# Giant Schnauzer Epilepsy/Seizure Study Report 2020

## Introduction

Epilepsy is the most common long-term neurological disorder experienced by dogs and is described as at least two unprovoked seizures occurring more than 24 hours apart. There is currently no specific diagnostic or DNA test available to determine whether a dog is affected, and the lack of a definitive diagnostic test and the variable age of onset makes it very difficult for breeders to select against the disorder [1]. The diagnosis is one of exclusion, where veterinary tests are performed in order to rule out any underlying cause, if no cause is found a diagnosis of Idiopathic Epilepsy is made, which means Epilepsy of unknown origin.

In April 2017 an epilepsy/seizure study commenced aimed at obtaining information from UK Giant Schnauzer owners. The purpose of the study was to initially identify individual dogs that met with the specific criteria for the Animal Health Trust's (AHT) 'Give a Dog a Genome' project (GDG). The AHT selected epilepsy in the Giant Schnauzer as a breed condition for which they would undertake a whole genome sequence. For the research project the AHT required a number of samples from which they would anonymously choose one affected Giant with idiopathic epilepsy. It was also hoped that additional dogs may potentially help with any other future research into the inherited form of epilepsy. The seizure study also served a dual purpose with an aim to try and determine the prevalence of seizures, and potentially highlight any causes and/or triggers for seizures, any familial links, what treatment is available, and generally provide a better understanding of the nature of seizures/epilepsy within the breed.

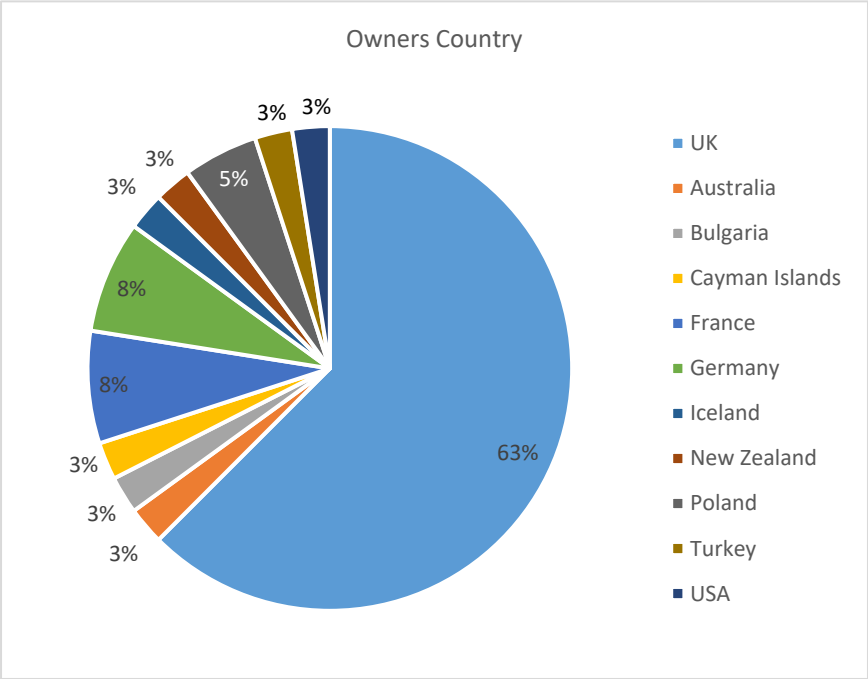
The study was advertised via breed club websites, social media pages and club magazines. In addition, the UK Kennel Club initially emailed registered Giant Schnauzer owners from the previous 10 years and requested those with affected dogs to take part in the online study. The Kennel Club had email contacts for 691 registered Giants, of which 412 emails were delivered successfully. Owners who had previously informed the breed club of a Giant having seizures in the past were also contacted and asked to take part in the study retrospectively.

The seizure study was left running for a significant amount of time in order to obtain a sufficient number of participants that may provide an analysis. No time limit was specified for affected dogs, and up to the 1st May 2020, after 3 years, 39 Giant Schnauzers had taken part in the study having seizures/epilepsy. In addition, 1 Giant Schnauzer cross breed from overseas participated and is included in the study figures also. Four of the dogs were entered anonymously without a registered Kennel Club name from overseas, and these have also been included in the study in good faith. The year of birth of reported dogs ranged from 1998-2018 and during this same period 5,052 Giant Schnauzer puppies were registered in the UK. Of the 5,052 puppies registered in the UK only 0.57% (29) participated in the seizure study. However, it was not possible for each individual owner of all dogs to be contacted or reached via advertising, and as such care must be taken interpreting the results as the number of affected dogs that took part in the study is relatively low.

All dogs that took part in the study experienced 2 or more seizures more than 24 hours apart.

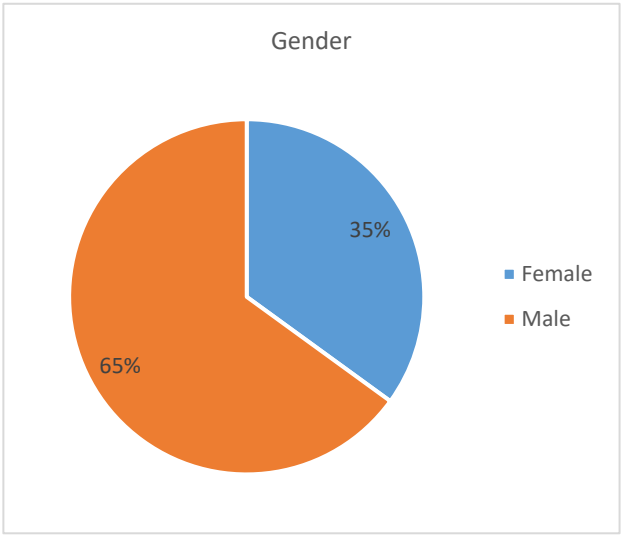
## Results

### Owners Country




Although the study was advertised in the UK, it was not limited to UK dogs only, 73% (29) of the dogs are known to have been bred in the UK, with 3 of these living in France and 1 in Cayman Islands. The remaining 27% (11) that took part were owned, and thought to have been bred overseas. However, the only overseas advertising would have been via UK social media groups, and therefore does not provide a representation of dogs worldwide.

### Gender

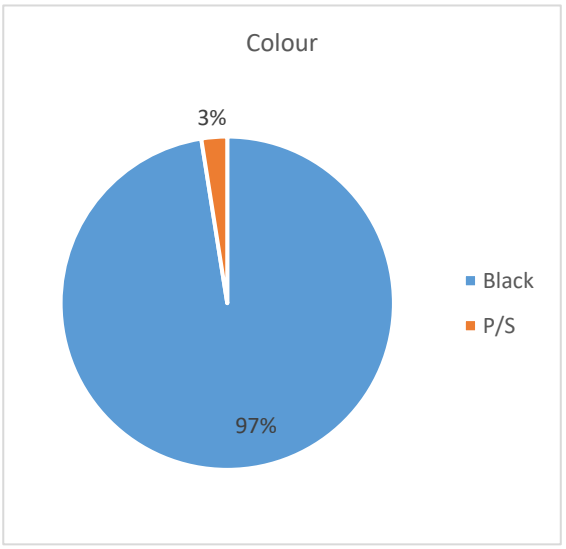



Males were 1.9 times as likely to be affected compared with females; 65% (26) were male, and 35% (14) were female.

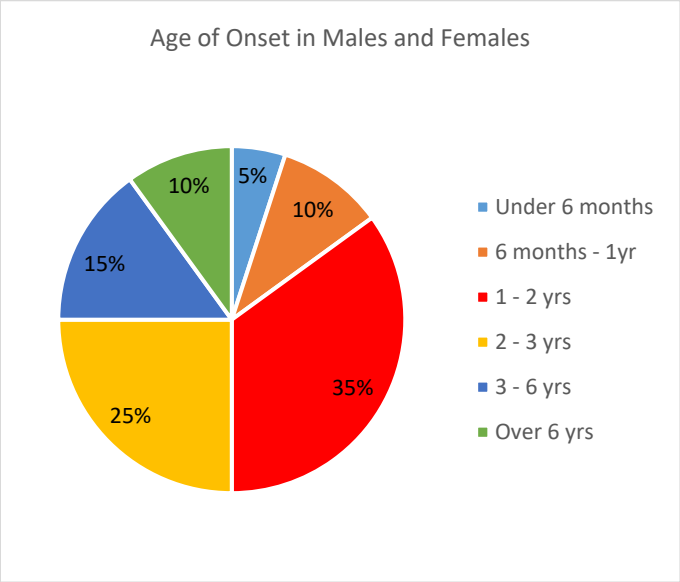
### Colour

The sample contained 97% (39) black Giant Schnauzers and 3% (1) pepper/salt. Three of the black dogs were a combination of pepper/salt and black breeding.

From 1998-2018 black Giant Schnauzer puppy registrations in the UK account for 88% (4,450) of all puppy registrations. 12% (586) were pepper/salt and 0.3% (16) were registered as a colour not recognised.



## Age of Onset (Males and Females)

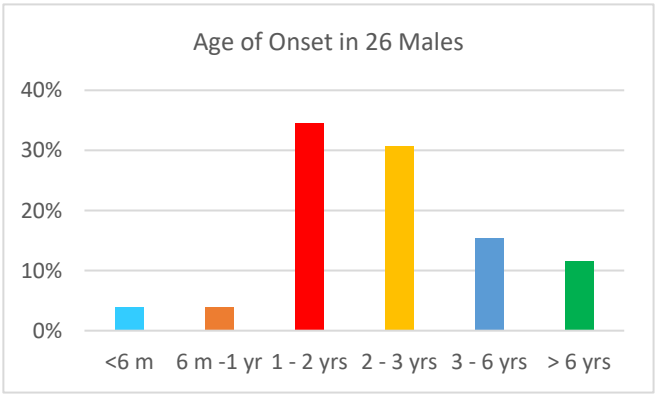


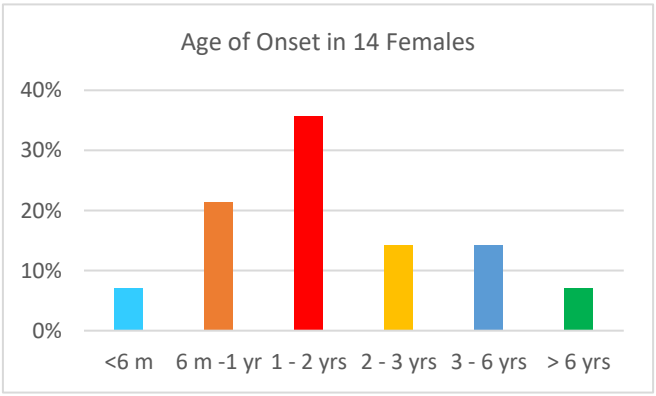

Only 5% (2) of the dogs had a first-time seizure under the age of 6 months. Although subsequent vet records identified one of these dogs may have been 10 months old. 10% (4) of the dogs were between 6 months and 1 year.

Of those that took part in the study the most common age of seizure onset was around the age of puberty; 35% (14) of the dogs were between 1 and 2 years, followed by 25% (10) between 2 and 3 years.

However, 15% (6) began having seizures aged 3 to 6 years, and only 10% (4) started having seizures over the age of 6 years.

