Inherited Epilepsy can be Devastating in Dogs
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Epilepsy is a common disease causing seizures in dogs. It is reported that between 0.5% - 5% of all dogs will develop epilepsy in their lifetime. A genetic basis has been proven in Beagles, Dachshunds, German Shepherds, Keeshonds, and Belgian Tervurens. There are many breeds, including English Springer Spaniels, with a high incidence of epilepsy, which are suspected to have a genetic component. Hospital admissions at veterinary teaching hospitals identify the breeds with high levels of epilepsy. However this does not represent that actual incidence of epilepsy in the general population. On average 0.82% of all first time admissions are for epilepsy, with a breed range of 0.1 % to 2.0%. For English Springer Spaniels epilepsy represents 1 .3% of all admissions, which is the 9th highest of 96 breeds reported.

A seizure is a sudden event with involuntary increases in either muscle tone (tonus) and/or movement (clonus: such as paddling). Animals may also exhibit abnormal sensations or behaviors which usually last seconds to minutes. The cause is uncontrolled, synchronous electrical activity of the brain. The actual seizure event is called the 'ictal period". An 'Aura' may occur minutes to hours before the seizure, and in dogs, can include pacing, licking, salivating, or barking. Most often though, the aura is not evident in dogs- The 'postictal' recovery period can last for minutes to hours after the seizure and include unusual behavior, disorientation, and neurological deficits.

It is imperative that the underlying cause of seizures in a dog is determined. Causes of seizures can be broken down into Primary Epileptic Seizures (PES), Secondary Epileptic Seizures (SES), and Reactive Epileptic Seizures (RES). Primary epileptic seizures are by definition without an underlying structural cause, and thought to be genetically influenced. Other synonyms for PES include; idiopathic, genetic, inherited or true epilepsy. From here on PES will be referred to as primary epilepsy. An estimated 65% of dogs with the onset of seizures between 4-5 years old have primary epilepsy. It is a diagnosis of exclusion. For dogs in this age group it is recommended that a diagnostic work-up should include a normal neurological exam and a blood chemistry panel to rule out other causes of seizures. Secondary Epileptic Seizures are caused by an identifiable abnormal process in the brain such as: tumor, infection, trauma, or hydrocephalus. They are diagnosed by cerebral spinal fluid (CSF) analysis and/or CT or MRI scans under full anesthesia. A small percentage of dogs with an onset of seizures less at that 6 months or age or older than 5 years of age have primary epilepsy. In these older and younger age groups SES (brain tumor or hydrocephalus) or RES (liver shunt or low blood sugar) are more likely. Reactive Epileptic Seizures (RES) are caused by metabolic abnormalities such as low blood sugar, low calcium, liver failure, toxins, kidney failure, and electrolyte abnormalities. A blood chemistry profile, liver function test, or a toxin screen determines the diagnosis of RES.

Some other disease conditions can mimic seizures, but are determined not to be a seizure condition based on the history, a description of the event, a physical examination, and laboratory tests. Conditions that can mimic seizures include, but are not limited to, heart arrhythmia's, narcolepsy, and myasthenia gravis (a muscular disorder).

Classic primary epilepsy is considered by most veterinary neurologists to have generalized (affecting the whole body from the start), tonic, clonic seizures without any detectable cause. To make a diagnosis of PES there usually must be repeated seizures, with the dog acting normal between seizures. Electroencephalograms (EEG's) can be abnormal in PES, but are less reliable in dogs than people because they won't stay still or need to be anesthetized to have an EEG performed. However, a recent study has indicated that, despite anesthesia, EEG readings were consistent and unique in dogs with PES.

Partial seizures are different than generalized seizures. They may start in one local muscle group such as twitching in the face, and/or the dog may show abnormal behavior. If all testing is normal in a dog with partial seizures, many neurologists consider these to be "Cyptogenic" (meaning hidden) seizures that actually have an underlying structural abnormality (i.e. SES), that is undetectable using current methods.

It is controversial whether partial seizures might be caused by a genetic defect. If they are caused by a genetic defect within a breed, there is a fairly strong likelihood that the defect would be different than the defect causing generalized seizures. It is debated whether "Springer Rage Syndrome" is a form of complex partial epilepsy or is a purely behavioral problem. A case report of three dogs, one English Springer Spaniel, in 1992, indicated that episodic dyscontrol (rage) in some cases may be a form of limbic or temporal lobe epilepsy. A complete physical examination, behavioral examination, and EEG recordings were performed in these cases.

