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Epilepsy in Irish Wolfhounds

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Abstract

During the last 15 years, breeders have reported an increase in the proportion of Irish Wolfhounds with seizure disorders. Clinical data and pedigrees from closely related Irish Wolfhounds were collected retrospectively and analyzed. Idiopathic epilepsy was diagnosed, by exclusion of other causes for seizures, in 146 (18.3%) of 796 Irish Wolfhounds from 115 litters. The first seizure occurred by the age of 3 years in 73% of all dogs. Males were more commonly affected than females (61.6% versus 38.4%), with males having a later average age of seizure onset. The life expectancy of affected dogs was decreased by 2 years when compared with the average Irish Wolfhound population. The heritability index for the affected dogs, their littermates, and unaffected parents was 0.87. No simple mode of inheritance explains the pattern of affected dogs in pedigrees. Hallmarks of dominant and sex-linked inheritance were notably absent, and the segregation ratio was less than would be expected for simple autosomal recessive inheritance. Assuming all affected dogs have the same form of epilepsy, the simplest description of the complex pattern of inheritance observed is autosomal recessive, with incomplete penetrance and male dogs at increased risk.

Keywords

Autosomal recessive; Canine; Genetic; Seizures

Seizures occur in 0.5–5.7% of dogs, and for those with recurring seizures, idiopathic epilepsy is the most common diagnosis.¹ Among the many breeds in which idiopathic epilepsy has been described, it has been suspected or shown to be a genetic disease in several.¹ Inheritance of epilepsy differs among breeds, including simple autosomal recessive² with a sex modifier,^{3,4} polygenic recessive⁵ with a sex predilection,⁶ polygenic with a large contribution by a single autosomal recessive gene,⁷ and a multilocus model.⁸ In this report, we document idiopathic epilepsy in the Irish Wolfhound and investigate the mode of inheritance based on information on affected and related, non-affected Irish Wolfhounds collected from questionnaires and pedigrees.

Materials and Methods

Animals

Medical records and pedigrees from 120 litters (N = 706) of Irish Wolfhounds and their parents were obtained from veterinarians and owners by detailed questionnaire, including requests for all laboratory reports. The diagnosis of idiopathic epilepsy in the 146 affected dogs was based on a history of more than 2 seizures in the absence of other medical

problems. Absence of other medical problems was confirmed for all affected dogs by normal physical and neurologic examination results, CBC, serum biochemical analysis, ammonia or bile acid values or both, and urine analysis. Additional information collected included date of birth, sex, age of first observed seizure, number of known seizures, age at death, and cause of death. Owners of epileptic dogs also provided information on the seizure characteristics, such as observation of partial or generalized motor problems, urination, defecation, salivation, collapse and relationship of seizure onset to the time of day, feeding, walking, sleeping, or estrus cycle. Postmortem examinations were performed on 14 affected dogs, with 11 performed at the University of Pennsylvania School of Veterinary Medicine and 1 each at the Virginia-Maryland Regional College of Veterinary Medicine, the Texas A&M College of Veterinary Medicine, and Department of Pathology of The Animal Medical Center in New York. Dogs were considered unaffected if no seizure had been observed during the dog's lifetime. Seizure-free dogs that died before the age of 4 years and 37 dogs who had seizures in the presence of seizure-associated conditions or diseases, such as hyperthermia, portosystemic shunts, head trauma, or brain or neurologic lesions, such as neoplasia and ehrlichiosis, were excluded from the study.