## Comparison of the Age of Onset between Males and Females

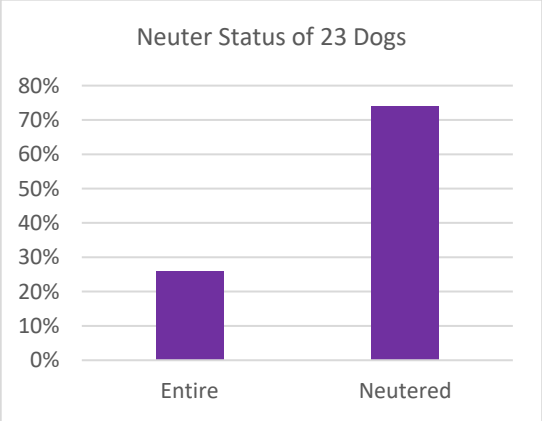


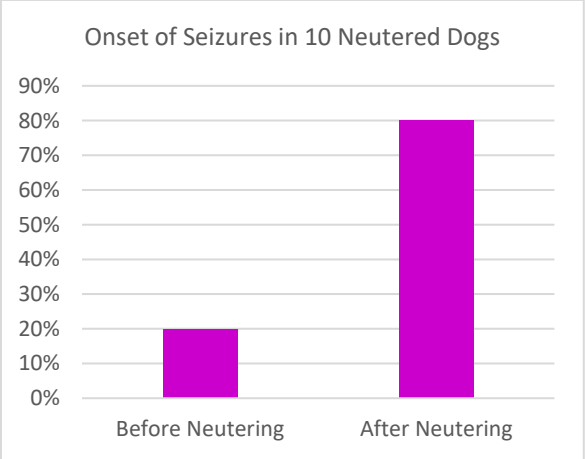




When comparing the age of onset between males and females, the study shows that 29% (4) of the female cohort started having seizures under 1 year compared to only 8% (2) of the males in the same age category. The age of onset for the majority of males, 35% (9) and also females, 36% (5) was between 1 and 2 years. However, more males, 31% (8) started having seizures between the age of 2 and 3 years, compared to 14% (2) of the females. In addition, 15% (4) of the males started having seizures between 3 and 6 years compared to only 14% (2) of the females. And 12% (3) of the males started having seizures over the age of 6 years compared to only 7% (1) of the females.

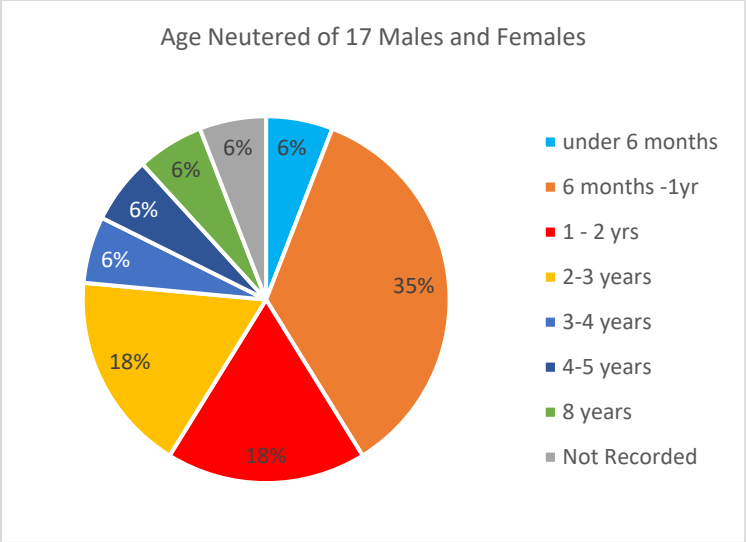
The most common age of onset in the female cohort was between 6 months and 2 years, and in the male cohort between 1 and 3 years.

**Neuter Status (Castration/Spaying) In Giant Schnauzers Having Seizures**



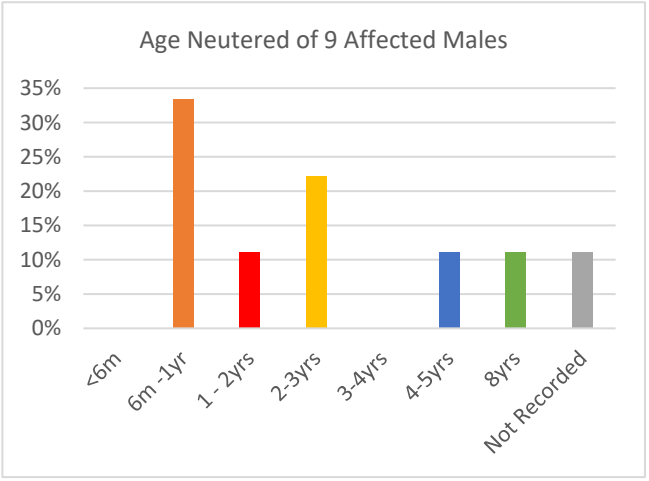



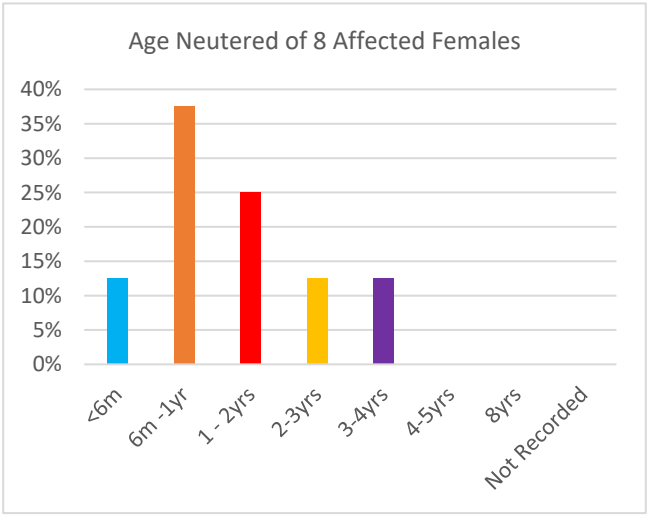

Only 58% (23) of the participants had their neuter status identified, and of these 74% (17) were castrated or spayed, and 26% (6) were entire. It was only possible to determine whether seizures started before or after neutering in 25% (10) of the dogs, in which case 80% (8) started having seizures following castration or spaying, and 20% (2) started having seizures before neutering.




Of the 74% (17) identified as being neutered, only 6% (1) of the dogs were neutered under the age of 6 months. The largest age group for neutering was between 6 months and 1 year; 35% (6). Followed by 18% (3) of the dogs neutered in each of the age brackets 1 to 2 years and 2 to 3 years. And 6% (1) of the dogs were neutered in each of the remaining age groups; 3 to 4 years, 4 to 5 years and 1 dog over the age of 8 years.

**Comparison of the Neuter Age between Males and Females**




None of the males from the sample were neutered under 6 months compared to 13% (1) of the female samples. In both males and females, the most common age for neutering was between the age of 6 months and 1year; 33% (3) of the males and 38% (3) females. Between the ages of 1 and 2 years 25% (2) of the females were neutered compared to 11% (1) of the males. Whereas an increased number of males, 22% (2), where neutered

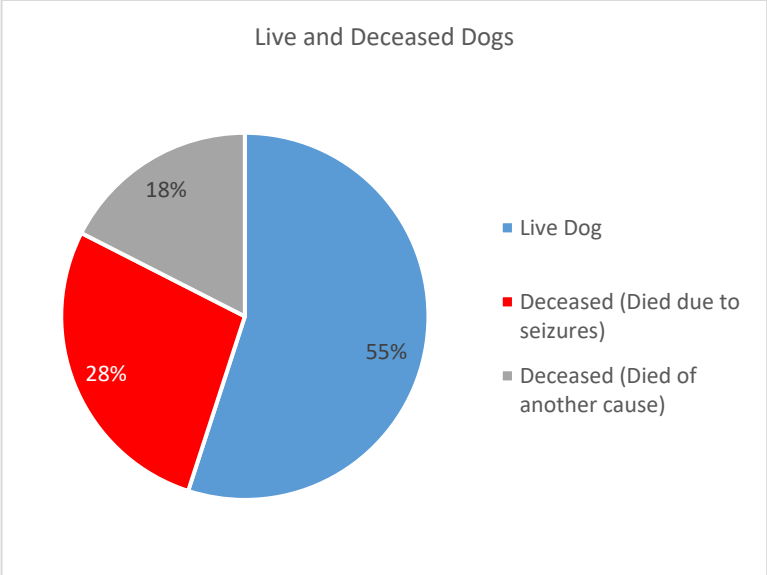
between 2 and 3 years, compared to only 13% (1) of the females in the same age category. No males were neutered between the age of 3 and 4 years, compared to 13% (1) of the females. And no females were neutered over the age of 4 years compared to 11% (1) of the males neutered between 4 and 5 years and 11% (1) aged 8 years. The age of neutering was not recorded for 1 male.

The graphs demonstrate that all of the females were neutered before 4 years of age, and mostly under 2 years. Between the age of 2 and 3 years more males were neutered compared to females, and males also continued to be neutered at an older age than females. This also correlates with the most common age of seizure onset in both males and females.

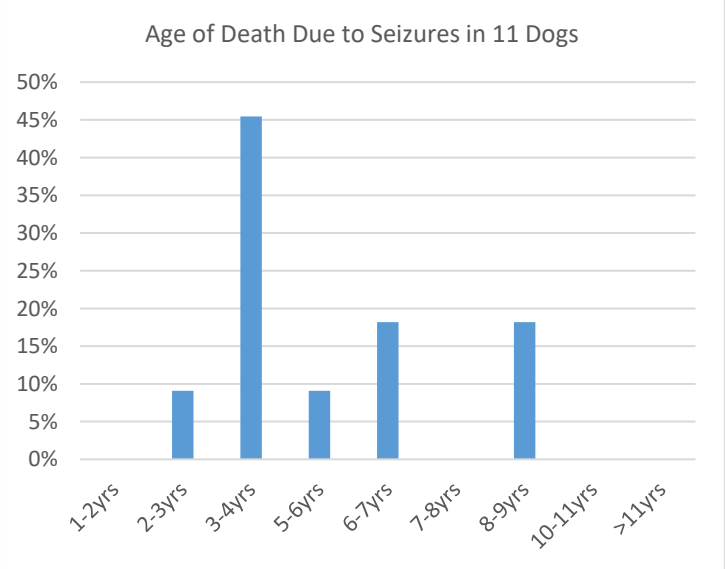
**Cause of Death**

Of the dogs that took part in the survey 55% (22) were currently alive and living with seizures, 28% (11) died as a direct result of seizures and 18% (7) died of another cause.

Of those that died as a direct result of seizures 55% (6) were euthanised, and 45% (5) died during a seizure, one of which had an underlying heart condition.

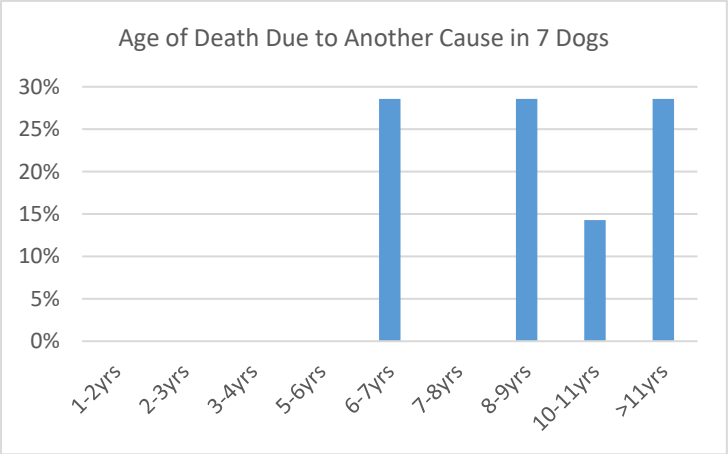



**Age of Death - Dogs That Died Due to Seizures**




None of the dogs that died as a direct result of seizures died under the age of 2 years. 9% (1) of the dogs died between 2 and 3 years. And the most common age of death was between 3 and 4 years with 45% (5) dying at this age. 9% (1) of the dogs died between 5 and 6 years, and 18% (2) dogs died in each of the age categories between 6 and 7 years, and 8 to 9 years.

