Signalment

Mandy, 8-month old, female, Pug, 8.2 kg, Case log #9

Chief Complaint

Mandy presented to the Purdue University Veterinary Teaching Hospital for progressive seizures, worsening in both frequency and severity despite increasing dosages of multiple anti-epileptic drugs (AED).

Patient History

Mandy began having seizures at 2 months of age, in which she would occasionally become stiff. Over the next 6 months the episodes progressed to tremors, and then generalized seizures. Seizures last 10-20 seconds, during which she is unresponsive, falls to one side, paddles and salivates. After a 2-minute post-ictal period, she returns to normal. Owners witness 5 to 13 seizures a day. Between seizures Mandy has a dull mentation. Current medications include phenobarbital (6 mg/kg PO q12h [48.6 mg total dose]) and potassium bromide (KBr) (12 mg/kg PO q12 h [100 mg total dose]). She has no other history of illness. Owners have owned her since 7 weeks of age. There are no other pets in the house. She eats IAMS puppy food free choice.

Patient's Presenting Status

Upon presentation Mandy exhibited obtunded mentation. This may have been a post-ictal effect, as she had a seizure en route to the appointment. Upon neurological examination Mandy exhibited proprioceptive ataxia in all four limbs, delayed conscious proprioceptive placing in the left pelvic limb, normal myotatic and flexor withdrawal reflexes, and absent menace response OS. All other aspects of the neurological exam were normal. Neuroanatomic localization was to the right forebrain. No other abnormalities were noted on general PE. Vital signs: Temperature

101.0 F; Pulse 128 bpm, no murmurs or arrhythmias ausculted, good pulse quality, no pulse deficits; Respiration 28 breaths per minute, lung auscultation clear, stertorous breathing was noted. Stat laboratory evaluation: PCV 44%, total protein 6.5 g/dl, blood glucose 123 mg/dl.

Problem List

Refractory seizures

Differential Diagnoses

Epilepsy is defined as recurrent seizures of any cause. Epilepsy can be classified as primary or secondary. Differentials in this case include:

Primary (idiopathic) epilepsy: common age of onset is 6 months to 6 years. Primary epilepsy may or may not be inherited. Diagnosis is by exclusion, in which no structural, intra-cranial or extra-cranial causes are identified. The cause of seizures is thought to be at the biochemical or biophysical level.

Secondary (symptomatic) epilepsy: a result of a structural abnormality of the brain such as congenital/developmental anomalies, neoplasia, trauma, or cerebrovascular event.

Secondary (reactive) epilepsy: a result of inflammatory, infectious, toxic, or extracranial diseases such as hypoglycemia, thiamine deficiency, hypocalcemia, hypo- or hypernatremia, hepatic encephalopathy, or renal disease. In reactive seizures, the brain may return to normal once the disease is treated.

Prognosis is dependent on the specific etiology, and therefore cannot be provided until further diagnostic evaluation has been performed.

Initial Diagnostic Plan

An IV catheter was placed in the right cephalic vein for administration of AEDs during hospitalization. A CBC, serum biochemical profile and urinalysis were performed to identify

metabolic abnormalities. Phenobarbital and KBr serum concentrations were submitted to ensure these medications were within therapeutic range. Fasted bile acids were performed to rule out a portosystemic shunt or other hepatic disease. Recommendations were made to perform an MRI of the brain to detect any structural abnormalities, and a CSF analysis to identify inflammatory or infectious causes of seizures. Mandy was admitted to the intensive care unit (ICU) for 24h observation pending MRI and CSF tap the following day.

Initial Diagnostic Results

CBC: Within normal limits (WNL) except for low RBC (5.22 cells/uL). Decreased RBC can be a result of hemolytic anemia, parasitic or infectious diseases, renal failure, or endocrine disease. The serum biochemical profile did not support these causes. Many puppies will have a mild anemia so this was not thought to be clinically significant at this time.

Serum biochemical profile: WNL except for increased CO_2 (27 mmol/L, reference range 13-24 mmol/L). Many brachycephalic breeds will exhibit a high CO_2 due to ventilation impairment; therefore this is not thought to be of clinical significance given the lack of additional clinical or biochemical evidence of pulmonary or metabolic functional impairment.