Genetic Analysis

Pedigrees were examined from dogs with clear identifiers, such as date of birth, age at death, sex, and known health status of littermates. The vertical pedigrees were drawn and scrutinized for compatibility of the phenotypes and the assumed genotypes with expectations under assumptions of the simple mendelian modes of inheritance. Segregation analysis was performed to correct for incomplete ascertainment,⁹ and heritability was calculated by standard methods.¹⁰

Results

Clinical Findings

Idiopathic epilepsy was diagnosed in 146 Irish Wolfhounds (18.3%) from 120 related litters that contained 796 dogs. For females, the ages of their first observed seizure ranged from 6–84 months (mean \pm SD, 27.6 \pm 16.8). The incidence of females with onset of seizures between 3 and 4 years of age was low, with 82% of first observed seizures occurring before 3 years of age. The age of onset for males ranged from 6–107 months (mean \pm SD, 33.9 \pm 18.5; Fig 1). Only 67% of males experienced their first seizure before the age of 3 years, whereas the onset of seizures occurred by 4 years of age in 83% of all male dogs. Overall, significantly more dogs had their first seizure before 3 years of life than after 3 years ($P < .05$; Fig 1). Significantly more males than females had their first seizure in the 37- to 42-month and the 43- to 48-month periods ($P < .05$ for each 6-month period). The ratio of affected male dogs (90) to female (56) was 1:0.62, which differed significantly from the 1:1.08 male-female ratio for the general Irish Wolfhound population during the same period ($P = .001$; an average of 2,502 dogs were born yearly). However, at 30 months of age, the ratio of affected male to affected females was close to 1:1 (43:40), and even at 3 years of age, the ratio of affected males to females (60:46) was not significantly different from the general Wolfhound population ($P = .27$).

The coefficient of inbreeding was calculated with both 5- and 10-generation pedigrees and was examined with respect to the age of onset of disease in all dogs and males and females separately. There was no significant correlation between age at first seizure and the coefficient of inbreeding, regardless of sex, or in all dogs considered together ($R^2 = 0.02$ – 0.06). However, in 23 litters with multiple affected dogs, the onset of seizures in littermates occurred within 12 months of each other, with the exception of 7 litters in which 1 dog of each litter had its first seizure later in life. In the single instance where affected full siblings

were born in separate litters (2 affected dogs in each of 2 litters), the age of first seizure covered a range of 3 years (18, 31, 39, and 54 months).

No significant difference in longevity was apparent after the first seizure between affected males and females (Fig 2). The average age of affected dogs at death was 56.4 months, which is almost 2 years younger than the average age of death within the general population of Irish Wolfhounds of 6.5 years.¹¹ Of the 126 affected dogs who died, 76 deaths (60.3%) were directly attributed to the seizure disorder, with the cause of death reported as death during seizure (16.1% of all seizure-related deaths), or euthanasia because of un-controlled seizures (65.8%), hepatotoxicity from pheno-barbital treatment (6.6%), aspiration during seizures that led to fatal pneumonia (6.6%), or euthanasia because of nonrecovery after a seizure (3.9%). Fifty affected dogs died of unrelated causes, and 20 affected dogs were still alive at the time of writing. Detailed postmortem examinations were performed on 14 of the affected Irish Wolfhounds, who ranged in age from 10–49 months (median, 21.5 months). No neurologic or systemic lesions that could explain the recurrent seizures were found in these 14 dogs.

Genetic Analysis

Affected dogs were born in 115 litters that contained 773 dogs. Five litters (23 dogs) without affected dogs were born to matings between parents who had both produced affected offspring in other matings. A representative portion of the larger pedigree illustrating the inheritance of idiopathic epilepsy is shown in Figure 3. The average inbreeding coefficient (calculated throughout 10 generations) for all the dogs entered into the study was 0.156, with a range of 0–0.35. The major observation made from pedigree examination was that most affected dogs were born to healthy parents (143 affected dogs from 112 litters). In 37 of the litters born to unaffected parents, 1 of the unaffected parents was related to other affected dogs. Only 3 of the affected dogs had an affected parent, and matings between an affected and an unaffected parent produced either all unaffected offspring or a mix of affected and unaffected offspring in the same litter. The segregation ratio and the heritability (h^2) were calculated from litters in which both parents never had a history of seizures, and in which medical information was available on all littermates. Ascertainment bias was corrected for by the singles method, as adopted by Nicholas.¹⁰ The analysis for all dogs resulted in an h^2 of 0.87 and an estimated segregation ratio of 0.083 ± 0.0001 , which is lower than value of 0.25 expected for a fully penetrant autosomal recessive trait.

