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Aetiology and Outcome in French Bulldogs with Epileptic Seizures. A retrospective study

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Summary

The history of twenty-two French Bulldogs with epileptic seizures was retrospectively investigated to describe the aetiology and the outcome. French Bulldogs with more than one unprovoked convulsive epileptic seizure more than 24 hours apart and that had been subjected to clinical and neurological examination were included; magnetic resonance imaging, computed tomography and histo-pathological examination were not mandatory. Idiopathic epilepsy (IE) was diagnosed in 16 dogs and structural epilepsy (SE) in six. Brain tumours were detected in four (18 %) cases. The survival time was longer in the IE group (720 days) than in the SE group (90 days). Antiepileptic drug control was excellent (seizure-free) in two cases (9 %), good (1–5 seizures/year) in five cases (23 %) and poor (>10 seizures/year) in six (27 %) cases; no reliable data were available for the remaining cases. The results suggest that the outcome of epilepsy in this breed is frequently bad: most patients did not survive for longer than three years.

Zusammenfassung

Retrospektive Studie zu Ätiologie und Krankheitsverlauf bei Französischen Bulldoggen mit epileptischen Anfällen

Daten von 22 Französischen Bulldoggen wurden retrospektiv untersucht, um die Ursache der Epilepsie und deren Folgen zu beschreiben. Französische Bulldoggen mit mehr als einem unprovozierten konvulsiv-epileptischen Anfall im Abstand von mehr als 24 Stunden sowie klinischer und neurologischer Untersuchung wurden in die Studie aufgenommen; Magnetresonanztomographie, Computertomographie und histopathologische Untersuchungen waren nicht verpflichtend. Die Patienten wurden in idiopathische (IE) oder strukturelle Epilepsie (SE) eingeteilt. Bei 16 Hunden wurde idiopathische Epilepsie und bei sechs Hunden strukturelle Epilepsie diagnostiziert. In 18 % der Fälle konnte ein Gehirntumor nachgewiesen werden. Tiere in der IE-Gruppe zeigten eine längere Überlebenszeit (720 Tage) verglichen mit Tieren aus der SE-Gruppe (90 Tage). Das Ansprechen auf Therapie mit Antiepileptika war in zwei Fällen (9 %) ausgezeichnet (anfallsfrei), in drei Fällen (23 %) gut (1–5 Anfälle/Jahr), in 6 Fällen (27 %) schlecht (>10 Anfälle/Jahr) und für die restlichen Fälle konnten keine zuverlässigen Daten erhoben werden. Unsere Studie zeigte, dass die Diagnose Epilepsie für diese Hunderasse größtenteils zu einem schlechten Ausgang führt, da die Mehrheit nicht länger als drei Jahre überlebte.

Abbreviations: AED = antiepileptic drug(s); CSF = cerebrospinal fluid; CT = computed tomography; FB(s) = French Bulldog(s); GME = granulomatous meningoencephalitis; IE = idiopathic epilepsy; MRI = magnetic resonance imaging; SE = structural epilepsy

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Introduction

Epilepsy has been investigated in several dog-breeds, in the French Bulldog (FB) although described (HAMAMOTO et al. 2016), not analysed systematically. The high prevalence of neurological disorders in FBs (MAYOUSSE et al., 2017) justifies an analysis of the aetiology and outcome in these patients.

Epilepsy can be classified into two types: idiopathic epilepsy (IE) and structural epilepsy (SE), with idiopathic epilepsy sub-classified into three groups (BERENDT et al., 2015): genetic epilepsy (a gene has been identified and/or confirmed as the cause of epilepsy), suspected genetic epilepsy (breeds with a high prevalence of epilepsy) and epilepsy of unknown origin (the cause is unknown and there is no indication of structural epilepsy). Many genetic defects have been correlated with the occurrence of epileptic seizures, e.g. degenerative encephalopathies (VANDEVELDE et al., 2012) and neuronal ceroid lipofuscinosis (MELVILLE et al., 2005). However, to date only three genes in three different breeds of dog have been shown to correlate with idiopathic epilepsy: in Lagotto Romagnolos (SEPPÄLÄ et al., 2011), in Belgian Shepherds (KOSKINEN et al., 2015) and in Rhodesian Ridgebacks (WIELAENDER et al., 2017). Epileptic seizures provoked by intracranial pathologies including vascular, inflammatory/infectious, traumatic, anomalous/developmental, neoplastic and degenerative defects are considered forms of structural epilepsy (BERENDT et al., 2015).