Bile acids: pre-prandial 3.9 umol/L (reference range <13 umol/L) and post-prandial 7.1 umol/L (reference range <25 umol/L) ruling out a hepatic encephalopathy.

Phenobarbital: 32 ug/ml (range 20-35 ug/ml).

KBr: 0.7 mg/ml (range 1.0-3.0 mg/ml)

Progress Notes 3/16/2010

Subjective: Obtunded mentation, unchanged from admission.

Objective: Temperature 100.6 F; Pulse 120 bpm; Respiration 28 breaths per minute. Mandy had 9 seizures through the night in ICU, of only a few seconds duration. Clinical

intervention was not deemed necessary. Neurologic exam was unchanged from presentation. She is urinating and defecating normally. She was fasted through the night for anesthesia today.

Assessment: Neuroanatomic localization is to the right forebrain. The three categories of seizures include primary epilepsy, symptomatic epilepsy and reactive epilepsy. Based upon Mandy's blood work from yesterday, extra-cranial causes for reactive seizures have been ruled out. Intra-cranial inflammatory diseases (one type of reactive seizures) remain a differential pending CSF tap analysis, as do primary epilepsy and symptomatic epilepsy.

Plan: Continue phenobarbital (48.6 mg PO q12h), and KBr (100 mg PO q12h). Perform an MRI of the brain to identify possible structural abnormalities, and a CSF analysis to detect infectious or non-infectious inflammatory disease.

Interventions and Diagnostic Results

Mandy was pre-medicated IV with hydromorphone (2mg/ml) at 0.05 mg/kg [total dose 0.41 mg (0.21 ml)]. Anesthesia was induced with propofol (10mg/ml) at 6 mg/kg, administered to affect [total dose 25.0 mg (2.5 ml)]. She was intubated using a size 7 endotracheal tube and maintained on 1.0% isoflurane and 1.0 L/min O_2 throughout the MRI and CSF tap. Mandy was positioned sternally in the MRI scanner and routine sequences were obtained in 3 planes. Gadolinium (470.0 mg/ml) was administered at 100 mg/kg IV [total dose 820 mg (1.74 ml)] for contrast imaging. Post-contrast T1-weighted transverse and sagittal images were obtained. The MRI showed enlarged cerebral hemispheres with a marked decrease in sulci and gyri formation predominately on the right cerebral hemisphere. The left cerebral hemisphere was also affected, but to a lesser degree. A distinctive line, normally indistinguishable, between the white and gray matter was appreciated on T1-weighted imaging. After the MRI, Mandy was placed in right lateral recumbency and the dorsal aspect of her neck from the occipital protruberance to the

cranial aspect of C2 was shaved and prepared according to standard asceptic technique. Her head was flexed to approximately 90 degrees with the nose parallel to the table, to enable the clinician to obtain CSF from the cerebellomedullary cistern. Spinal fluid can safely be removed at approximately 1.0 ml per 5.0 kg body weight. A total of 1.0 ml was obtained from Mandy for analysis. The CSF results were WNL (WBC 1 cell/uL [reference range < 5 cells/uL], RBC 172 cells/uL, and protein 17.1 mg/dl [reference range < 25 mg/dl]), which rules out infectious or non-infectious inflammatory causes for Mandy's seizures.

Diagnosis

Based on MRI findings Mandy was diagnosed with lissencephaly.

Final Outcome

Mandy was discharged with instructions to have periodic blood tests performed to monitor both the AED serum concentrations and liver function. Clients were educated regarding the nature of her disease, in that Mandy will require lifelong AED therapy in an attempt to control her seizures since there is no cure for lissencephaly. The goal of therapy is to minimize the frequency and severity of seizures; therefore they may not be completely eliminated. Since Mandy is currently not responding to drug therapy, a third drug (zonisamide) has been added. Her medications are as follows: Phenobarbital 48.6 mg (6 mg/kg) PO q12h, KBr 300 mg (37 mg/kg) PO q24h, and Zonisamide 100 mg (12 mg/kg) PO q12h. Consistency of medication administration is important; no doses should be missed and the medications should never be stopped abruptly without first consulting a veterinarian to avoid precipitating severe seizure activity. Side effects of the medications were discussed including sedation, polydypsia, polyuria, polyphagia, the potential for liver disease and blood dyscrasias associated with phenobarbital, and the potential for hypersensitivity reactions with zonisamide. The majority of Mandy's drug-