### Age of Death - Dogs That Died Due to Another Cause




The 7 dogs having seizures that died of another cause lived longer, with none dying before the age of 6 years. 29% (2) of the dogs died between 6 and 7 years, one being due to an accident and one having squamous cell carcinoma of the toe. A further 29% (2) of the dogs died between 8 and 9 years; 1 cancer and 1 renal failure. 14% (1) of the dogs lived to between 10 and 11 years also having renal failure. And 29% (2) of the dogs lived over the age of 11 years, 1 had cancer and the other had spinal degeneration. Of the 2 dogs that died of renal failure owners reported that their dogs did not receive anti-epileptic medication.

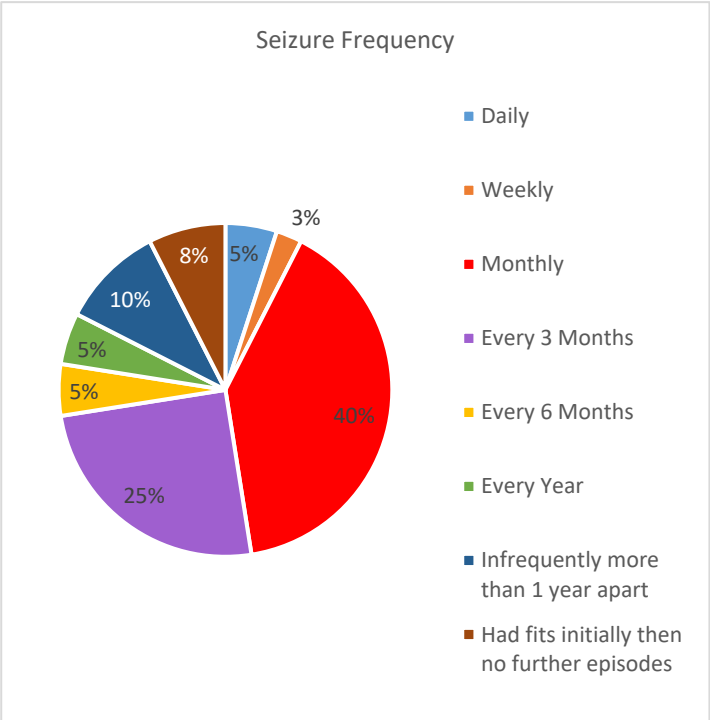
### Seizure Frequency

73% (29) of the dogs that took part in the survey had seizures quite frequently; 5% (2) on a daily basis, 3% (1) on a weekly basis, the majority of 40% (16), had seizures every month and 25% (10) every 3 months.

The remainder of the dogs had seizures less frequently; 5% (2) every 6 months, 5% (2) every year and 10% (4) had seizures more than 1 year apart. In 8% (3) of the dogs, seizures were reported to have stopped with no further episodes.

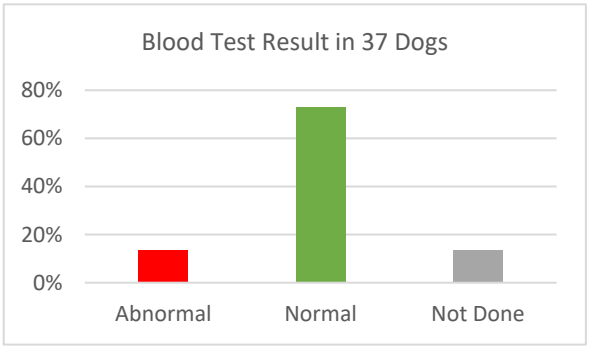
Of those having seizures infrequently, one owner documented an association with a full moon. In addition, another owner reported the frequency of the seizures related to environmental events such as thunder or fireworks, or a change in routine such as a vacation.

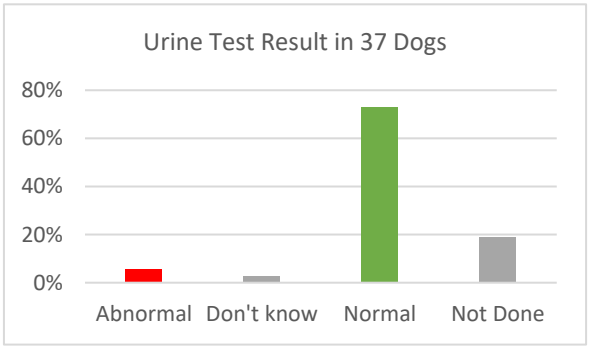
The owner of another dog commented that the frequency of seizures had a correlation with unstable barometric air pressure. And two other owners stated the frequency may be affected by flea treatment triggering seizures and stress.



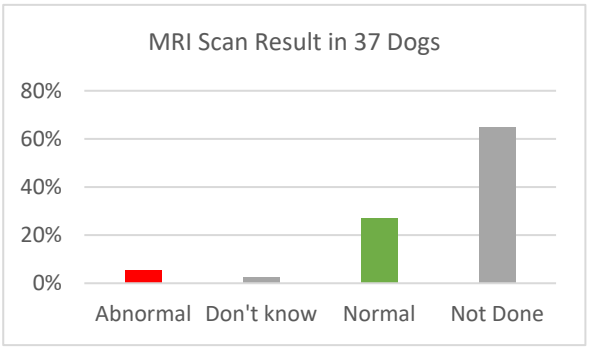

### Veterinary Attention and Testing

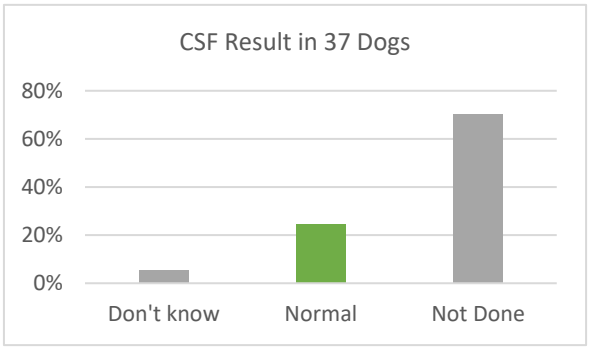
The majority of the dogs, 93% (37), attended a veterinary practice due to seizures, only 8% (3) of the dogs didn't see a vet at all. Of the 3 that didn't see a vet, all had infrequent seizures more than a year apart, or had seizures initially which then stopped. Most of the dogs seen by a vet had normal blood results 73% (27), and 14% (5) were reported as abnormal; 1 had kidney problems and Addison's disease, and another had hypothyroidism, otherwise the abnormal result was not specified. The majority of urine test results were also found to be normal 73% (27). Of those that attended a veterinary practice 11% (4) received no tests at all.



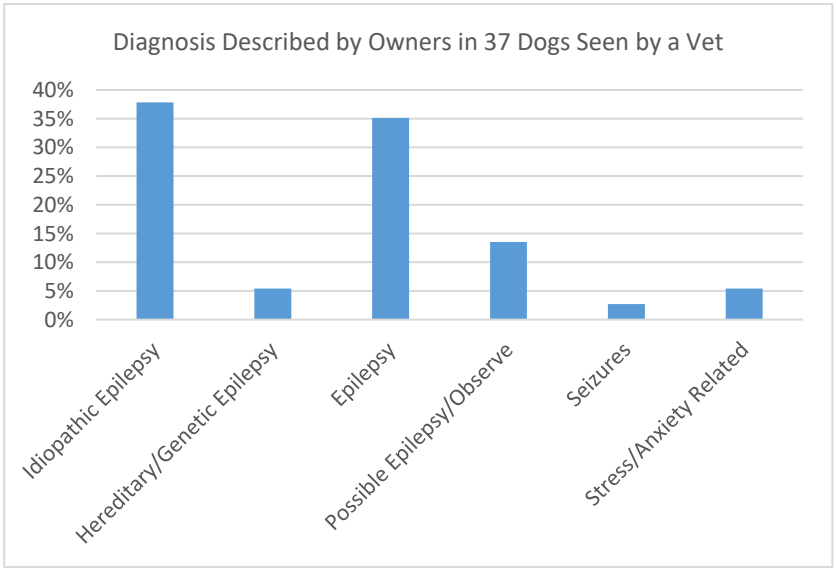

Of the 37 dogs, 65% (24) did not undergo either a magnetic resonance imaging (MRI) scan of the brain or cerebrospinal fluid (CSF) analysis to rule out intercranial problems or inflammation. Of those who had an MRI, 27% (10) were 'normal' and 5% (2) were recorded, by the owner, as 'abnormal', although the abnormality was not identified. 24% (9) dogs had a CSF analysis and all recorded 'normal'. Only 16% (6) dogs had all tests completed with 'normal' results, meeting the criteria for the Animal Health Trust's 'Give A Dog A Genome' project (see p19). Five of these, with no underlying health conditions, submitted DNA (cheek swab) samples for the project.



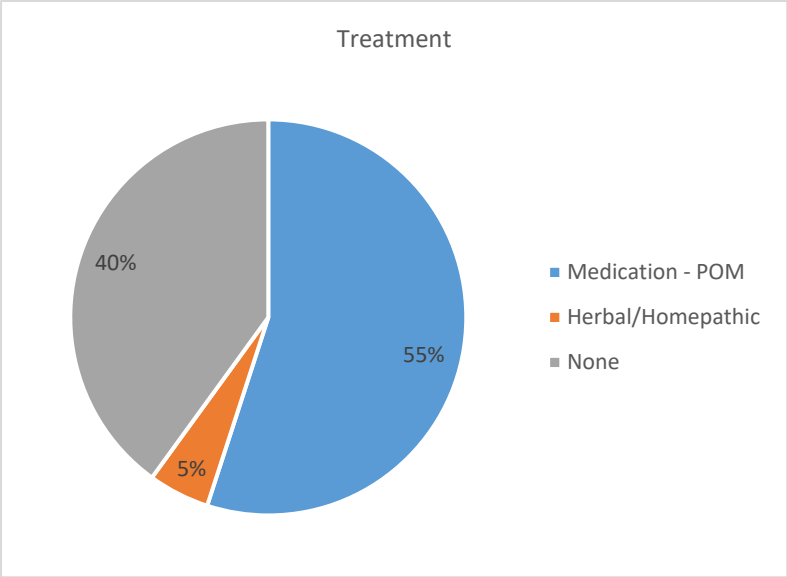




**Owners Description of the Veterinary Diagnosis**

The most common diagnosis owners reported was either Idiopathic Epilepsy in 38% (14) of the dogs or Epilepsy in 35% (13). 5% (2) of the owners commented their dog had been diagnosed with hereditary or genetic epilepsy. 5% (2) of the owners described their dog as being diagnosed with stress or anxiety related seizures, and 14% (5) of the owners commented their dog had possible epilepsy and/or to observe. 3% (1) of the owners commented their dog had been diagnosed with seizures.

