globulin	3.2 g/dL	1.6-3.6 g/dL
A/G Ratio	1.1	0.8-2.0
Cholesterol	123 mg/dL	92-324 mg/dL
BUN	14 mg/dL	6-25 mg/dL
Creatinine	0.7 mg/dL	0.5-1.6 mg/dL
BUN/Creatinine Ratio	20	4-27
Phosphorus	4.8 mg/dL	2.5-6.0 mg/dL
Calcium	**11.7 mg/dL (HIGH)**	**8.9-11.4 mg/dL**
Glucose	114 mg/dL	70-138 mg/dL
Amylase	530 IU/L	290-1125 IU/L
Lipase	328 IU/L	77-695 IU/L
Sodium	150 mEq/L	139-154 mEq/L
Potassium	4.6 mEq/L	3.6-5.5 mEq/L
Na/K Ratio	33	27-38
Chloride	119 mEq/L	102-120 mEq/L
CPK	66 IU/L	59-895 IU/L
Triglyceride	160 mg/dL	29-291 mg/dL
Magnesium	**2.6 mEq/L (HIGH)**	**1.5-2.5 mEq/L**

Table 4 - Continued

Complete Blood Count		
Tests	Results	Reference Range
WBC	8.5 103/µL	4.0-15.5 103/µL
RBC	7.1 106/ µL	4.8-9.3 106/ µL
HGB	17.3 g/dL	12.1-20.3 g/dL
HCT	49 %	36-60 %
MCV	69 fL	58-79 fL
MCH	24.3 pg	19-28 pg
MCHC	35 g/dL	30-38 g/dL
Differential	**Absolute**	
Neutrophils	5950/µL	2060-10600/µL
Lymphocytes	2040/µL	690-4500/µL
Monocytes	510/µL	0-840/µL
Eosinophils	0/µL	0-1200/µL
Basophils	0/µL	0-150/µL
Platelet Estimate	Adequate	
Platelet Count	377 103/µL	170-400 103/µL
T3 (RIA)	114	45-150 ng/dL
T4 (RIA)	1.55	1.0-4.0 µg/dL
Free T4	**56.9 PMOL/L (HIGH)**	**8-40 PMOL/L**
Free T3	5.3 pg/mL	1.7-5.3 pg/mL
T3AA	1.0	Less than 2.0
T4AA	1.5 µg/dL	Less than 2.0
TSH	0.14 ng/mL	0-0.60 ng/mL
Thyroglobulin Autoantibody	13 %	<20%
Phenobarbital	25.9 µg/mL	15-45 µg/mL
Bromide	1.2 mg/mL	1 -3 mg/mL

Questions:

1. Is the patient hypothyroid?
2. What is a likely etiology for this dog's hyperlipidemia?
3. Did the hyperlipidemia have anything to do with the seizures?
4. Is the high calcium significant?
5. How would you follow up on this patient now?

Discussion:

Hyperlipidemia refers to increased serum lipids, usually due to increased triglycerides and / or cholesterol. A visible milky serum usually indicates increased triglycerides in the form of chylomicrons. Hypercholesterolemia does not cause visible hyperlipidemia. Both triglycerides and cholesterol are unable to circulate in the blood without being incorporated into a complex molecule called lipoprotein. There are four different types of lipoprotein complexes which can be differentiated by their size, density, electrophoretic mobility, and which can be separated by ultracentrifugation based on their buoyant density.

Chylomicrons are derived from **dietary fat** and are formed **in the intestinal mucosa.** These are the largest and least dense lipoproteins and contain about 90% triglycerides. Chylomicrons are responsible for the transport of dietary triglycerides and cholesterol to the liver and other body tissues. When acted upon by tissue lipoprotein lipase, chylomicrons are broken down into glycerol, free fatty acids, and cholesterol for cellular utilization.

Very low density lipoproteins (VLDL) are produced **in the liver** mostly **from endogenously derived triglycerides.** These are also catabolized by tissue lipoprotein lipase as are chylomicrons.

Low density lipoproteins (LDL) are a **by-product of VLDL catabolism and are responsible for transporting endogenously synthesized lipids, mostly cholesterol, from the liver to the body tissues.** VLDLs, following their catabolism by lipoprotein lipase removing most of the triglyceridecomponent, are altered by the liver into LDLs which distribute the remaining cholesterol to other body tissues. In people, 70% of cholesterol is carried by the LDL molecule, but in animals most of cholesterol is transported by high density lipoprotein molecules.