associated sedation should resolve after the first 1-2 months of therapy. A log should be kept documenting the date, time, frequency, duration and severity of each seizure to aid in medication adjustments. The owners were instructed that if Mandy has a seizure lasting longer than 5 min or has more than one seizure in a 24h period, they should contact a veterinarian immediately. Mandy should be confined when not under direct supervision to avoid injuring herself by falling off furniture or down stairways during a seizure. The client was also informed that Mandy should have a stable diet without any changes in salt and protein content that could alter the bioavailability and excretion of medications.

Discussion of Case

Lissencephaly is a genetic developmental disorder that occurs most commonly in Lhasa Apsos, but has also been reported in Irish Setters and Wire-Haired Fox Terriers. It is characterized by reduced to absent numbers of gyri on the surface of the cerebral cortex. This is thought to occur in utero where neuronal migration of brain development is abnormal. Although neuronal migration disorders are not typically progressive, if the patient's clinical signs (e.g., seizures) cannot be controlled, then the disease can be viewed as both progressive and potentially fatal. Since there is no cure for this disease, treatment is limited to supportive and symptomatic care, such as controlling seizures and other clinical signs.

A seizure is characterized by a hypersynchronous electrical activity in the cerebral cortex. Glutamate is the primary excitatory neurotransmitter in the brain, and gamma-aminobutyric acid (GABA) is the primary inhibitory neurotransmitter in the brain. When conditions disrupt the balance between ion channels that are influenced by glutamate and GABA and the enzymes responsible for their activity, then a paroxysmal depolarizing shift of neurons result, and a seizure occurs. Seizures are classified as focal motor (simple partial, complex partial) and

generalized (tonic-clonic) seizures. The seizure type noted in this case was a generalized tonic-clonic seizure. Generalized seizures exhibit 4 stages. The first stage is the prodromal stage and marks the time period prior to the seizure onset. The second stage is the aura and is the initiation of electrical activity in the brain. Auras are much shorter than the prodromal stage and are often the first observable signs of the ictus, which is the seizure itself. The fourth and last stage is the postictal stage and is characterized by transient abnormalities in brain function. This stage usually resolves within several minutes, but can last up to several days. During the ictal stage of a generalized seizure the patient experiences a tonic phase where all of the muscles contract simultaneously. The patient then loses consciousness and often falls onto one side exhibiting an opisthotonic posture. Autonomic signs such as urination, defecation and salivation are common. The clonic phase follows the tonic phase and consists of paddling of the limbs and chomping of the jaws. Breathing is irregular, eyes are dilated and the patient is unresponsive.

Seizures can be controlled by using a variety of AEDs. The AEDs utilized in this case were phenobarbital, KBr, and zonisamide. Phenobarbital is a common first-line AED, has high bioavalability and is rapidly absorbed in 2 hours. Maximum plasma levels are obtained in 4-8 hours and it reaches steady state in about 10-14 days. Phenobarbital enhances the inhibitory processes by facilitating neuronal responsivity to GABA. It is primarily metabolized by the liver. Possible adverse effects include sedation, ataxia, polyuria/polydipsia, polyphagia, liver disease, blood dyscrasias (less commonly) and it induces the P450 (hepatic microsomal enzyme) system leading to a reduction in elimination half-life of itself, as well as other hepatically metabolized drugs. Phenobarbital also decreases T4 and increases TSH without inducing clinical signs of hypothyroidism. The liver enzyme alkaline phosphatase is commonly induced with the administration of phenobarbital; therefore, bile acids are a more clinically relevant test for

hepatotoxicity and should be monitored every 6-12 months along with serum drug concentrations.

KBr is also considered a first-line AED. The half-life of KBr is 24 days in dogs, with a steady state reached at approximately 120 days. KBr also facilitates GABA, but by hyperpolarizing the neuronal membranes of chloride channels through influx of the negative bromide ion through the GABA receptor. KBr is primarily excreted through the kidneys and competes with chloride for renal elimination. Dietary salt intake (i.e. NaCl) should be kept consistent since chloride will increase bromide elimination. Similarly IV fluid administration may provide a source of chloride for competitive excretion of bromide. Major possible side effects include sedation, weakness, polydipsia, polyphagia, and ataxia. Gastrointestinal irritation and pancreatitis have also been reported.