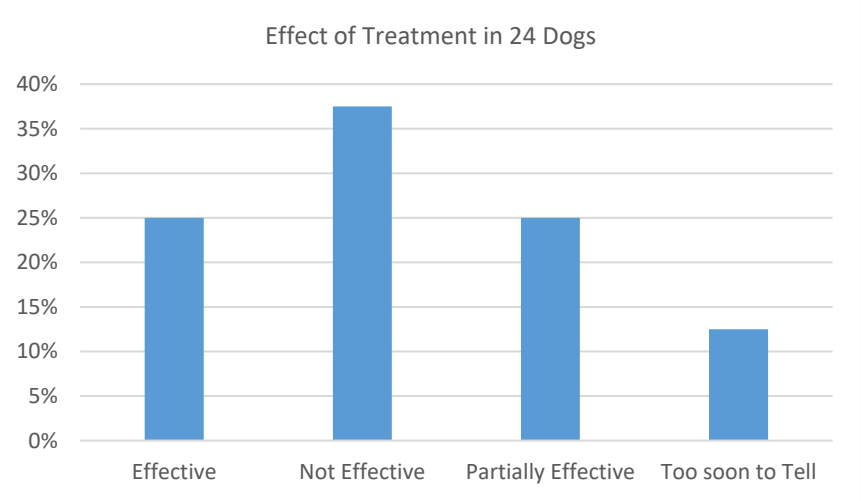


## Treatment

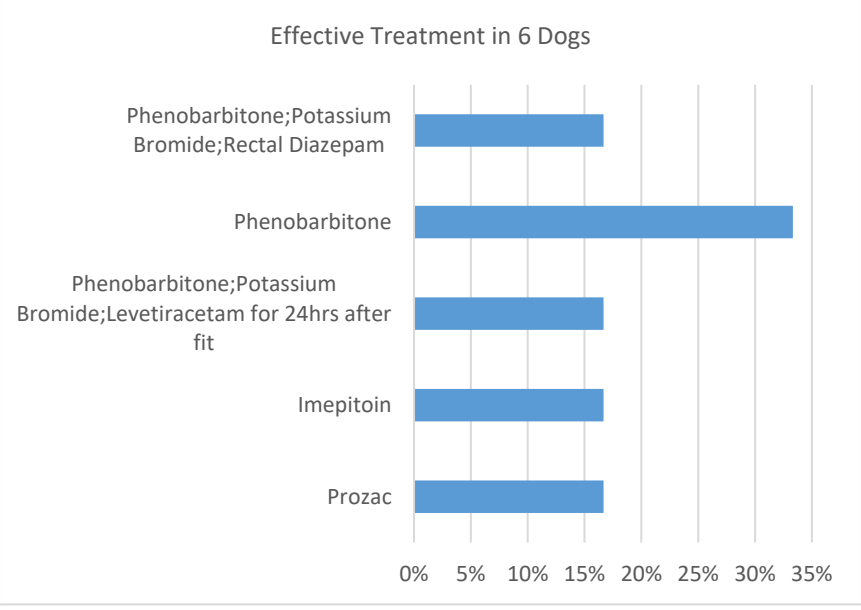



Owners were asked if their dog received treatment for seizures, 55% (22) of the dogs received prescription only medication, 5% (2) were given herbal or homeopathic remedies and 40% (16) were given no treatment at all. In addition, 1 of the dogs receiving prescription only medication was also given CBD oil.

## Success of Treatments



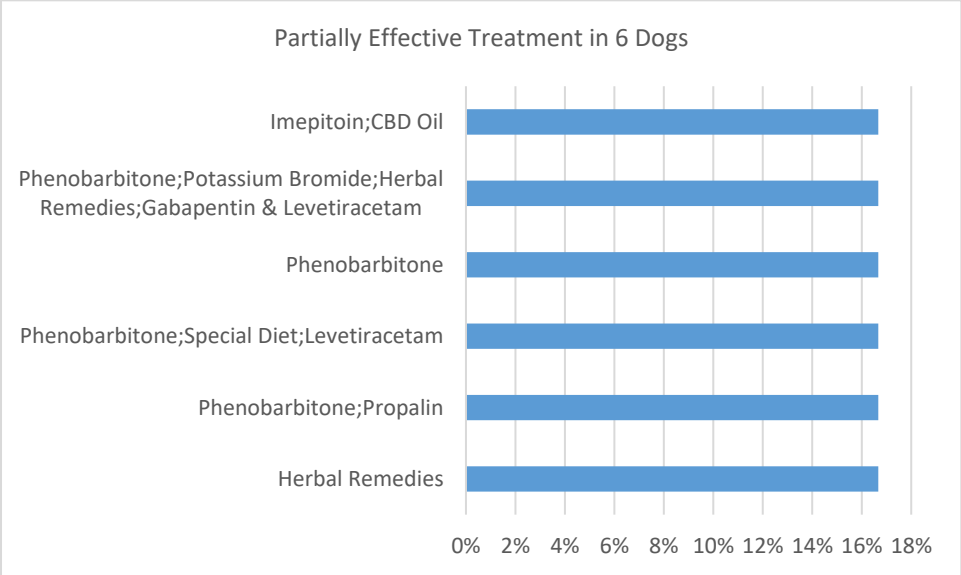

Owners indicated if the treatment they were giving had been effective. Improvement was seen in 50% (12) of the dogs. Of these 25% (6) said the treatment had been effective and 25% (6) said there had been a partial improvement. Those who reported a partial response noted either a slight reduction in the number of seizures or the intensity. 38% (9) of the owners indicated their dog showed no improvement at all with treatment. And 13% (3) of the owners stated it was too soon to tell.



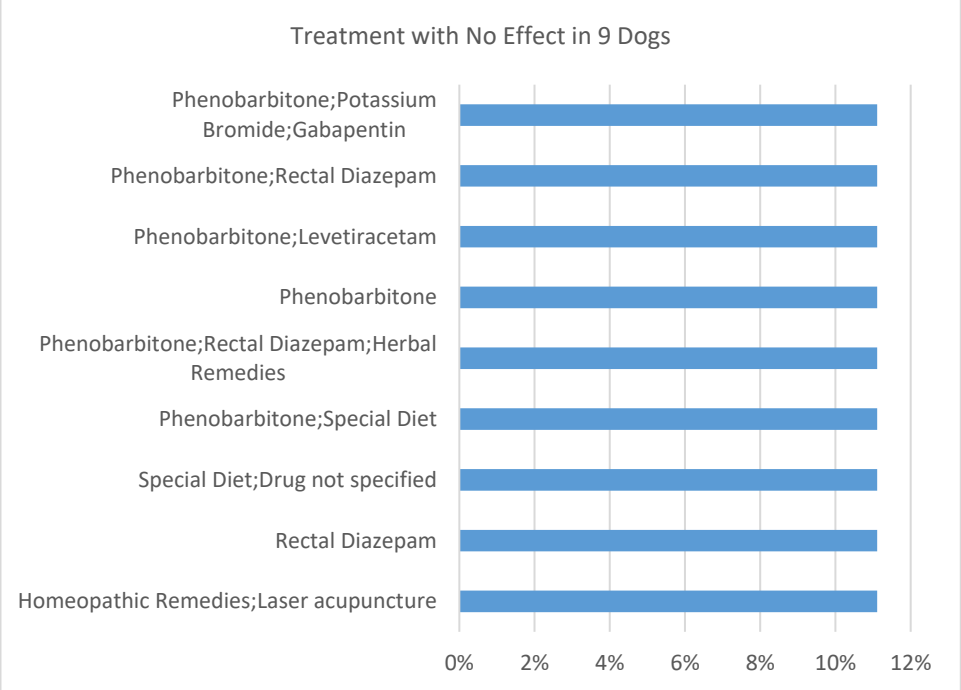

Where the owner reported improvement following treatment 33% (2) of the dogs received a single drug therapy treatment of phenobarbitone. 17% (1) received a single drug therapy of Imepitoin, and 17% (1) having anxiety related seizures improved with Prozac, although the seizure frequency was quite low; more than a year apart.

17% (1) of the dogs improved on a combination of phenobarbitone and potassium bromide and 1 dog was also prescribed rectal diazepam. A further 17% (1) of the dogs improved on a combination of phenobarbitone, potassium bromide and levetiracetam for 24 hours post seizure, reporting a reduction in seizure frequency from monthly to 3 monthly.

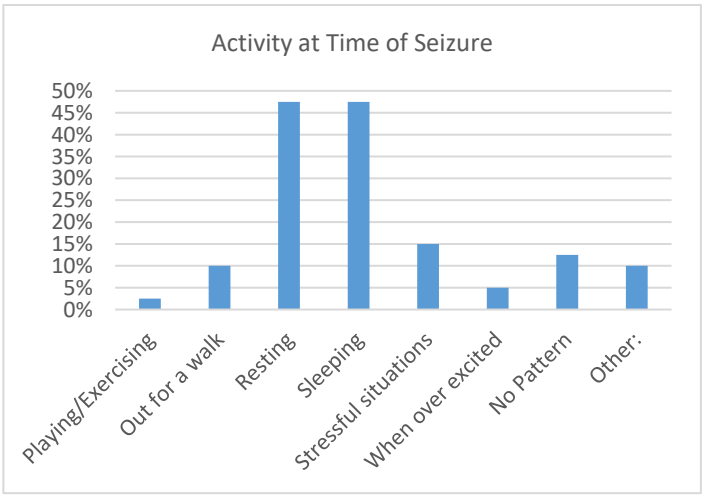
17% (1) of each of the 6 dogs that had a partial improvement following treatment were also prescribed Imepitoin, phenobarbitone, potassium bromide and levetiracetam, either as a single or combination drug therapy. 17% (1) also received Gabapentin as part of the combination. 17% (1) of the owners additionally gave CBD oil. And 17% (1) received an herbal calming remedy where the first-time seizure was thought to be stress related.




11% (1) of each of the 9 dogs that saw no improvement were also prescribed the same medications; Imepitoin, phenobarbitone, potassium bromide, levetiracetam, and gabapentin either as a single or combination drug therapy. Including 11% (1) given homeopathic remedies and laser acupuncture.



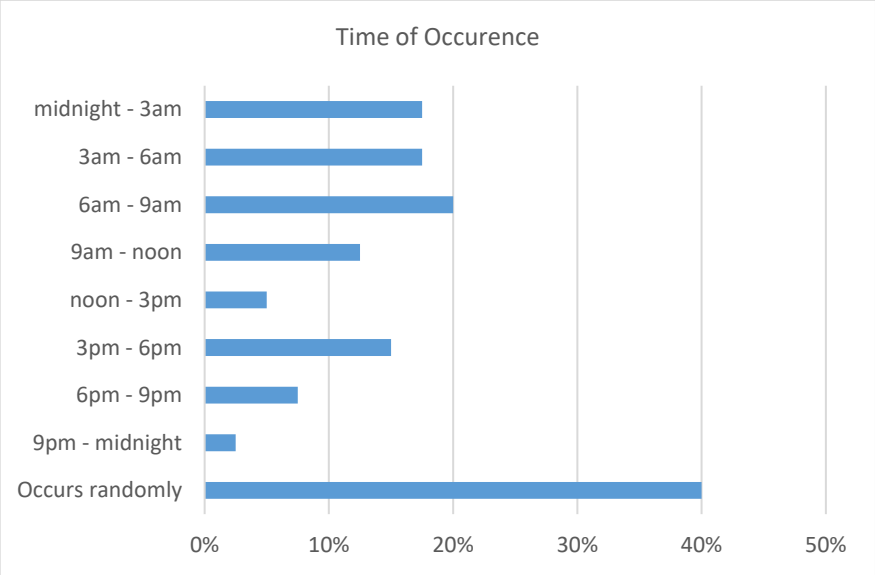

**Activity at Time of Seizure**




Owners were asked to identify what their dog was doing at the time a seizure occurred, a number of owners reported the same dog may have seizures under different circumstances.