Discussion

Idiopathic epilepsy has been described in a variety of dog breeds, along with different apparent or suspected modes of inheritance. A familial predisposition had been recognized early on in Keeshonds, terriers, corgis, retrievers, Pointers, setters, spaniels, Collies, Alsatian dogs, Boxers, Pekinese,^{12,13} Belgian Tervueren,¹⁴ Dachs-hunds,¹⁵ and the Horak laboratory dog.¹⁶ In the German Shepherd and in the Keeshond, idiopathic epilepsy was thought to have a simple autosomal recessive basis.^{2,17–19} For epilepsy in the Golden Retriever, a multifactorial etiology, including genetic and environmental factors, has been described.⁸ In the Labrador Retriever, pedigrees from 44 families with 55 epileptic Labrador Retrievers were analyzed, and the results were suggestive of a polygenic, recessive mode of inheritance.⁵ Analysis of pedigrees from 4,005 Bernese Mountain Dogs with 50 affected dogs revealed a polygenic, recessive mode of inheritance with a predisposition for males.⁶ The Belgian Tervueren has been described as the dog breed with one of the highest incidences of seizures.^{14,20} Not surprisingly, a number of genetic studies have been performed in this breed, with results proposing a single major gene with a large effect on seizures.^{7,20–22} This is the first report of hereditary epilepsy in the Irish Wolfhound breed.

In this study, as in other studies, particularly, retrospective studies, the diagnosis of idiopathic epilepsy is problematic.²³ In this study, it is probable that at least 2 types of misdiagnosis occurred: false diagnosis of idiopathic epilepsy by failure to recognize a primary cause of seizures and diagnosis of a dog as unaffected when idiopathic epilepsy was present. The most advanced diagnostic tools were not used to evaluate every dog who had seizures. It can be argued that, for the panel of tests used in this study, misdiagnosis is more likely to occur in an older dog. Many common causes for seizures in young dogs are ruled out by standard blood, urine, and liver function analysis²³ as used in this study, whereas older dogs are more likely to develop seizures because of intracranial causes that require brain imaging or postmortem examination for diagnosis. A false diagnosis of unaffected could have also occurred for a number of reasons, such as the failure of owners to observe or report seizures. Use of 4 years as the minimum age for assigning the unaffected status could also have resulted in false unaffected diagnoses.

It is also possible that idiopathic epilepsy in Irish Wolfhounds has multiple origins. Although we assume, for much of the analysis herein, that the seizure disorder in all affected dogs is caused by a common underlying defect or defects, this may certainly be an oversimplification. The higher incidence in males of onset of seizures later in life points to this possibility, but the study is not large enough to address these issues directly.

Most of the affected Irish Wolfhounds had clinical signs and grand mal-type seizures, consistent with findings in almost all other studied dog breeds.^{1,3,6,8,24} Life expectancy of affected Irish Wolfhounds was decreased by 2 years compared with the general Wolfhound population.¹¹ This may be attributable to inadequate treatment, adverse effects of therapy, or management issues that relate to the dogs' large size.

In Irish Wolfhounds, the age at first seizure is similar to what has been observed in the general canine population^{1,24} and specific breeds.^{4-6,8} In contrast, a study in Danish Labrador Retrievers revealed that most seizures that occurred before 4 years of age were only partial seizures and an equal number of generalized seizures occurred before and after 4 years of age.²⁵

In this study, an 18.3% incidence of idiopathic epilepsy was found among related Irish Wolfhounds with a high heritability of 0.87 for the trait. These results suggest the presence of a major gene, because the heritability was higher than 0.5. In a similarly performed study, a heritability of 0.77 was estimated for epilepsy in the Belgian Tervueren and 0.76 for epilepsy in the Belgian Sheepdog.⁷ In the Irish Wolfhounds, significantly more males were affected than females. This is in contrast to all but 2 other studies in which no sex predilection was found.^{2,5,7,8} The results in the Irish Wolfhounds are similar to the findings in the beagle and the Bernese Mountain Dog,^{3,4,6} where the involvement of a sex-modifier gene was hypothesized. However, when only those dogs with onset of seizure activity before 3 years of age were taken into account, there was not a significant difference between the percentage of affected females and males. This finding raises the possibilities that the later-onset seizures may have a different cause than early-onset seizures, that the dogs in the older-onset group had misdiagnosed conditions, emphasizing the need for accurate diagnosis in any age group, or that there is a bias of owners or breeders to report seizures when they occur in a male dog.