Material and Methods

Subjects and instrumentation

This retrospective study focused on FBs with convulsive epileptic seizures 24 hours apart and that were presented to the University of Veterinary Medicine, Vienna over the past 14 years. The aetiology and the outcome were analysed by age at first onset; type of epilepsy (idiopathic, structural); type of seizure (generalized, focal and myoclonic); number of seizures before presentation; *Status epilepticus* or cluster seizure; routine blood work and diagnostics; time of survival after presentation; outcome (seizure control, anti-epileptic drug tolerability); and annual number of seizures with antiepileptic drug (AED) therapy. Non-obligatory diagnostics were MRI, CSF and histological examination of brain tissue. Survival time was calculated from the day of the onset of the first seizure until the latest information or death. European College of Veterinary Internal Medicine (ECVIM) residents and interns performed clinical examinations. A diplomate of the European College of Veterinary Neurology (ECVN) (the senior author of this publication) or a senior neurologist (the second author) supervised all cases.

FBs with the diagnosis of IE were categorized by the Three-Tier System (Tier I, Tier II, Tier III) according to DE RISIO et al. (2015b). Tier I: the diagnosis of IE is based on a history of two or more unprovoked epileptic seizures occurring at least 24 hours apart, age of onset of epileptic seizure between six months and six years, unremarkable inter-ictal physical and neurological examination and no significant abnormalities on minimum database blood test and urine analysis. Tier II: the diagnosis of IE is based on the factors listed in Tier I and on unremarkable fasting and post-prandial bile acids, MRI of the brain and CSF analysis. Tier III: the diagnosis of IE is based on the factors listed in Tiers I and II and on the identification of electroencephalographic abnormalities characteristic of seizure disorders. The category "IE that does not satisfy the criteria of the Three-Tier System" was introduced for cases with convulsive epileptic seizures but with no neurological abnormalities and with incomplete diagnostic work-up or that are out of the age range for IE.

To classify the extent of seizure control we used the terms seizure-free; seizures continue with partial therapeutic success (prevention of cluster seizures or *Status epilepticus*, reduction of frequency or severity of seizures); seizures continue without partial therapeutic success; and undetermined. AED tolerability was classified into no adverse effects; adverse effects; treatment not tolerated; and undetermined. We grouped the annual number of seizures into four categories as suggested by PAKOZDY et al. (2012): excellent control/seizure-free (without any seizures after AED therapy); good control (1–5 seizures per year); moderate control (6–10 seizures per year); and poor control (>10 seizures per year).

Two MRI and two CT devices were used during the study period. The Mehrzeiler SOMATOM® Emotion 16-slice configuration (Siemens AG Medical Solution, Erlangen, Germany) was used from 2009 to 2011, while since then the Magnetom Espree® 1.5T (Siemens AG Medical Solution, Erlangen, Germany) has been used. An Einzeiler CT-PACE® (General Electric, Milwaukee, WI) was used from 2002 to 2009 and since 2009 Outlook Gold Performance® 0.23T MRI (Philips Medizinische Systeme, Vienna, Austria) has been used.

Statistics

Microsoft Excel® for Mac 2011, Version 14.0.0 (Microsoft Corporation, Redmond, Washington, USA) was used for various calculations, data analysis and some graphs.

The Spearman's Rho correlation, Kaplan-Meier estimator and frequency distribution were calculated and the graphs prepared by IBM SPSS® Statistics v17 (SPSS Inc., Chicago: SPSS Inc.). The Spearman's Rho correlation test was used to establish whether the age of onset of the first seizure correlated with the survival time. The Kaplan-Meier estimator was used to show the mean, median and estimation of survival function of lifetime data. Frequency distribution was used to determine whether a *Status epilepticus* or a cluster seizure is more common in the IE or SE group.

Results

Signalment

Twenty-two FBs (n = 16 IE, n = 6 SE) fitted the criteria: eleven male (four neutered) and eleven female FBs (ten neutered). Six FBs of the IE group were between six months and six years of age and thus met the criteria of the Three-Tier System. Two were younger than six months and eight were older than six years, so were included in "IE that does not satisfy the criteria of the Three-Tier System". Five dogs in the SE group were older than six years at onset of first seizure and one was younger than six years. The average weight of the dogs in both groups was 11.59 kg (range: 9–13.50 kg).