46% (19) of the dogs had seizures whilst resting and equally 46% (19) whilst sleeping. The next most common activity involved stressful situations in 15% (6) dogs, followed by 13% (5) dogs where no pattern could be identified. 10% (4) had seizures when out walking, 3% (1) when exercising, and 5% (2) when over excited. Of the 10% (4) recorded as 'Other', 1 owner commented seizures occurred during clipping/grooming which could be either noise or vibration sensitivity or a stress reaction, although the participant stated the same dog did have seizures at other times also. One owner commented that seizures never occurred on a walk, and one noted it occurred after vomiting. In addition, an owner stated seizures occurred just being outside.

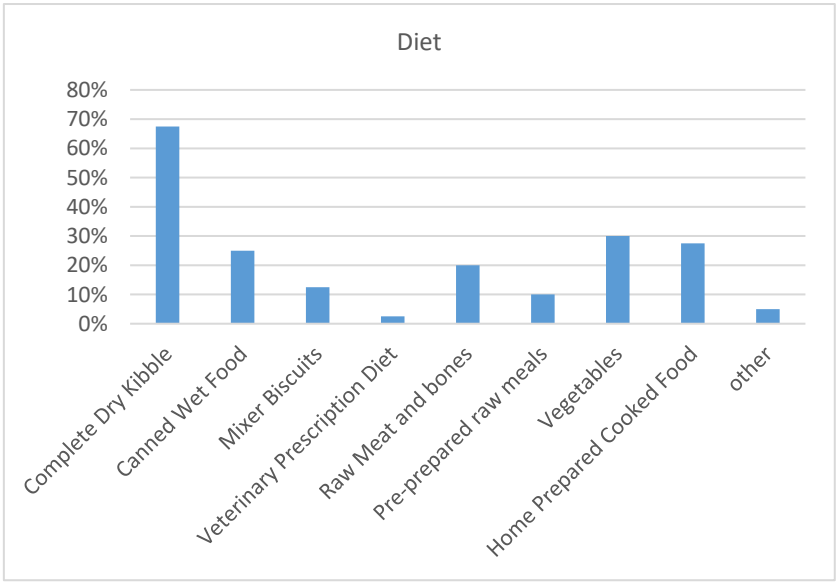
## Time of Occurrence




50% (20) of the owners reported that the same dog may have seizures at more than one time of day. The results of the study show that seizures occurred at random times in 40% (16) of the dogs. However, 55% (22) occurred during the night from midnight to 9am, compared to 30% (12) dogs having a seizure in the afternoon or evening from midday to midnight.

Half of the dogs 50% (20) only ever had a seizure at the same time.

## Diet

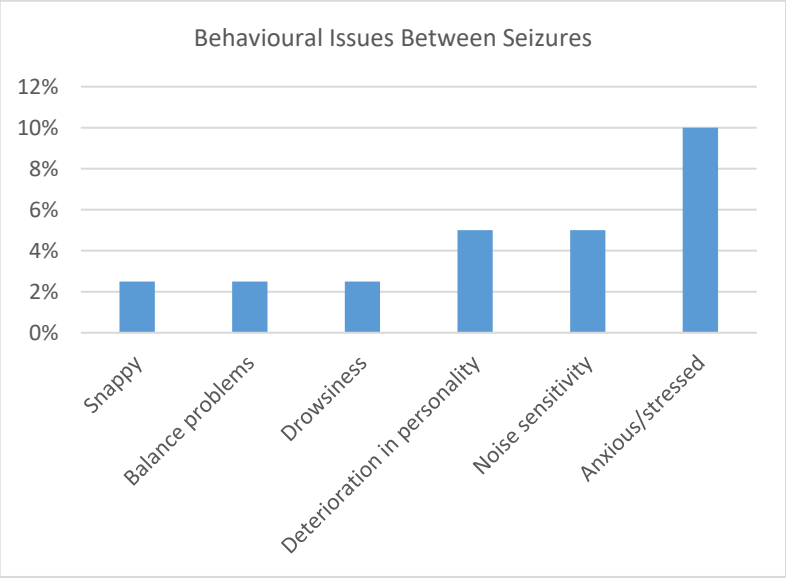



In order to determine if there were any dietary associations, owners were asked to specify what type of diet their dog received. Most dogs were fed a combination diet, however 68% (27) of the dogs were fed complete dry kibble. Only 9 of these received an exclusive complete dry kibble diet, and the remainder were fed a combination of complete kibble along with one or more of canned wet food, raw meat and bones, home prepared food and/or vegetables. Of those that did not receive complete dry kibble at all, 8% (3) were fed mixer biscuits as a combination food. And 13% (5) were raw fed with the addition of vegetables and home cooked food. A further 5% (2) received a pre-prepared raw diet and 5% (2) received canned wet food only. 3% (1) received a veterinary prescription urinary diet due to struvite crystals. Of those recorded as 'other'; these included pasta, egg and sardines given as an addition to raw food, and not fed as a single dietary source.

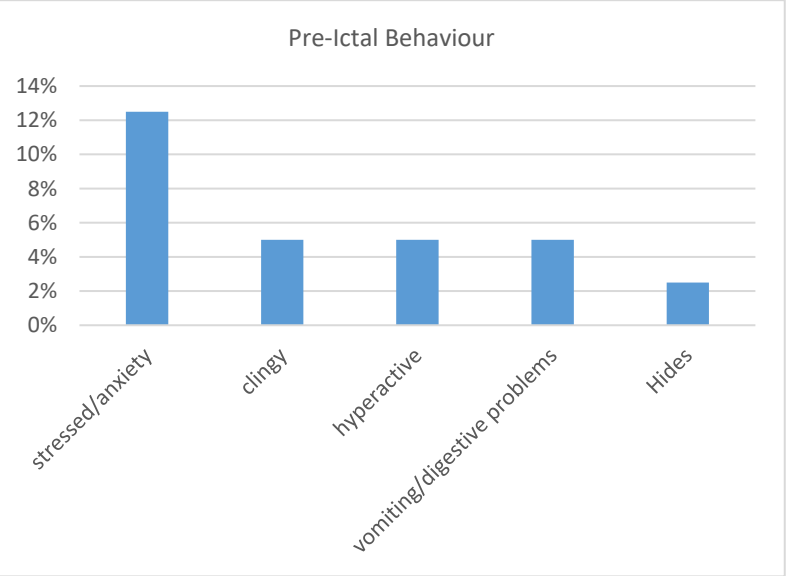
It was not possible to determine from the survey if dogs were fed the reported diet prior to seizures or whether the diet was changed following seizure onset.

When asked which brand of food dogs received, no particular brand stood out significantly and 26 different brands of food were used with no more than 2-3 dogs receiving the same brand.

## Behavioural Issues

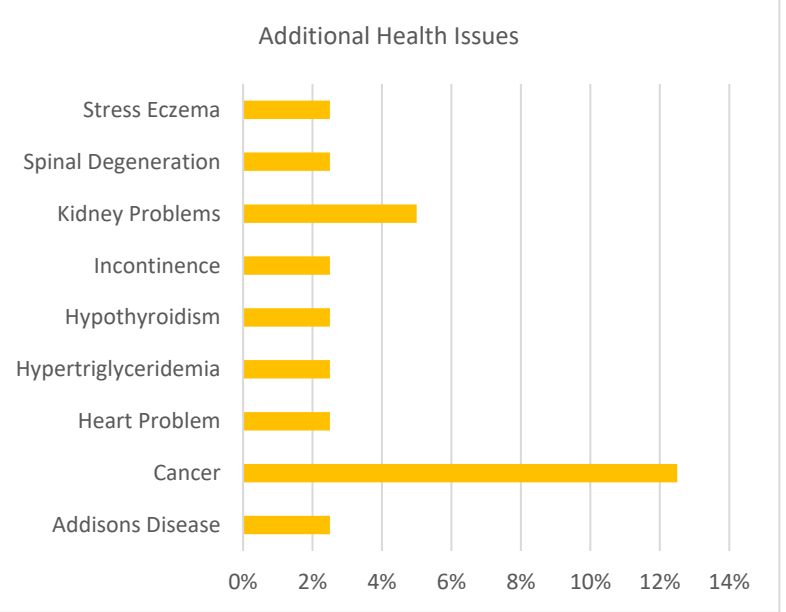



Most owners, 73% (29), stated their dog had no behavioural issues between seizures, and of those who commented some described symptoms that occurred just before or just after a seizure, along with side effects of medication. Those who noted behavioural issues between seizures, 10% (4) described their dog as having an anxious or generally stressed temperament and 5% (2) were bothered by loud noises. 5% (2) of the owners also noted their dog suffered a general deterioration in personality and 3% (1) exhibited drowsiness. 3% (1) of the dogs was snappy and an additional 3% (1) had balance problems.



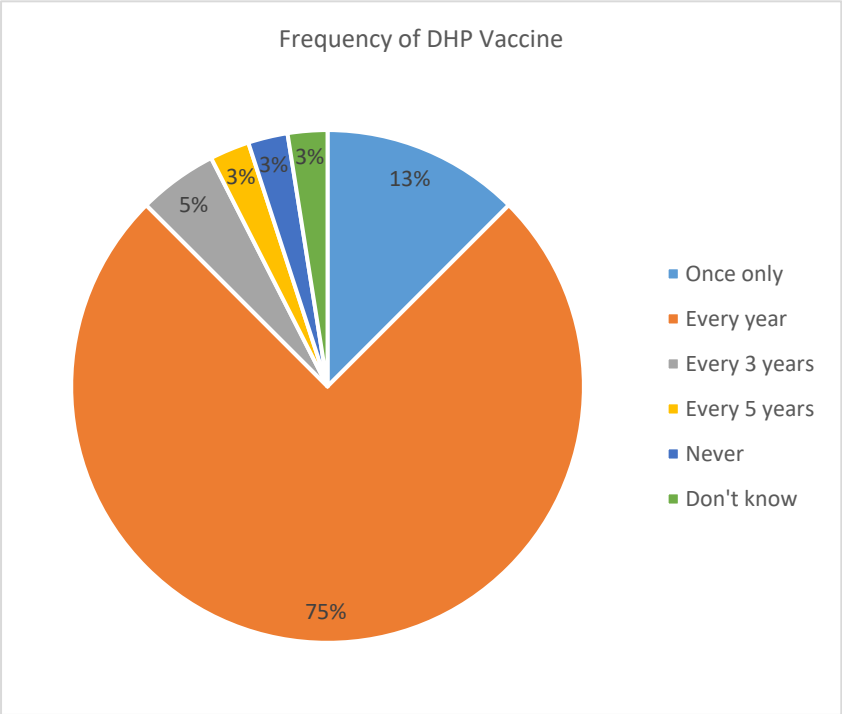

The period before a seizure begins is known as the pre-ictal phase. During this period of time owners identified their dog's behaviour and were able to determine a fit was about to occur. Most often 13% (5) of the dogs displayed signs of becoming quite stressed or anxious and 5% (2) became hyperactive. 5% (2) would seek out their owner and become clingier whilst another 3% (1) of the dogs found somewhere to hide such as under a table. 5% (2) of the owners identified that their dog vomits or has digestive issues just prior to a seizure. However, since a lot of dogs were reported as having seizures whilst resting or sleeping the pre-ictal phase may be unnoticed.

## Additional Health Issues




A total of 25% (10) owners reported additional health conditions, with 8% (3) having more than one additional health issue. The most common additional illness was cancer recorded by 13% (5) of the owners. 3% (1) also had hypertriglyceridemia. And another 3% (1) also had spinal degeneration as well as stress eczema. 5% (2) of the dogs had kidney problems, 1 of which also had Addison's disease. 3% (1) of the owners noted incontinence in a male after neutering and onset of seizures. 3% (1) of the dogs had a heart condition; aortic stenosis. Hypothyroidism was also reported in 3% (1).