Pedigree examination revealed several features consistent with an autosomal recessive mode of inheritance. A simple dominant mode of inheritance can be excluded because most affected dogs were born to clinically normal parents. Although an X-linked mode of inheritance must be entertained because the incidence of seizures in males was significantly higher than in females, in an X-linked recessive trait the fathers of affected females must

also be affected. In this study, 55 of 56 of the affected females were born to clinically normal fathers. Consistent with an autosomal recessive mode of inheritance, most affected dogs were born to normal parents. However, the estimated segregation ratio is not consistent with a fully penetrant simple autosomal recessive mode of inheritance. Idiopathic epilepsy in Irish Wolfhounds, although highly heritable, is genetically complex. It was therefore concluded that seizures in the Irish Wolfhounds are inherited as an incompletely penetrant recessive trait with a sex predilection for older males in all of the affected dogs.

Genetic studies in humans and mice with idiopathic epilepsy have revealed a number of causative genes for specific forms of epilepsy.²⁶ Mutations for monogenic epilepsies have been found primarily in genes coding for ion channels²⁷ and in 2 different proteins that may be involved in neurogenesis.²⁸ More recently, the molecular basis for autosomal recessive progressive myoclonic epilepsy (Lafora disease) in the Miniature Wirehaired Dachshund has been identified.²⁹ However, this well-defined form of epilepsy (not idiopathic), which is characterized by myoclonic-type seizures with rapid, progressive mental deterioration and polyglucosan intracellular inclusions,³⁰ is clearly distinct from the form or forms of epilepsy observed in Irish Wolfhounds and many other breeds. In considering the genetic bases for epilepsy in various dog breeds, including Irish Wolfhounds, it is important to consider that most forms of idiopathic generalized epilepsy in humans are inherited as complex genetic traits.³¹ A more recent study in humans has demonstrated a major susceptibility gene with modifiers that influence the clinical appearance of the seizure.³² We suspect that a similar mechanism is responsible for the phenotypic appearance of idiopathic epilepsy in the Irish Wolfhound. Given the high heritability of epilepsy in this breed, linkage analysis studies to determine the genes involved are feasible.

The high incidence of seizures in the Irish Wolfhound, along with the decreased longevity in affected animals, underscore the need for a breeding program designed to eliminate the disease from the breed. Documentation of the inheritance pattern of the disease is important not only in designing such a program but also in performing additional genetic studies that can lead to the development of DNA-based genetic tests for the identification of disease-predisposing alleles, which can greatly enhance the efficiency of such a program.

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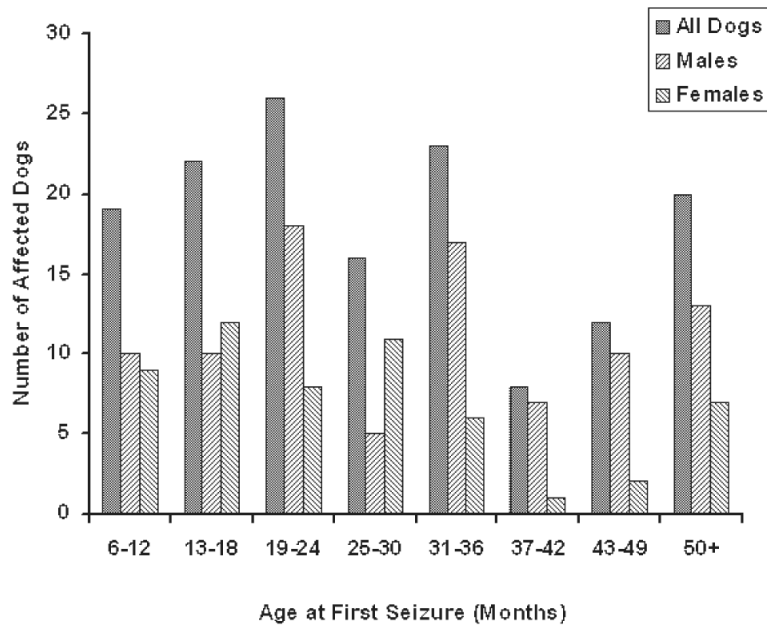


