Topics in Compan An Med 28 (2013) 51–58

Topical Review

Inherited Epilepsy in Dogs

Kari J. Ekenstedt, DVM, PhD[a,*], Anita M. Oberbauer, PhD[b]

Keywords:
dog
epilepsy
gene
inheritance
seizures
progressive myoclonic epilepsy

[a]*Department of Animal and Food Science, College of Agriculture, Food, and Environmental Sciences, University of Wisconsin – River Falls, River Falls, WI, USA*
[b]*Department of Animal Science, College of Agricultural and Environmental Sciences, University of California, Davis, CA, USA*

*Address reprint requests to Kari J. Ekenstedt, University of Wisconsin—River Falls, 246 Agriculture Science Building, 410 South Third Street, River Falls, WI 54022, USA.

E-mail: kari.ekenstedt@uwrf.edu, eken0003@umn.edu (K.J. Ekenstedt)

Epilepsy is the most common neurologic disease in dogs and many forms are considered to have a genetic basis. In contrast, some seizure disorders are also heritable, but are not technically defined as epilepsy. Investigation of true canine epilepsies has uncovered genetic associations in some cases, however, many remain unexplained. Gene mutations have been described for 2 forms of canine epilepsy: primary epilepsy (PE) and progressive myoclonic epilepsies. To date, 9 genes have been described to underlie progressive myoclonic epilepsies in several dog breeds. Investigations into genetic PE have been less successful, with only 1 causative gene described. Genetic testing as an aid to diagnosis, prognosis, and breeding decisions is available for these 10 forms. Additional studies utilizing genome-wide tools have identified PE loci of interest; however, specific genetic tests are not yet developed. Many studies of dog breeds with PE have failed to identify genes or loci of interest, suggesting that, similar to what is seen in many human genetic epilepsies, inheritance is likely complex, involving several or many genes, and reflective of environmental interactions. An individual dog's response to therapeutic intervention for epilepsy may also be genetically complex. Although the field of inherited epilepsy has faced challenges, particularly with PE, newer technologies contribute to further advances.

Introduction

Epilepsy is the most common chronic neurologic disorder in dogs, reported at a prevalence of between 0.5% and 5% in a nonreferral population,[1] and humans, where it is estimated to affect 1%-3% of the population.[2] However, epilepsy is not a single disease but a group of disorders characterized by a broad array of clinical signs, age of onset, and underlying causes. The International League Against Epilepsy classifies human epilepsies and defines terminology for the various etiologies; these terminologies are as follows: (1) genetic (or primary), (2) structural/metabolic (including symptomatic), and (3) unknown, in which the mechanistic basis is not yet elucidated.[3] The proposed canine classification for epilepsy is a slight modification of that by the International League Against Epilepsy: (1) primary/genetic epilepsy (often termed "idiopathic" epilepsy), (2) structural epilepsy (symptomatic epilepsies resulting from structural brain abnormalities), (3) reactive seizures (symptomatic epilepsies resulting from metabolic or toxic abnormalities), and (4) unknown. Some epilepsies bridge these categories; for example, genetic mutations may be the cause of a metabolic abnormality that results in epilepsy. Owing to clinical presentation, these epilepsies are still classified as metabolic, despite the genetic cause of their disorder. When chronic, recurring seizures occur and no underlying abnormality is detected, the syndrome is classified typically as primary epilepsy (PE) and presumed to be genetically regulated. Indeed, in humans, primary (or idiopathic) epilepsy is generally accepted to have an underlying genetic origin.[4]