Diagnosis

Clinicians based their diagnosis on findings and diagnostic work-up. IE was diagnosed in 16 FBs and SE in 6 cases. The aetiology of SE was tumours (n = 4, oligodendroglioma; Fig. 1), encephalitis (n = 1, granulomatous meningoencephalitis (GME)) and undetermined (n = 1, circling, blindness, seizures). Tumours and GME were diagnosed with CT/MRI and/or pathohistological examination. The brain tumour was either in the right cerebral hemisphere or in the frontal lobe.

Type of seizure

The type of seizure was categorized as generalized epileptic seizures (n = 13), focal seizures (n = 6) or focal-generalized seizures (n = 3) (Tab. 1). Cluster seizures (n = 12) were more common than *Status epilepticus* (n = 5) in both groups. Interestingly, *Status epilepticus* and cluster seizures occurred more often in the IE group (87.5 %) than in the SE group (50 %) (p=0.01). Two other dogs had cluster seizures that progressed into *Status epilepticus* (Tab. 1).

Long-term treatment of the IE and SE group

Phenobarbital was the most commonly used AED for long-term therapy, either alone (n = 5) or in combination with gabapentin, levetiracetam, pregabalin, potassium bromide and/or clonazepam (n = 5, Tab. 2). Data on long-term treatment were available for 10 of the 16 IE cases. Three of the four dogs with a brain tumour were treated with AED and one received radiation therapy.

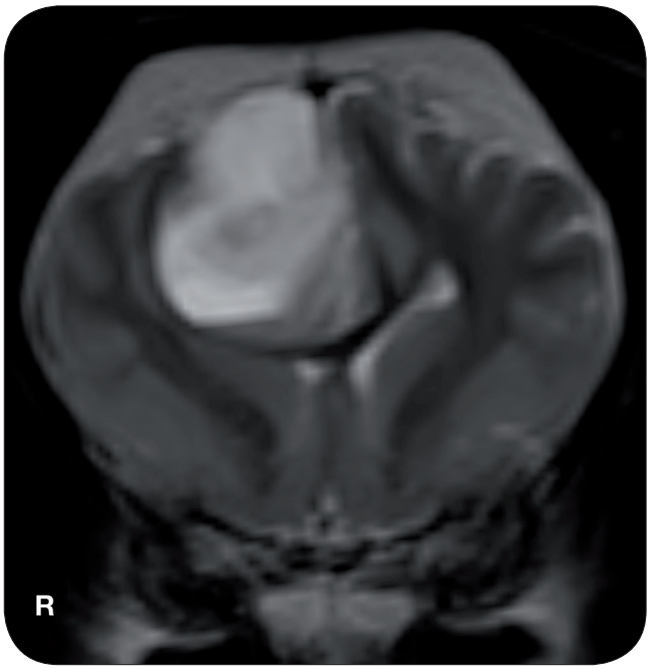

Fig. 1: T2- weighted transverse MRI image of a large intracranial mass in the right frontal and parietal lobe with associated mild midline shift and compression of the ipsilateral ventricle. Histopathology confirmed oligodendroglioma. / T2-gewichtetes Magnetresonanztomographiebild einer großen, intrakranialen Raumforderung des *Lobus frontalis* und *parietalis* mit geringgradiger Mittellinienverschiebung, sowie Kompression des ipsilateralen Seitenventrikels. Die histologische Untersuchung bestätigte ein Oligodendrogliom.

Comparison of age of onset of seizures, survival time and outcome of the IE and SE groups

The age of onset of seizures ranged widely in the IE group (4.23 ± 3.09 years; range: 0.5–11.51), whereas the lowest age of onset of seizures in the SE group was 5.85 years, with an average of 7.62 ± 2.53 years (range: 5.85–13.19 years). The Spearman's Rho correlation test showed no significant difference in age of onset between the groups, although the p value of 0.05 was close to the limit for significance (<0.05). Survival time data were available in 18/22 FBs (IE n = 13, SE n = 5). Survival time was 1–2416 days (median 720 days) in the IE group and 1–136 days (median 90 days) in the SE group, a significant difference between the groups (p=0.01). The survival rate was evaluated in the IE group: eight dogs (36.4 %) survived one year, three dogs (13.6 %) two years and two dogs (9.0 %) three or more years after onset of seizures. A Spearman's Rho correlation test showed no correlation between the number