Fig 1. Number of dogs at various ages at first seizure. Statistically significant differences in the age of onset of seizures ($P < .05$) were seen between females from 37–48 months of age and the rest of the groups and between males and females for both the 37- to 42-month and the 43- to 48-month groups. Note the precipitous decrease in dogs with onset of seizure activity in the 37- to 42-month category followed by an increase.

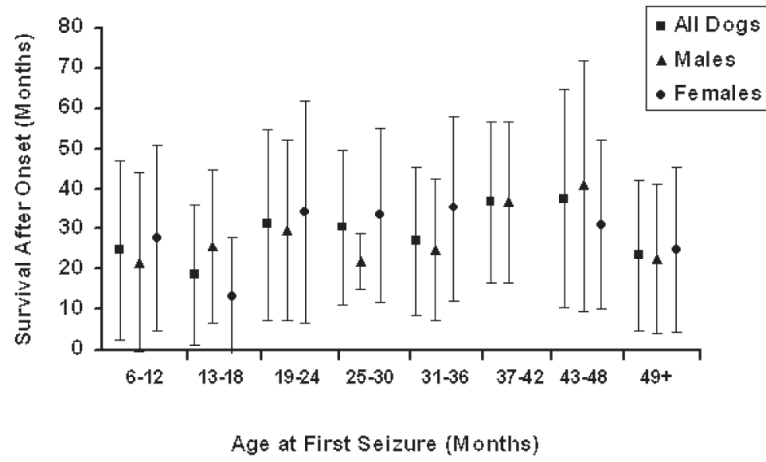


Fig 2. Life expectancy plotted against age at first seizure (\pm SEM). There was no statistically significant difference between any of the groups ($P < .05$).

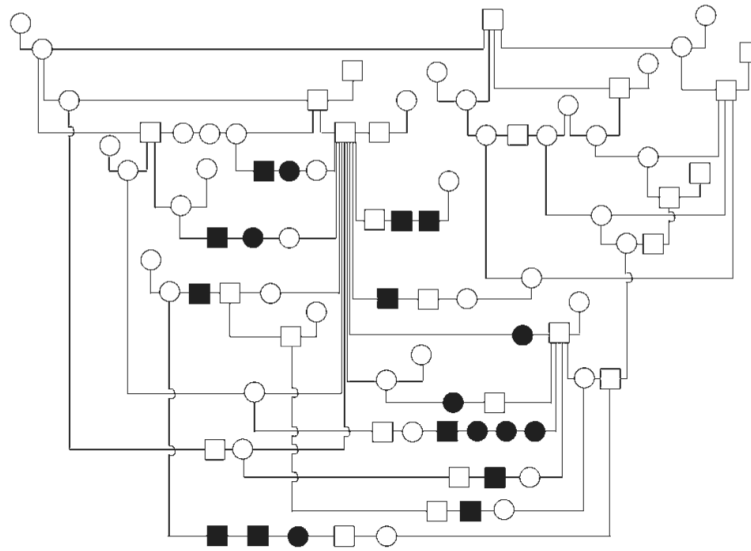


Fig 3. Small portion of the much larger pedigree of Irish Wolf-hounds with idiopathic epilepsy. Squares and circles represent males and females, respectively. Open and filled symbols designate normal dogs and affected Irish Wolfhounds, respectively. Although not always indicated, all dogs in this pedigree have common ancestors.