Zonisamide is a newer generation AED. It is well absorbed and the time to steady state is 3-4 days. Zonisamide is a sulfonamide derivative that decreases the seizure onset by blocking sodium channels, decreases the seizure spread by blocking calcium channels, and binds to chloride channels associated with GABA. Zonisamide is eliminated through the hepatic system; therefore, when utilized in conjunction with phenobarbital, the elimination half-life is dramatically shorter. Major adverse side effects include sedation, ataxia and inappetence; though like many sulfonamides, may cause hypersensitivity reactions. Zonisamide has a high margin of safety and is well tolerated in dogs.

Mandy's case provides an example of an unusual developmental disorder that manifested as a common clinical presentation. Interesting neurodiagnostic findings, combined with advanced medical management of refractory seizures, makes this a good case example for

discussion of differential diagnoses, seizure classification, clinical management and client education of secondary epilepsy.

References: Mandy Poulson

De Lahunta et al. Veterinary Neuroanatomy and Clinical Neurology 2009

Dewey CW, A Practical Guide to Canine and Feline Neurology 2008

Oliver JE, et al. handbook of Veterinary Neurology 1997

Platt SR et al. BSAVA Manual of Canine and Feline Neurology 2004

HEMATOLOGY LAB CHART Mandy Poulson

Test	Date 3/15/2010	Date	Date	Date	Reference
WBC	6.54 x 10^3/ul				6 - 17 x 10^3/ul
RBC	5.22 x 10^3/ul				5.5 – 8.5 x 10^6/ul
HGB	12.8 g/dl				12 – 18 g/dl
PCV	37.8 %				6.0 – 8.0 %
MCV	72.5 fl				60 – 75 fl
MCHC	33.9 g/dl				32 – 36 g/dl
PLAPROT	6.1 g/dl				6.0 – 8.0 g/dl
PLATELET	560 x 10^3/ul				200 – 900 x 10^3/ul
SEGS	3.27 x 10^3/ul				3.00 – 12.00 x 10^3/ul
ABSONEUT					
LYMPHS	2.35 x 10^3/ul				1.0 – 5.0 x 10^3/ul
ABLYMPH					
MONOS	0.72 x 10^3/ul				0.15 – 1.35 x 10^3/ul
ABSMONO					
EOS	0.20 x 10^3/ul				0.10 – 1.25 x 10^3/ul
ABSEOS					
NRBC					
BANDS					

ABSBANDS					

URINALYSIS

Test	Date	Date	Date	Date	Reference
COLOR					
SPGR					
PH					
PRO					
GLUC					
KETO					
BILI					
BLOOD					
UROB					
VOLSUB					
VOLCENT					
WBC/lpf					
UR/LIP					

CHEMISTRY

Test	Date 3/15/2010	Date	Date	Date	Reference
GLU	94 mg/dl				68 – 132 mg/dl
CHOL	193 mg/dl				125 – 301 mg/dl
BUN	17 mg/dl				7 – 32 mg/dl
CREA	0.7 mg/dl				0.5 – 1.5 mg/dl
Mg					
Ca	11.4 mg/dl				9.7 – 12.3 mg/dl
PHOS	6.0 mg/dl				2.2 – 7.9 mg/dl
TP	5.3 g/dl				4.8 – 6.9 g/dl
ALB	2.5 g/dl				2.3 – 3.9 g/dl
GLOB	2.7 g/dl				1.7 – 3.8 g/dl
ALT	65 IU/L				3 – 69 IU/L

ALKP	117 IU/L				20 – 157 IU/L
GGT	10 IU/L				5 – 16 IU/L
TBIL	0.1 mg/dl				.1 - .8 mg/dl
Na+	140 mmol/L				138 – 148 mmol/L
K+	5.0 mmol/L				3.5 – 5.0 mmol/L
Cl-					105 -117 mmol/L
ECO2	27 mmol/l				13 – 24 mmol/L
AGPK					