Tab. 1: Summary of cases / Übersicht aller Fälle dieser retrospektiven Studie

Group	Mean age at onset of seizures	Seizure type[4]	Number of dogs with status epilepticus or cluster seizures[4]
IE (n = 16) (Idiopathic epilepsy)	4.23 years	generalized: 10 (62.5 %)	total: 14 (87.5 %)[1]
		focal: 5 (31.2 %)	*Status epilepticus:* 4 (62.5 %)
		focal-generalized: 1 (6.3 %)	cluster seizure: 10 (25.0 %)
SE[3] (n = 6) (Structural epilepsy)	7.62 years	generalized: 3 (50.0 %)	total: 3 (50.0 %)[2]
		focal: 1 (16.7 %)	*Status epilepticus:* 1 (16.7 %)
		focal-generalized: 2 (33.3 %)	cluster seizure: 2 (33.3 %)

[1] Tonic-clonic seizures were shown in seven dogs and myoclonic seizures in three dogs.
[2] Two dogs had seizures due to encephalitis.
[3] Four dogs had a brain tumour, one had encephalitis and one had structural epilepsy of unclear aetiology.
[4] Percentages relate to the number of IE and SE cases.

Tab. 2: Summary of dose of medication received from the day of presentation to the time of last follow-up or death. Legend: BID: twice per day; TID: three times per day. / Zusammenfassung der Dosierung der Medikamente vom Tag der Vorstellung bis zum Zeitpunkt der letzten Nachverfolgbarkeit oder des Todes. Legende: BID: Latein für „bis in die" bedeutet zweimal täglich; TID: Latein für „ter in die" bedeutet dreimal täglich.

Drug	Initial and add-on treatment
Phenobarbital	initial dose 2.5 mg/kg BID, p. o., Phenoleptil® Le Vet B.V., TV Oudewater, Netherlands
Gabapentin	10–30 mg/kg BID–TID, p. o., Gabapentin Hexal®, Hexal Pharma GmbH, Vienna, Austria
Levetiracetam	10–20 mg/kg TID, p. o., Keppra®, UCB Pharma SA, Brussels, Belgium
Pregabalin	initial dose 2 mg/kg BID–TID, p. o., Lyrica®, Pfizer Corporation Austria GesmbH, Vienna, Austria
Potassium bromide	10–20 mg/kg BID, p. o., Kaliumbromid Sandoz®, Hexal AG, Holzkirchen, Germany
Clonazepam	0.1–0.5 mg/kg BID–TID, p. o., Rivotril®, Roche Pharma AG, Grenzach-Wyhlen, Germany

of seizures before presentation and the survival time (p=0.45) (Fig. 2). Seizures were measured according to POTSCHKA et al. (2015): an excellent control (seizure-free) of annual seizure outcome with AED therapy was reported in two cases in the IE group, good control (seizures continue with partial therapeutic success) in three and poor control (seizures continue without partial therapeutic success) in six; there was no reliable information for the remaining cases (Tab. 3). Six FBs were euthanized during AED therapy because of bad condition and/or seizure control: two of them showed 25 or more seizures per year after presentation.

The outcome in the SE group (n = 6) was very poor. Four dogs died of a brain tumour and one of encephalitis and one dog was lost for follow-up. 60 % died within the first three months and the dog that was irradiated died after 4.5 months. The IE group thus had a better outcome than the SE group.

Discussion

This is the first retrospective study of epileptic seizures in FBs. We find that the causes of epileptic seizures in FB are structural in approximately one third of cases, whereas two thirds of cases can be classified as idiopathic. It should be kept in mind that the diagnostic work-up was frequently incomplete.

The mean age at onset of seizures was lower in the IE group (4.23 years) than in the SE group (7.62 years), although the difference was not significant (p=0.05). Similarly, there was no correlation between the number of seizures before presentation and the survival time (p=0.45). We conclude that the age of the first seizure does not influence the survival time in the IE group. In contrast, Border Collies have a significantly lower survival time when the onset of seizures is before the age of 2 years (HÜLSMEYER et al., 2010). The median survival time of 720 days (1.9 years) in our FBs with IE was low. A similarly low survival time has only been reported in epileptic Border Collies (median survival of 2.1 years) (HÜLSMEYER et al., 2010); many other dog breeds show longer survival times with IE (e.g. Belgian Shepherd 2.5 years, Australian Shepherd 3.1 years and Golden Retriever 3.8 years) (HÜLSMEYER et al., 2015).