Genetic epilepsies have been studied extensively in humans and mice, and, although an in-depth review of these species has not been undertaken in this article, it is worth noting that many parallels exist between syndromes in humans, mice, and dogs. In humans, genes underlying several rare, monogenic mendelian genetic epilepsies have been identified. Many are categorized as "ion channelopathies," with mutations in genes encoding sodium, calcium, potassium, and chloride ion channels. Causal mutations have also been observed in other genes involved in neuronal signaling, including neurotransmitter receptor genes, such as gamma-aminobutyric acid receptors or acetylcholine receptors. A small number of non–ion channel genes, previously unknown to be involved in the neural system, have also been implicated. Additional details on these known human genetic epilepsy mutations can be found in reviews.[4–10] Despite these discoveries, most of the human genetic epilepsies remain unsolved at the molecular level, and although most appear to have a strong genetic basis, their inheritance patterns are complex, with many contributing genetic and environmental factors. Greater than 95% of human non-mendelian epilepsies appear to be complexly inherited.[11] Genome-wide investigations have failed to uncover major regulatory loci suggesting that the underlying cause includes both rare and common allele variants each contributing small effects that may confer risk or protection for epilepsy.[12] Great interest exists to identify casual mutations to reduce the risk of epilepsy or inform and improve therapies.

Dozens of epileptic mouse models exist, each representing different causative mutations. A few represent spontaneous mutations, though most have been engineered intentionally.[13,14] As is the case for humans, many of these are ion channels genes, although non–ion channel genes can also underlie single gene murine epilepsy. For complexly inherited epilepsy, the epilepsy-like mouse strain suffers seizures in response to physical stimuli, such as moving a mouse from one cage to another.[15] The epilepsy-like mouse exhibits a polygenic complex phenotype and has at

1527-3369/$ - see front matter © 2013 Topics in Companion Animal Medicine. Published by Elsevier Inc.
http://dx.doi.org/10.1053/j.tcam.2013.07.001

least 6 different loci apparently contributing to seizure susceptibility, indicating gene interactions, locus heterogeneity, and gene-by-environment interactions.[16-19]

Recently the dog has received much attention as a model organism for the discovery of the molecular mechanisms underlying genetic diseases in humans. The unique features that make the canine species so tractable to the study of inherited conditions include significant intrabreed homogeneity and sizeable interbreed heterogeneity.[20] A popular sire or founder effect observed in many breeds also contributes to intrabreed homogeneity, possibly rendering the genetic basis for diseases such as epilepsy less complex in dogs than humans.[21,22] Thus, relatively inbred dog populations that have naturally occurring epilepsy segregating within a breed may prove a relevant model for human genetic epilepsies. Investigations of canine epilepsy may be superior at identifying genetic underpinnings when compared with similar studies in humans, which are plagued by locus heterogeneity, or mouse models with discrete mutations. The dog model for PE was predicted to permit the identification of novel genes involved in central nervous system function. To some degree, this has proven true as genes have now been identified for several reactive (symptomatic metabolic) epilepsies and 1 PE in dogs. However, canine epilepsy, similar to its human counterpart, remains plagued with complex and difficult-to-elucidate inheritance. The present review discusses dog breeds suggested to have inherited PEs, describes the known canine epilepsy genes, details suggestive genes or loci involved in PE, and briefly, presents pharmacogenetic investigations of how canine epilepsy responds to drug therapies.

Breeds With Clinical Descriptions of Inherited PEs

Primary (genetic) epilepsies in dogs are a diagnosis of exclusion, where history, physical and neurologic examinations, blood chemistry tests, brain imaging, and cerebral spinal fluid analysis have ruled out other causes of recurrent seizure activity. Most canine patients with PE are entirely normal between seizure episodes,[23] although some may express mild abnormalities, such as episodic ataxia, between seizures.[24] Although the general prevalence of PE in dogs is typically considered to be 0.5%-5%,[1] it can be much higher within a single breed. For example, in the Belgian Shepherd, the prevalence has been estimated from 9.5%-33%[25] in 1 extended family.[26] The hereditary basis of PE in many breeds is supported by a growing body of literature,[27] and PE has been reported in nearly every breed as well as in mixed breed dogs, with the latter having a prevalence of 0.91% in a study of approximately 90,000 dogs.[28] A recent study examining over 1200 PE cases from nearly 80 pedigree breeds and mixed breed dogs observed that the mixed breed dogs comprised the largest percentage of their cohort (20.5%), with Labrador retrievers as the next highest (11.0%).[29] This epidemiologic study also observed a significant overrepresentation of males in the epileptic cohort, compared with a geographically similar nonepileptic control group.