## Vaccinations




### Distemper/Hepatitis/Parvo

Most dogs 75% (30) were vaccinated every year for Distemper, hepatitis and parvo.

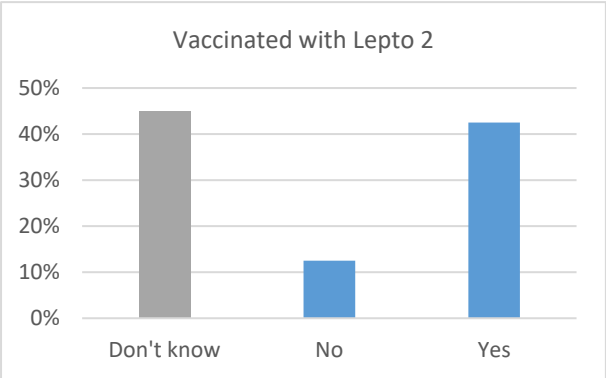
13% (5) were vaccinated once only.

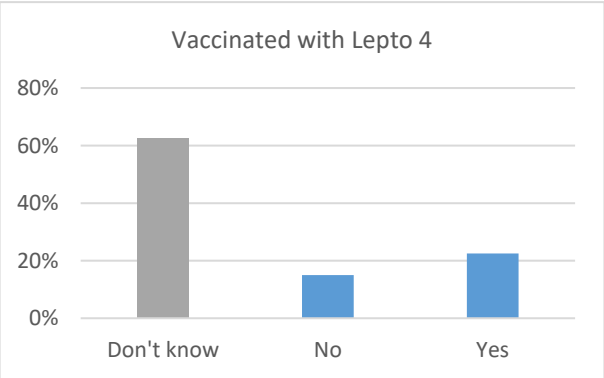
3% (1) of the dogs were vaccinated every 5 years and a further 3% (1) never received a vaccination at all.

Only 5 % (3) were vaccinated every 3 years as per the Veterinary Medicines Directorate authorised vaccinations schedule for dogs [15].

### Leptospirosis Vaccine

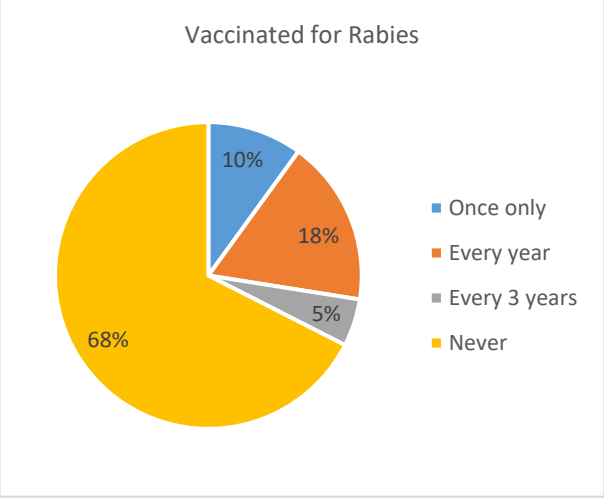
Owners were more unsure regarding Leptospirosis vaccination, however 40% (16) of the dogs received the vaccination every year. 8% (3) of the dogs received the vaccination only once, and 6% (2) owners stated their dog received leptospirosis vaccination either every 3 or every 5 years. A large number of owners were unaware whether their dog received Lepto 2 vaccine or Lepto 4; 45% (18) and 63% (25) respectively. Of those who were aware which vaccine had been given 43% (17) stated Lepto 2 and 23% (9) recorded Lepto 4.



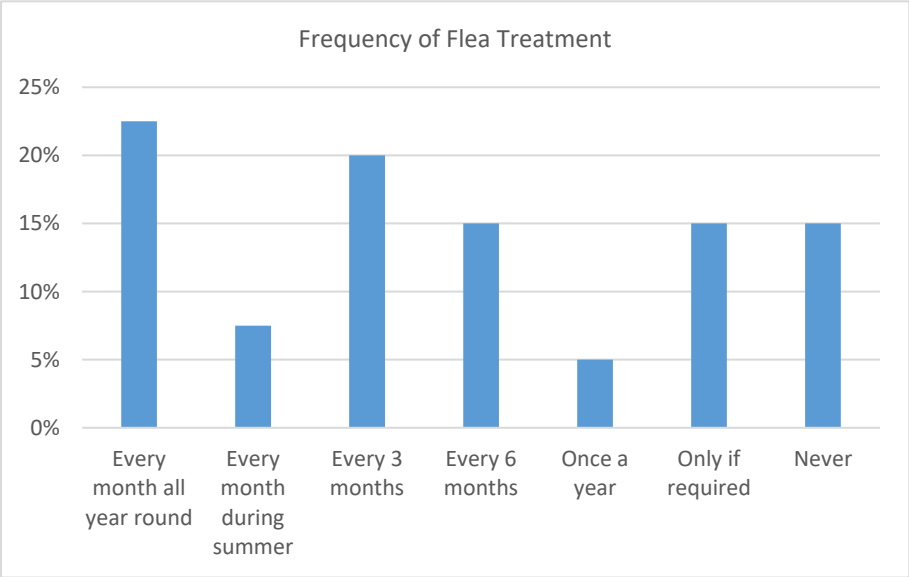




### Rabies Vaccination

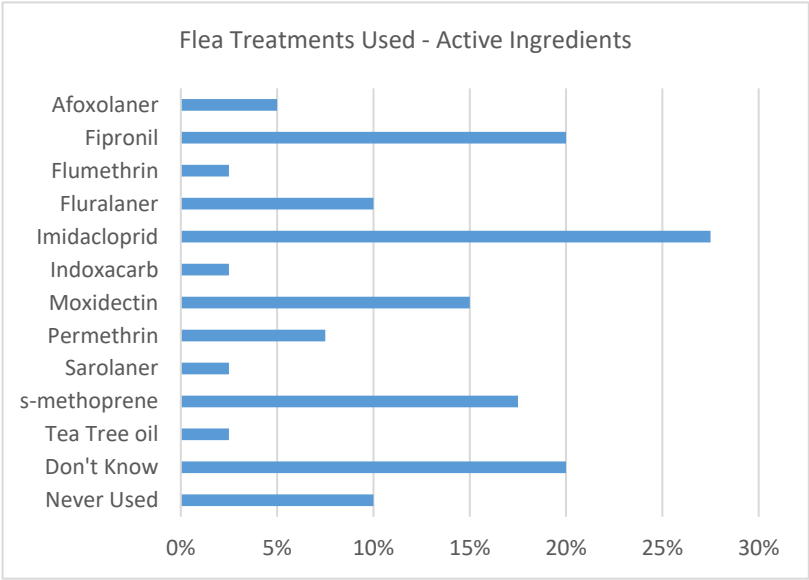
Since rabies vaccination is only required when travelling abroad it is not surprising that most dogs, 68% (27), never received a rabies vaccination. 10% (4) were vaccinated only once, and 23% (9) received a rabies vaccination regularly either annually or every 3 years.



## Flea Treatments Used



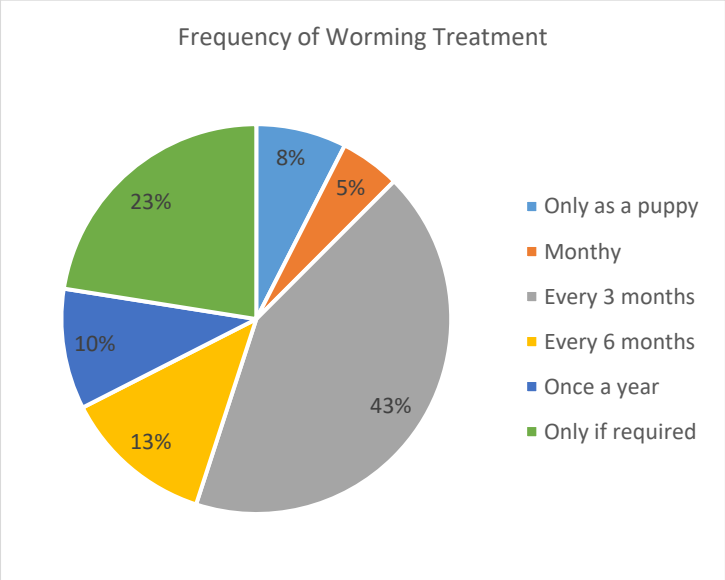

Most dogs, 65% (26), were flea treated on a regular basis, either monthly, or every 3 to 6 months. However, the owners of 15% (6) stated their dog received no flea treated at all. And a further 15% (6) were treated only if required.




A number of flea treatment products contain more than one active ingredient. However, insecticides containing Imidacloprid were amongst the most common flea treatments used by 28% (11). These comprised a variety of products; Advantage, Advantix, Advocate, Seresto (also containing Flumethrin), Prinovox and MiPet Endectrid. The second most common flea treatment contained the broad-spectrum insecticide Fipronil, found in Frontline products in conjunction with s-methoprene used by 20% (8). 18% (7) of the dogs received a pesticide belonging to the Isoxazoline class; Bravecto (fluralaner), Nexgard (afoxalaner) and Simparica (sarolaner). 15% (6) of the dogs received Moxidectin found in Advocate, Prinovox and MiPet Endectrid. Indoxacarb, contained in Activyl, was given to 3% (1) of the dogs, and Permethrin an active ingredient found in Advantix and Exspot was given to 8% (3) of the dogs. 10% (4) stated they never used any flea treatments, and 3% (1) used tea tree oil.

Out of the owners who completed the study 20% (8) did not know which flea treatment their dog received.

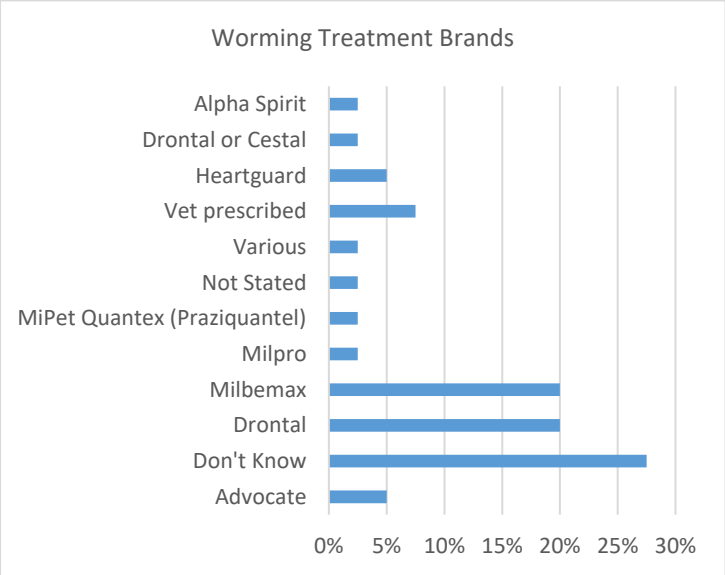
### Worming Treatment




All dogs received worming treatment, however 8% (3) were treated only as a puppy. Heartguard, a monthly treatment for heart worm, was given to 5% (2) of the dogs from different foreign countries.

Most dogs, 43% (17), were treated every 3 months. 13% (5) were treated every 6 months, and 10% (4) were treated annually.

23% (9) were treated only if required.




The majority of owners, 28% (11), were unsure which dewormer they administered. However, Drontal, 20% (8), and Milbemax, 20% (8), were the most common.