Half of the dogs with IE experienced generalized seizures. Focal seizures were present in 27.3 % and focal-generalized seizures in 33.3 % of IE and SE dogs. Previous reports suggest that seizures in Irish Wolfhound (CASAL et al., 2006), in rough and smooth Collies (MUÑANA et al., 2012) and in Shetland Sheepdogs (MORITA et al., 2002) are predominantly generalized. *Status epilepticus* and cluster seizures occurred more frequently in the IE group (87.5 %) than in the SE group (50.0 %) (p=0.01). FBs with IE also had a higher tendency to develop cluster seizures or status epilepsy (87.5 %). MONTEIRO et al. (2012) found that German Shepherds and Boxers were significantly more likely to suffer from cluster seizures than Labrador Retrievers. A high prevalence of cluster seizures was also found in Italian Spinone (72 %) (DE RISIO et al., 2015a), in Dalmatians (63.3 %) and in Border Collies (45 %) (HÜLSMEYER et al., 2015). DE RISIO et al.

Tab. 3: Summary of annual seizure control of IE group. The annual numbers of seizures are per individual and per year. Legend: * alive [29/01/2017], ⇑euthanized; n/a: not available, undetermined: is a category of seizure control and tolerability; n/u: no or unclear information in the patients´ records. / Zusammenfassung über die jährliche Anfallskontrolle der IE-Gruppe. Die jährlichen Anfallszahlen gelten pro Individuum und Jahr. Legende: * lebend [29.01.2017], ⇑euthanasiert; n/a: nicht verfügbar, undetermined: ist eine Kategorie der Anfallskontrolle und Tolerierbarkeit; n/u: keine oder unklare Informationen in den Krankenakten.

seizure control[1]	number of dogs	annual seizure no.	tolerability
seizure-free	2	0*	no adverse effects
seizures continue with partial therapeutic success	6	3*, 4, 4, 41, 54*, 60	adverse effects n/a
seizures continue without partial therapeutic success	5	12*, 25, 15, n/u⇑, n/u⇑	adverse effects no adverse effects n/a
n/a	1	n/u	n/a
undetermined	2	n/u	undetermined

[1] scheme according to POTSCHKA et al. (2015).

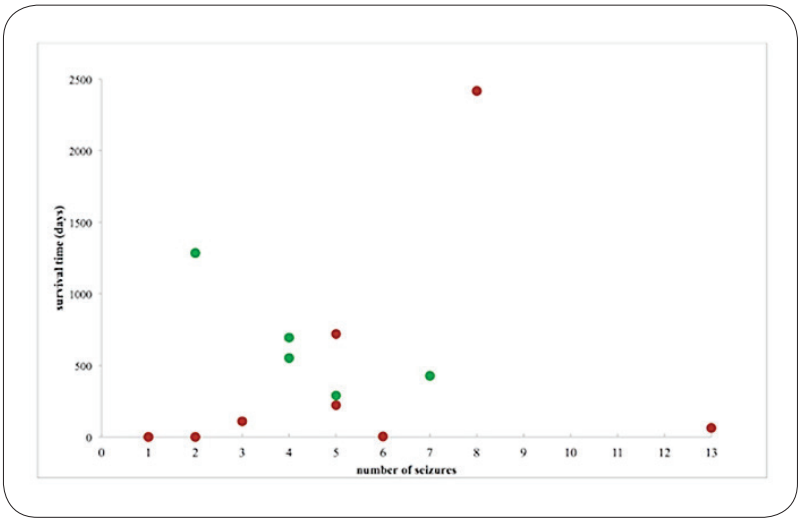

Fig. 2: Survival time in relation to frequency of seizures before presentation. Red dots: dead dogs (n = 8); green dots: living dogs (n = 5) / Überlebenszeit in Abhängigkeit von der Anfallshäufigkeit vor Vorstellung. Legende: rote Punkte: tote Hunde (n = 8), grüne Punkte: lebende Hunde (n = 5)

(2015a) showed that the survival time of Italian Spinone with IE is significantly shorter when they have cluster seizures than when they do not.