Many breeds with a high prevalence of PE have had their epilepsy characterized, with descriptions of the clinical phenotype and suggestions for potential modes of inheritance based on pedigree relationships. Table 1 lists those breeds identified as having a genetic or familial basis to PE. To date, 1 PE gene mutation (in the Lagotto Romagnolo) and 1 associated locus (in the Belgian Shepherd) have been described and are discussed in more detail later in the article. Many additional breeds are subjects of PE genetic investigations, and their PE is suggested to be inherited, but clinical descriptions or putative modes of inheritance have not been published.

Other breeds lack sufficient information to definitively classify their condition as PE or even as an inherited epilepsy syndrome. For example, the Finnish Spitz is reported to have a genetic epilepsy,[51,52] but pedigree analysis has not been conducted and a possible mode of inheritance has not been reported. The Shetland Sheepdog has an epilepsy syndrome inherited in a multifactorial or autosomal dominant fashion although affected dogs also have histopathologic changes in their brain tissue.[53] It is unknown if those lesions represent primary pathology that induced seizures or if the lesions were a consequence of the seizures; in case of the latter, this would certainly be classified as PE. Lastly, a study of Boxers calculated medium-to-high heritability estimates for epilepsy in that breed.[54] However, the report did not indicate that the epilepsy cases underwent thorough testing and follow-up to sufficiently rule out nonheritable causes of seizures, creating some uncertainty about the diagnosis of PE.

Among the published PE studies that examined the mode of inheritance, many breeds showed evidence for autosomal recessive inheritance. Yet, many of those studies could not rule out polygenic inheritance (Table 1), suggesting the genetic basis for PE may be quite complicated within dogs. Complex inheritance is further supported by the observed variability in seizure phenotype. For example, the epileptic condition may manifest as generalized seizures from the onset, focal onset only, or focal onset progressing to generalized seizures. Likewise, the frequency of cluster seizures, status epilepticus, and response to antiepileptic drugs (AEDs) (i.e., success in managing seizures) also vary between breeds. Taken together, is has become increasingly clear that, as in humans and even some mouse models, multiple PE loci exist in dogs. In addition, it is probable that within a breed, more than 1 locus is causal for the varied PE phenotypes expressed.

Known Genetic Epilepsy Genes—PE

Only 1 mutation causing PE has been described to date (Table 2). The Lagotto Romagnolo breed segregates a recessive benign familial epilepsy, which typically remits by 4 months of age.[24] The mutated gene underlying PE in this breed is a truncating mutation in *LGI2*, an ortholog of the human epilepsy gene *LGI1*.[55] The LGI proteins are critical in synaptic function. The developmental stage–specific expression of *LGI1* and *LGI2*, both acting on a-disintegrin-and-metalloproteinase (ADAM) receptors, appears to protect the brain during the pruning phase of postnatal neuronal development. The discovery of the mutation in Lagotto Romagnolo was the first canine epilepsy mutation described for any PE and revealed a novel molecular pathway involved in epilepsy.

Progress in identifying additional canine PE genes has been slow. Candidate gene and genome-wide association (GWA) studies have identified associations between PE and specific genes or chromosomal loci, although none appears to be causative nor are they available as genetic tests. The lack of definitively causal mutations underscores the multifactorial nature of the condition; this has been discussed in greater detail later.

Known Genetic Epilepsy Genes—Reactive Epilepsy

Progressive myoclonic epilepsies (PMEs) are reactive seizures caused by metabolic abnormalities. They are a group of clinically and genetically heterogeneous, severe, and intractable disorders characterized by epilepsy, myoclonous, and progressive neurologic deterioration. Dogs affected with PMEs often have abnormal mentation between seizures, measurable abnormal metabolites, and histopathologic abnormalities that may be observed on postmortem analysis.

In contrast to PE, considerable progress has been made in identifying the mutations underlying canine PMEs; to date, 9 genes have been described for reactive (metabolic) epilepsy in dogs. The first canine metabolic epilepsy mutation to be described was for