## Discussion

### Prevalence/Incidence

Prevalence and incidence are somewhat difficult to determine since all surveys were based entirely on voluntary completion and, as such, may be subject to under-recording and/or self-selection bias. The Canine Epilepsy Research Group at the Royal Veterinary College (RVC) was contacted via the Kennel Club Health and Research team; they had no specific information regarding epilepsy in the Giant Schnauzer, with just one or two reported as study participants in a handful of epilepsy treatment papers. The lack of RVC information relating to the breed simply reflects the relatively small population in the UK overall compared to other breeds. However, two independent UK health surveys, with the largest number of responses for Giant Schnauzers, both reported similar prevalence data. The UK Schnauzer Breed Clubs 2013/2014 Joint Schnauzer Breeds Health Survey reported a prevalence of 4% (11) out of 275 live Giant Schnauzers [2]. And the UK Kennel Club's Health Survey 2014 found the prevalence to be 3.7% (3/82 live dogs) [3]. The prevalence of epilepsy in the general dog population is not truly known but significant studies have estimated it to be 0.6-0.8% [4], therefore the prevalence in the Giant Schnauzer appears to be slightly above that of all dogs in general.

With the information obtained from the seizure study it was possible to identify the number of new cases per year compared to the number of UK puppy registrations, in order to determine the incidence of epilepsy. To provide a more accurate picture of the current status, those born and registered in the UK over the previous 10 years; 2009-2018 (19) dogs, were compared against UK KC puppy registrations for the same period (2,194), indicating an incidence of 0.9% (see Table 1).

Therefore, whilst 3.7 - 4% of the population may be living with epilepsy the seizure study shows that the risk of a puppy developing epilepsy was 0.9%.

In addition, males in the study were 1.9 times more likely to be affected than females.

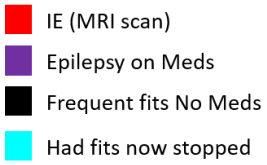
| Year | Pups Registered | Affected | % Affected |
|---|---|---|---|
| 2009 | 214 | 2 | 0.9% |
| 2010 | 228 | 4 | 1.8% |
| 2011 | 214 | 1 | 0.5% |
| 2012 | 221 | 2 | 0.9% |
| 2013 | 187 | 3 | 1.6% |
| 2014 | 242 | 4 | 1.7% |
| 2015 | 188 | 2 | 1.1% |
| 2016 | 243 | 0 | 0.0% |
| 2017 | 238 | 0 | 0.0% |
| 2018 | 219 | 1 | 0.5% |

*Table 1*

**Inheritance and Breeding**

In order to determine whether a possible inheritance pattern could be identified, in addition to any potential breeding advice, following the initial cohort of the study, pedigree diagrams were drawn using Pedigree Draw online software from 3 groups of dogs. The diagrams and information initially available from the first wave of dogs captured by the seizure study were sent to the Kennel Club geneticists, and also the Animal Health Trust.

An example of a pedigree diagram from one group of dogs is shown below in Diagram 1. Males are represented by a square and females by a circle, the diagram shows one generation progressing to the next. The pedigree chart demonstrates the complexity due to inbreeding, since many dogs have multiple litters and are interrelated with different breeding partners. In Diagram 1 below, dogs linked with the same letter are the same dog often mated to another breeding partner. E.g. Male 'A' is linked to male 'A' since they identify the same dog. The males labelled 'F1' and 'F2' are actually brothers, however, due to the complexity of the diagram, it is difficult to show their relationship. The colour key shows the status of the seizures i.e. those in red are dogs diagnosed with Idiopathic Epilepsy following all veterinary examinations including normal MRI scan and CSF. Those with a diagonal line are thought to have died prematurely. The dogs shown on the diagram also share a number of common ancestors that each go back to the popular dogs that were used to shape the breed in the past. And as such, this further adds to the complexity since there are a larger number of unaffected healthy dogs that also go back to the same ancestry.



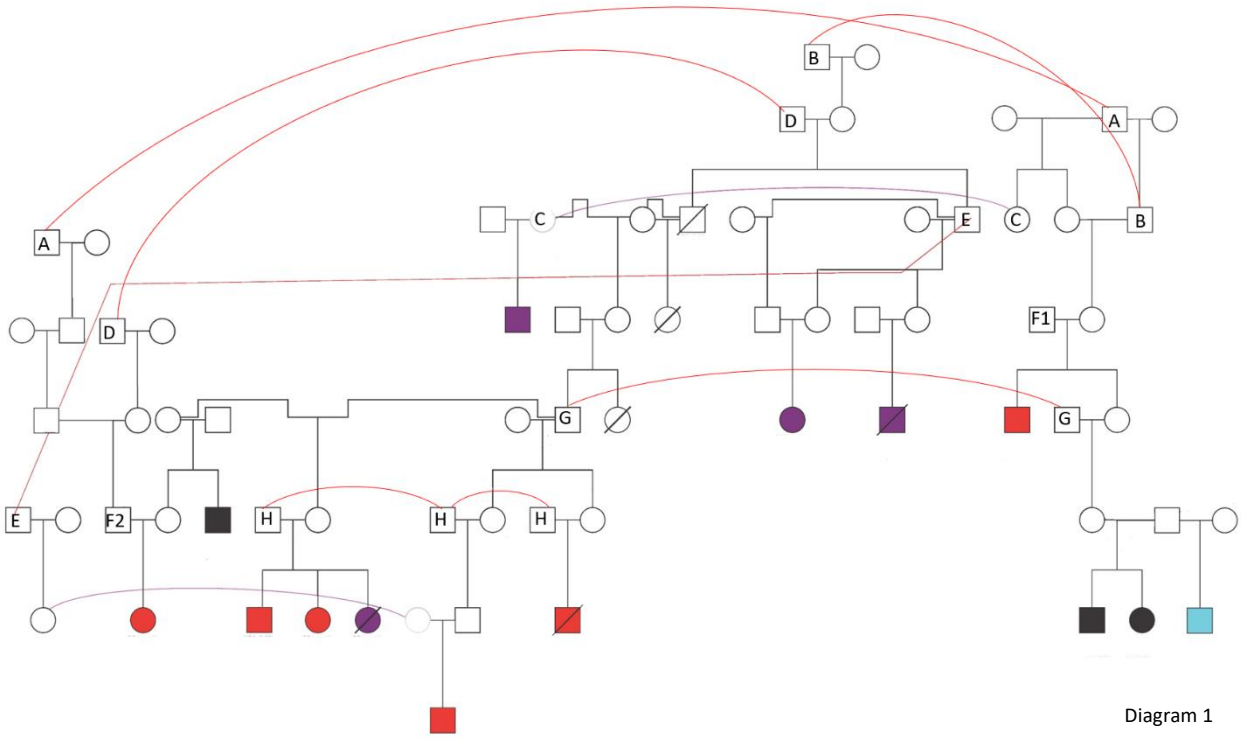



Diagram 1

Following submission of pedigree diagrams from 3 groups of dogs along with associated information, the response from the Kennel Club health and research team stated *"Epilepsy is a difficult condition about which to give breeding recommendations. There are a handful of breeds in which a single gene responsible for a particular form of epilepsy has been found and they are in some ways the lucky ones. In most breeds, "idiopathic epilepsy" (now defined as two or more unprovoked seizures at least 24 hours apart with no identifiable caused other than a suspected genetic origin) is considered likely to be a complex condition affected by many genes and also environmental effects. For complex conditions, breeding decisions in many ways become about risk management. However, how much risk any particular mating represents is hard to define at this stage. You can see from the pedigree diagrams you sent that the picture is complicated. Do the different presentations of "affected" dog e.g. seizures more than 1 year apart versus frequent seizures requiring medication represent different degrees of severity of the same condition, or do they actually represent different conditions? At this stage we really don't know.*

*Regarding breeding advice, as explained above it is hard to know what to say without further research. However, at the very least we can say that it would probably be unwise to repeat a mating which has produced puppies that have gone on to be diagnosed with idiopathic epilepsy."*

The KC website provides general guidance for complex inherited diseases where no test is available such as some forms of epilepsy. The guidelines may be useful in formulating an action plan as a way forward, however whilst the information may help reduce the risk of producing affected puppies, it cannot be used as a guarantee [5]. A summary of the guidelines is provided below:

Breeding from an affected dog

- Not recommended

Breeding from an unaffected dog that already produced affected puppies

- Do not repeat a mating that produced affected offspring
- If the dog is unaffected themselves if choosing an alternative mate, ensure there is no record of the condition in their line, paying particular care to immediate relatives

Breeding from an unaffected dog with affected siblings or parent

- Only consider breeding later on in life, ensuring the dog does not become affected later. Choose a mate where there is no record of the condition in their line, paying particular care to immediate relatives.

Breeding from an unaffected dog with affected distant relatives

- Choose a mate with no record of the condition in their line, paying particular care to immediate relatives.

Unaffected dogs with no history of affected relatives

- Low risk

Regarding breeding later on in life to ensure the dog does not become affected later, the information provided by the age of onset analysis may be useful in determining the minimum age after which the risk of developing epilepsy may begin to reduce. In females the incidence appears to reduce slightly after the age of 2 years and in males after the age of 3 years, in both males and females the risk is reduced further after the age of 6 years. However, the statistics also show that seizures have been known to occur beyond these ages in some cases and therefore provides no guarantee. Consideration should also be given to dogs producing epilepsy when mated to more than one breeding partner, and whether it is wise to continue breeding from a dog associated with multiple instances of epilepsy.

The inbreeding coefficients of those affected vary from as high as 20% in a number of dogs down to 0.6%. This shows that utilising a breeding strategy based solely on a low inbreeding coefficient may not necessarily suffice. Consideration for the health status of dogs on both sides of the pedigree is also required in order to manage the risk, even though breeding mates may appear to be unrelated.

**MDR1 Gene Mutation**

Whilst the AHT were unable to provide advice regarding inheritance or breeding, they were happy to receive DNA samples from affected dogs, and during the study owners of dogs that met with the specified criteria were asked to send DNA cheek swab samples. The AHT kindly funded and carried out an additional test on the DNA samples they received. This test was for the multi-drug resistant gene MDR1 which is a genetic disorder found in a number of dog breeds. Affected dogs treated with certain common drugs, such as some flea treatments and medications, are unable to pump these drugs from the brain, resulting in poisoning and a range of neurological symptoms. Each of the dogs affected with idiopathic epilepsy tested normal for the MDR1 gene, indicating that the Giant Schnauzers having seizures were not caused by the defective MDR1 responsible for multi drug resistance.

**Potential Triggers in Dogs Predisposed to Seizures**

Owners were able to predict when their dog may have a seizure by identifying a change in behaviour and monitoring the frequency of seizures along with the dog's activity. Reported behavioural changes included, anxiety, hyperactivity, clinginess, hiding and vomiting. Although seizures were noted at all different times of the day, the most likely time for a seizure to occur appears to be after midnight into the early hours of the morning up to 9am whilst the dog is sleeping or resting. The Royal Veterinary College developed an epilepsy tracker app which a few owners downloaded and used to map seizure activity and medication requirements via mobile phone or tablet. The app contains information about epilepsy, diagnostic methods and practical advice on what to do in the event of a seizure. It can also remind owners when medication is due, and includes a seizure diary for recording episodes, pre- and post-ictal behaviour, duration and severity rating [6]. Almost a third of owners were able to ascertain specific events that may trigger a seizure to occur. The ability to recognise potential triggers may facilitate management of the condition in some dogs by avoiding exposure to known triggers and environmental influences. However, a large number of owners stated that seizures were experienced on random occasions with no obvious triggers noted.