The brachycephalic head could contribute to the development of severe epilepsy in FBs. The truncation of the skull correlates with a reduction in size of the olfactory lobe and may influence canine behaviour and health (ROBERTS et al., 2010; SCHOENEBECK and OSTRANDER, 2013). The brachycephalic brain is unable to control the intracranial pressure due to skull reduction, contributing to cell damage and convulsions (SONG et al., 2013). Respiratory problems during seizures or independently of them may lead to chronic hypoxia, oxidative stress and potentially to brain damage (PLANELLAS et al., 2012).

No associations were found between survival and age at seizure onset, or between time from IE onset to start of therapy or frequency of seizures before the start of therapy in Italian Spinone (DE RISIO et al., 2015a). Similarly, we found no correlation between the start of AED therapy and the outcome. The tolerability and seizure control of AED was excellent in only two (9.0 %) of the IE dogs treated and we found good control in three (13.6 %) of them. Control was poor in a high proportion of the dogs (6, or 27.3 %). The results are consistent with findings on the outcome and seizure control in epileptic (IE) Italian Spinone, where only 4 % had an excellent outcome (DE RISIO et al., 2015a).

Oligodendroglioma was the most frequent type of brain tumour diagnosed in our FBs, which is not surprising in the light of previous reports. SONG et al. (2013) showed that FBs had an increased risk of primary intracranial tumours, especially oligodendroglioma, and that glial neoplasms are overrepresented in brachycephalic breeds (except Pug and Pekinese) compared to other dogs. MAYOUSSE et al. (2017) found that glioma as the most common brain tumour in FBs (25/68, 36.8 %). HAYES et al. (1975) suggested a correlation between glial tumours and chronic hypoxia but the cause is not yet known. SNYDER et al. (2006) showed that dogs with oligodendrogliomas were 3.6 times more likely to have seizures than dogs with other brain tumours. Neoplastic tissue in the frontal lobe was more likely to be associated with seizures than affected regions in other areas of the brain (SCHWARTZ et al., 2011). The highest proportion of seizures occurred when the temporal, frontal, parietal or the olfactory bulb contained neoplastic tissue (BAGLEY et al., 1999). The human literature also makes a connection with epileptogenesis when these areas are affected, while involvement of the occipital lobe is less associated with epileptogenesis (LIEU and HOWNG, 2000; LYNAM et al., 2007).

Our study suffers from a number of limitations. The number of cases was low and the work-up was incomplete in several cases. In addition, it is the nature of a retrospective study that many dogs were lost for follow-up, making it difficult to draw clear conclusions. However, the data enable us to conclude that epileptic seizures in French Bulldogs are usually difficult to control.

Conclusion

No underlying disease could be identified in 72.7 % of epileptic cases, whereas 16.6 % of cases were caused by brain tumour (oligodendroglioma). Although survival time was better for the IE group than for the SE group, even dogs with IE rarely survived for over two years (only 23 % of cases). Seizure control was excellent in a minority (9.0%) of cases, and the majority was resistant to AEDs. FBs with epilepsy have a high tendency for cluster seizures/*status epilepticus* and the outcome is frequently poor. Even FBs without no identifiable aetiology rarely show a good response to AED therapy.

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Fazit für die Praxis:
In 72,7 % der Fälle konnte bei Französischen Bulldoggen mit Epilepsie keine genaue Ursache gefunden werden, während bei 16,6 % ein Gehirntumor (Oligodendrogliom) als Grund der Epilepsie identifiziert wurde. Die Überlebenszeit ist bei idiopathischer Epilepsie (IE) besser als bei struktureller Epilepsie, aber selbst bei Hunden mit IE betrug sie nur in 23 % der Fälle mehr als zwei Jahre. Die Minderheit der Tiere zeigte eine hervorragende Anfallskontrolle (9 %), während die Mehrheit gegenüber der Antiepileptika-Therapie resistent war. Es scheint, dass Französische Bulldoggen mit Epilepsie zu Cluster-Anfällen/*Status epilepticus* neigen und meistens ein schlechtes Outcome haben. Ein geringer Anteil der Tiere zeigte einen Gehirntumor und selbst unter Französischen Bulldoggen mit unklarer Ursache ist ein gutes Ansprechen auf eine Therapie selten.

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