High density lipoproteins (HDL) are made mostly in the liver and are responsible for **scavenging excess cholesterol from cell membranes** as a result of normal cellular turn over of body tissues **and transports it back to the liver for recycling.**

Chylomicrons being the least dense and largest in size will create a "cream" layer in lipemic serum if allowed to sit for several hours under refrigeration. This cream layer distinguishes chylomicrons from other lipoproteins. If the infranatant (the sinking, water based fluid under the chylomicrons) is milky in color, then an increase in VLDLs is likely. The presence of chylomicrons in a normal unfasted patient suggests post-prandial lipemia which can last 4-6 hours after eating. A persistent hyperchylomicronemia in a fasted patient suggests an abnormality in lipid metabolism.

Secondary hyperlipidemia is an acquired alteration in lipid metabolism that is seen with endocrine diseases such as diabetes mellitus, hyperadrenocorticism, hypothyroidism, as well as pancreatitis and protein losing nephropathy. Secondary hyperlipidemia will generally resolve once the metabolic disease is corrected.

Primary hyperlipidemia is most common as a familial disease of middle age to older Schnauzers, although it has been reported in Shelties and mixed breed dogs. An increased chylomicronemia with increases in triglyceride and VLDL's with mild elevations in cholesterol is seen. The exact mechanism for this malady has not be established but is thought to represent a deficiency of lipoprotein lipase.

Clinical signs related to overt hyperlipidemia include abdominal pain and diarrhea independent of pancreatitis; dermatologic abnormalities including pruritis and alopecia; ocular manifestations such as lipid keratopathy, stromal dystrophy, lipid in the aqueous humor, uveitis, and blindness; and central nervous system disturbances characterized by seizures, behavioral changes, and peripheral neuropathies.

Persistent hyperlipidemia is usually addressed with a combination of therapies, once any underlying cause for hyperlipidemia is managed (e.g. – diabetes mellitus). The first treatment is a low fat diet. I have had good success with the Royal Canin low fat diet (16.3% fat in canned and 15.7% fat in the dry food on an M.E. basis), although there are other suitable low fat diets. Omega 3 fatty acids at 10-30 mg/kg PO daily will help reduce triglycerides and cholesterol levels by decreasing the synthesis of VLDL and LDL lipoproteins. Chitin or Chitosan is a fiber made from shellfish that reportedly binds lipids in food preventing their absorption. 150mg-300mg given 30 minutes prior to feeding has been recommended. Niacin at 50 200mg/dog/day can be divided into two daily doses, and acts to reduce liver triglyceride synthesis. Niacin will cause vasodilatation and skin flushing which can cause temporary pruritis and face scratching 10-30 minutes after dosing. It is best given with food to avoid or reduce these side effects. Gemfibrozil (Lopid) is a fibric acid derivative that reduces the production of VLDL and triglycerides in the liver and may increase the production of HDL lipoproteins. Dosage recommendations vary between 7.5-25mg/kg yielding a dose of 150-300 mg PO BID.

A useful trick to reduce lipemia in overtly hyperlipidemic dogs due to primary or secondary hyperlipidemia is to give 200U/kg of heparin IV which will dramatically reduce lipemia within 30-90 minutes. This works due to heparin's ability to activate tissue lipoprotein lipase.

In the case presented, it is unlikely that the patient was hypothyroid since T4, free T4 and TSH levels were all normal on the original thyroid profile and no evidence of thyroid or thyroglobulin antibodies were present.

Seizures can be seen in hyperlipidemic patients once triglycerides reach 500-1000mg/dL. In the case presented, the seizures which were refractory to good control prior to management of hyperlipidemia, became well controlled once the hyperlipidemia was adequately managed. Although the role of hyperlipidemia being the etiology for the seizures could be debated, the fact that the seizures abated and became well controlled once the lipemia resolved was dramatic. The lipoprotein electrophoretic pattern and the lack of an underlying cause for the hyperlipidemia in this Sheltie would suggest the etiology to most likely be primary familial hyperlipidemia. The high calcium observed on two of the biochemical panels is likely an artifact since hyperlipidemia can cause calcium to be elevated or reduced depending on the methodology used for the assay.

Follow up phone conservations with the owner showed the patient to have no further seizures while on medication for the hyperlipidemia. He remains on phenobarbital and potassium bromide due to the owner's preference to not wean him from medication to determine if seizure medication is still required.