<u>Stress</u>

Some dogs, 10%, had an overly anxious or stressed general disposition which also included noise sensitivity, and 15% of owners reported seizures to be triggered by stress, such behavioural comorbidities have previously been highlighted in epileptic dogs [7]. Specific stressful situations that were noted to be a trigger included a change in routine, moving house, other dogs in season, or situations where a loud noise preceded a seizure such as low flying aircraft, thunder and fireworks.

<u>Diet</u>

Diet is often thought to be a potential trigger in some dogs, 68% of those having seizures were fed a complete dry kibble diet and 18% were fed raw or pre-prepared raw food. However, without further research it was not

possible to determine any common dietary associations, such as nutritional content or whether foods contained similar preservatives, grains etc. as 26 different brands were used and individual varieties were not specified. One owner specifically identified pigs' ears and ox tail as a dietary related trigger. Following accidental over-ingestion and further investigation, hypertriglyceridemia was discovered and the owner noted seizures improved after the trigger was discontinued. It has previously been suggested that if a dog diagnosed with epilepsy and is eating a poor diet, the diet should be switched immediately to a better-quality diet [8]. Some diets have been found to be deficient in Vitamin B1 (Thiamine) which is also associated with seizures in dogs [9]. And it may also be worth considering a hypoallergenic diet in dogs with refractory epilepsy and other possible signs of food intolerance, for example, skin or gastrointestinal disease, as there have been a few anecdotal case reports of such dogs whose clinical signs resolved or improved when fed a restricted diet [1]. The Royal Veterinary College also stated that small changes to the diets of dogs with hard-to-treat epilepsy has the potential to reduce the number of seizures and improve the quality of life for affected dogs and their owners. A recent study carried out by the RVC showed that an oil, which contains a specific type of fat known as medium-chain triglyceride (MCT) could have beneficial effects when given as a supplement to a dog's existing diet. The experimental MCT oil was a commercially available dietary supplement suitable for human consumption containing 50%-65% octanoic acid (C8) and 30%-50% decanoic acid (C10). Overall, the RVC research found that dogs had significantly fewer seizures with MCT oil, and an improved quality of life [10].

Puberty/Hormones and Neutering

The study shows that the most common age of seizure onset for females was between 6 months and 2 years, and males between 1 and 3 years, which also coincides with puberty as females tend to mature slightly quicker than males, and could be seen as a potential trigger. Whilst there may be a link with fear phases in this age group, it raises a question as to whether hormonal changes may be associated with the onset of seizures in some Giant Schnauzers. In addition, of the dogs where the neuter status was identified the majority (74%) were neutered, and the age of onset of seizures also coincided similarly with the most common age of neutering in both males and females. Where it was possible to determine whether seizures started before or after neutering 80% started having seizures after castration or spaying. This also coincides with the findings of a specific study in 2019 investigating associations between neutering and idiopathic epilepsy in Labrador retrievers and Border collies under primary veterinary care in the UK [11]. The study used clinical data from the VetCompass Animal Surveillance project, and also found that 74% of neutered Labrador retrievers and Border collies diagnosed with idiopathic epilepsy were neutered before the onset of seizures. Their study found that neuter status was not associated with the occurrence of cluster seizures, however concluded that intact dogs had the longest survival times and went on to say that their results do not support recommendations to neuter dogs with idiopathic epilepsy within an evidence-based treatment plan. Although the seizure study statistics indicated that neutering may be a possible non-genetic risk factor in some Giant Schnauzers, the sample size for this category is quite small. And future studies involving a larger sample of those neutered, and whether seizures started before or after neutering would be beneficial, along with a more in-depth study related to hormone levels in dogs having seizures.

Flea Treatment

Flea treatments are frequently documented as triggers for seizures, and 65% received flea treatment on a regular basis. One owner commented that they thought Advocate may have initially been a trigger for their dog's seizures, and another commented that Frontline seemed to be a trigger as well as stress, with a further owner stating that seizures started following administration of Bravecto. Seven dogs continued to be treated on a regular basis with a pesticide belonging to the Isoxazoline class; Bravecto (fluralaner), Nexgard (afoxalaner) and Simparica (sarolaner), of which the US Food and Drugs Agency (FDA) issued an alert in 2018 for pet owners and veterinarians to be aware of the potential for neurologic adverse events [12]. The FDA stated some animals experienced muscle tremors, ataxia, and seizures. Bravecto now carries a warning on its data sheet stating it should be used with caution in dogs with pre-existing epilepsy. Nexgard datasheets lists neurological signs (convulsions, ataxia and muscle tremors) as an adverse reaction, along with Simparica.

Worming

As with Leptospirosis vaccine, owners were often not aware which worming treatment they administered, however most dogs were treated regularly or at least once a year. None of the owners specifically associated worming treatment as a precursor to seizures. Although the datasheet for Milbemax lists convulsions as an adverse reaction on very rare occasions [13]. Drontal and Milbemax were the most commonly used medications for de-worming.

Weather

One owner noticed that seizures were triggered by periods of unstable barometric air pressure, and a number of articles discuss the effects on behaviour during changes in atmospheric pressure, mostly associated with a

fear response to imminent bad weather [14]. Another dog also reacted to thunder; however, it is not known if this was due to a change in atmospheric pressure or related to noise sensitivity. In addition, another owner linked seizures with a full moon.

Health Issues

Additional health issues were noted in 10 dogs, these included; heart problems, hypothyroidism, cancer, hypertriglyceridemia, Addison's disease, kidney problems, spinal degeneration, stress eczema and incontinence. It is not known whether the hypothyroidism was a precursor to seizures or a side effect of medication, similarly with the case of hypertriglyceridemia and incontinence. It is important that a dog having seizures undergoes a veterinary assessment to rule out any underlying health causes.

Vaccinations

Most dogs, 75%, were vaccinated every year for distemper, hepatitis and parvo with one owner noting seizures started following over-vaccination. The Veterinary Medicines Directorate (VMD) states that for the majority of UK authorised dog vaccines the re-vaccination interval for the core vaccines canine distemper (CDV), canine parvovirus (CPV) and canine adenovirus (CAV) is at least every three years. These authorised re-vaccination schedules are in accord with the WSAVA Guidelines which state "revaccination (booster) at either 6 months or 1 year of age, then not more often than every 3 years" [15]. However, 75% of the dogs having seizures were reported to receive distemper/hepatitis/parvo vaccination every year.

With regards to Leptospirosis vaccination 45% of owners were unaware as to whether their dog had received the vaccination or not. And most often, where a dog had received the vaccination, owners were uncertain whether they received L2 or L4. A number of media and social media reports raise concerns following cases of serious adverse events, including seizures, after dogs received the vaccine containing four strains of Leptospira bacteria (L4). A statement released in response by the VMD in 2017 stated that reactions were rare, however, advised that veterinary surgeons and the client should discuss and agree a vaccination programme for an individual animal. And this should be based on the local epidemiological situation and risk of leptospirosis, balanced with potential risks [16].

Vaccination against rabies is only a requirement in the UK for the pet passport scheme and 68% were not vaccinated against rabies.

**Give a Dog a Genome Project**

The Give a Dog a Genome project was launched by the Kennel Club Genetics Centre at the Animal Health Trust, with the aim to improve dog health by sequencing the entire genomes (all 2.4 billion letters of DNA) of at least 77 different dog breeds, and creating the UK's largest canine genome bank. The project is hoped to have a profound effect on the ability to identify mutations which cause inherited diseases in purebred dogs, and the rate at which new DNA tests can be developed as tools for breeders. The breed clubs representing Giant Schnauzers contributed funding to the AHT towards sequencing the genome of an individual Schnauzer. And the AHT subsequently chose Idiopathic Epilepsy as the breed condition they wanted to sequence for the Giant Schnauzer. The seizure study was able to identify 5 affected dogs that met with the very strict criteria required by the AHT which is set out below:

- The dog had at least two seizures which occurred 24 or more hours apart.
- The first seizures occurred when the dog was between six months and six years of age.
- A vet performed examinations and found the dog to be normal between seizures.
- Blood and urine test results were all returned normal.
- Magnetic Resonance Imaging (MRI) analysis was found to be normal.
- Testing found that cerebrospinal fluid (CSF) was normal.

Once the samples were received at the AHT, they anonymously selected one DNA sample for sequencing at a commercial laboratory. The extensive amount of sequencing data generated was then processed and analysed by the AHT. Additional analysis of the data to attempt to identify any variants that contribute to Epilepsy will take far longer and the sequence data can also be shared with other scientists as and when deemed necessary or helpful. The AHT also stated that it is entirely possible that they will not be able to identify any variants that contribute to Idiopathic Epilepsy. However, even if this is the case, the data still can and will be used in investigations of inherited disease in other breeds.

**Treatment**

The treatment options varied from 40% of affected dogs receiving no treatment at all, to 55% receiving single or combination anti-epileptic drugs (AEDs). And a small number of dogs received an alternative herbal or homeopathic remedy. Treatments that worked for some dogs do not appear to work for all affected dogs.

Owners reported improvement or partial improvement following treatment with AED's, 1 given in combination with CBD oil, and one owner noticed an improvement after treating with Fluoxetine (Prozac) for underlying anxiety issues, along with another who treated anxiety with an herbal calming medication. Successful AED treatment included imepitoin and Phenobarbitone as single therapies and also combination drug therapies such as Phenobarbitone prescribed along with Potassium Bromide, and also Levetiracetam. The same AED's and similar combination therapies showed no improvement in some dogs. And one owner noted no improvement with homeopathic remedies and acupuncture. One of the dogs having seizures regularly with no response to medication later went on to have a vagus nerve stimulator fitted which also proved to have no effect.

**Summary**

Consideration should be given for the relatively small sample and possibility of under-recording and/or self-selection bias.

Breed health surveys found that 3.7 - 4% of Giant Schnauzers were living with epilepsy.

The seizure study found the incidence and therefore risk of a puppy developing epilepsy was 0.9%.

It is currently not possible to determine the mode of inheritance, however it appears to be inherited in a complex manner, with potential environmental and non-genetic risk factors in some, but not all, cases.

An agreed set of guidelines for breeding may be helpful in managing the risk of producing affected dogs.

Giant Schnauzers do not appear to be affected by the MDR1 gene mutation for multi drug resistance.

Potential triggers in those that took part in the study include; stress/anxiety, noise sensitivity, diet, puberty, neutering, weather, flea and worming treatment, underlying health conditions and vaccinations.

Dietary changes may be beneficial in some dogs as an add-on therapy.

Different treatment regimes have proved to have varying degrees of success and appear to be individual to each particular dog.

The DNA of an affected Giant Schnauzer has been sequenced and in the process of extensive analysis as part of the Give a Dog a Genome project.

The study also highlighted that a lot of owners are not aware which flea, worming and vaccinations their dog received.

**Conclusion**

It is hoped that the information provided by the seizure study may provide useful information towards the Breed's Health Conservation Plan to manage the risk of producing affected dogs. It would also be useful to provide practical advice for owners of dogs having seizures based on the information gained from the study.

It is also hoped that the AHT or another recognised research body will continue to collect DNA samples from affected dogs that may contribute to genetic research into canine idiopathic epilepsy in the future.

**Acknowledgements**

Grateful thanks go to all owners of participating dogs, and to the breed clubs and Kennel Club for their support of the study. In addition, many thanks to Breed Health Co-ordinators/Breed Club Health Representatives; Tony McDermott and Christine Ellingworth for their assessment and review of both the study questionnaire and report manuscript.

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