The mechanism causing seizures in primary epilepsy is thought to be an imbalance in excitatory and inhibitory signals in the brain.7 Every dog, or person, has a seizure threshold of neurological electrical activity. Normally the excitatory and inhibitory signals are in balance keeping the electrical activity below the seizure threshold. If there is too much excitatory activity or too little inhibitory activity the balance may allow the overall effect of many neurons (electrical brain cells) to go above the seizure threshold and a seizure occurs. Glutamate is one of the major excitatory chemical signals (neurotransmitters) in the brain. It acts by binding to specific receptors and allowing sodium (Na+) or calcium (Ca+) to move into brain cells through channels. There are also Na+ or Ca+ channels in neurons that are activated by changes in electrical activity (voltage gated). Gamma amino butyric acid (GABA) is the major inhibitory chemical signal in the brain. It acts by binding to specific receptors causing chloride (CI-) to move into the cells or potassium (K+) to move out of the cells. Mechanisms proposed to lead to primary epilepsy include: an excess of Glutamine; over responsive Glutamine receptor; too easy movement of Na+ or Ca+ into cells; too little GABA; poorly responsive GABA receptors; or impeded movement of K+ or CL-. Primary epilepsy will be likely to involve one or more defects in genes for Glutamine and GABA production or breakdown; receptor production, transport, or configuration; or Na+, Ca+, K+, CL- channel production, transport or configuration.

The genes that, in theory, might cause epilepsy are called "candidate genes". In all dog breeds, or all people, there will probably be 10's to 100's of individual genes involved in primary epilepsy. In any one-dog breed, due to inbreeding and linebreeding, there will probably be only one gene or a few genes involved in causing epilepsy. It may be one gene (recessive or dominant), one gene of major influence, or a number of genes (a polygenic threshold trait). Since humans, generally, are not as related to one and another, as are dogs from one breed, it is likely that primary epilepsy in most humans will be polygenic. If this is true, it will be more efficient to identify genes in specific dog breeds first and this may eventually help identify epilepsy genes in humans. In humans only 3 genes have been identified, in some rare forms of familial idiopathic epilepsy. Two related potassium (K+) channel defects in benign familial neonatal convulsions (BFNC) have recently been identified. A defect in a receptor for a different neurotransmitter (acetylcholine) has previously been identified in a family with autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE), which was later shown to affect calcium (Ca+) movement. In humans, so far, there has not been any success in identifying genes associated with more common primary epilepsy syndromes such as juvenile absence epilepsy and juvenile myoclonic epilepsy (JME). No gene or marker linked to an epilepsy gene has been identified in any dog breed, as yet. This is probably due to the fact the canine genetic map has just been made available in its first forms, whereas the human genetic map is already very detailed. Continued work on the canine genetic map will probably progress very rapidly in the next few years.

In our study of primary epilepsy, in English Springer Spaniels, Vizslas, and research Beagles the first step will be to determine the mode of inheritance for each breed (simple recessive, simple dominant, sex-linked, or polygenic). To do this we will collect pedigrees that have two or more epileptic dogs and include at least three generations. We will need to collect information on seizuring dogs through a written survey and/or a telephone interview along with veterinary records to determine if the seizures are PES, SES, or RES, and generalized or partial. This data is essential to ensure that the phenotype (visible symptoms of a disease) is correctly categorized.

Pedigree analysis has been published in only a limited number of dog breeds. The mode of inheritance has been determined to possibly be, autosomal recessive in Keeshonds, polygenic with one gene of major influence in Belgian Tervurens, and polygenic recessive in Golden Retrievers. Once the mode of inheritance is determined within a breed, we will determine the best technique to try and find a genetic

marker linked to epilepsy gene(s) in each breed. (Dr. Gary Johnson's article will go into the details of genetic linkage analysis and different types of markers). If the mode of inheritance is determined to be due to one gene we are confidant that a marker will be found linked to that gene within a number of years. The exact time frame will depend on the speed of progress in getting a more detailed canine genetic map, and to some extent "luck", whether we happen to randomly pick a marker close to the epilepsy gene to test, sooner or later. A clearly linked marker would be able to, through a simple blood test, determine carriers, affected, and unaffected dogs with a high degree of certainty. If the disease, in any one breed, ends up being polygenic, it will be more complicated, and time consuming. Genetic analysis will make progress in the long term and eventual blood tests will be helpful, but the results will not be as clear cut.

Treatment for primary epilepsy usually includes anti-epileptic drugs (AED's). The ideal AED would maintain a seizure free status without unacceptable side effects. Unfortunately this is a rare occurrence, with significantly less than 50% of dogs achieving this goal, A more realistic therapeutic goal is one single seizure event that lasts less than 5 minutes, and occurs less than once every 6-8 weeks" In order to determine whether AED's are decreasing the seizure pattern, the seizure pattern needs to be established first. If there is a single event less than once every two months therapy is not recommended. This is because the likelihood that medications will decrease the seizure frequency is low. In such dogs the potential for side effects of AED's is significant.

There are numerous human AED's, but unfortunately many of them are toxic to the dog's liver, or too rapidly metabolized to be safe or useful. Three drugs; phenobarbital, potassium bromide, and diazepam, have consistently shown the best results for treating epileptic dogs. Phenobarbitol and diazepam bind to GABA receptors causing increased CI-movement, which inhibit brain electrical signals, thus raising the seizure threshold. The bromide in potassium bromide mimics the effects of chloride, producing the same results as phenobarbitol and diazepam.

Phenobarbitol is considered by most veterinarians to be the drug of first choice. It is a barbiturate. Common side effects include an increased thirst, increased appetite, and sedation for a short time. Occasionally phenobarbitol can cause liver damage. Liver enzyme function tests and blood levels of phenobarbitol should be monitored to be sure significant liver injury in not occurring and that therapeutic levels are achieved. In many dogs with epilepsy, phenobarbitol alone can control the seizures with minimal long-term side effects. Unfortunately there is a significant proportion of dogs in which phenobarbitol alone is not enough. This tends to occur more in medium to large breed dogs. Potassium bromide is usually used as a second line drug in combination with phenobarbitol for "refractory cases". Its side effects can include sedation and rarely pancreatitis. Blood levels should be monitored. It is slow to act and takes 3-4 months to obtain steady levels versus phenobarbitol, which takes about one week.

Unfortunately, there is still a significant portion of epileptic dogs in which both drugs together do not adequately control the seizures. Any time the seizures are too frequent they can cause a process call 'kindling' in which further (non-epileptic) brain cells are affected adversely leading to the next set of seizures occurring even sooner or lasting longer. Eventually some dogs have very frequent clusters of seizures happening multiple time in one day, or go into a continuous seizure (status epilepticus) which is life threatening and can lead to permanent brain damage or death. Most dogs with cluster seizures, or status epilepticus can be treated by your veterinarian or an emergency center by intravenous or rectal diazepam, and stopped within minutes to hours. Occasionally a constant intravenous drip of diazepam or barbiturates is needed. However this can be a very emotional experience for you and your dog, and each emergency hospitalization usually costs hundreds of dollars. To avoid frequent or prolonged seizures other drugs such as Glutamate blockers; phenytoin, gabapentin, carbamazepine; and longer acting diazepam like drugs such as chlorazepate have been tried. Unfortunately, many times, they are not effective, and many are very expensive. Experimental treatments such as acupuncture, gold bead implants, herbal products, and surgery have also been tried. Unfortunately, an unacceptable proportion of dogs with 'refractory' epilepsy are euthanized due to poor quality of life with frequent seizures.

Living with a dog having refractory epilepsy can be a devastating emotional experience for you and your dog. If the seizures continue to become more and more frequent, despite all reasonable treatment efforts, it can be an exasperating experience for all involved. You and your dog are subjected to repeated, prolonged

seizures beyond your control. You experience a roller coaster ride of unacceptable seizures with your dog near death, and large financial loss, and then a few days later your dog appears completely normal. Unfortunately the next cluster is around the corner. It can be similar to a diagnosis of cancer in which some treatments bring a reasonable remission time with normal quality of life, but it keeps coming back. At this point there is no chance for cure, and reasonable control is extremely difficult to attain in some cases.

Epilepsy is very difficult to control in purebred dog because it's onset is often not observed until a dog has been breed, and there currently is no way to detect asymptotic carriers. A linkage test or direct gene test (like PFK-phosphofructokinase deficiency) would make control and carrier detection possible. Our lab at the University of Minnesota College of Veterinary Medicine and Dr. Gary Johnson's lab at the University of Missouri -Columbia College of Veterinary Medicine have a cooperative effort trying to find a marker to detect genetic epilepsy in English Springer Spaniels. All submissions will be confidential with only key personnel having access to information, and dogs identified by an anonymous code. If you have any questions feel free to contact either our lab, or Karen Foster as the breed contact person. Dr. patterson is a resident in veterinary internal medicine and is working on a PhD dissertation on the Genetics of Canine Epilepsy. The Minnesota team also includes Dr. Jane Armstrong DVM, MS who is board certified in veterinary internal medicine, and an accomplished researcher in canine and feline diseases, and Dr. Jim Mickeslon PhD, a biochemist and molecular biologist with extensive research into molecular biology and genetics. In addition we have collaborators that include two - board certified veterinary neurologists, a human molecular geneticist, and a human neurologist. We are very excited to take on this project and will be keeping you updated on our progress.