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Premature Death, Risk Factors, and Life Patterns in Dogs with Epilepsy

Mette Berendt, Hanne Gredal, Annette Kjaer Ersbøll, and Jørgen Alving

Background: Epilepsy in dogs is often difficult to medically control, resulting in premature death of dogs with epilepsy. However, the risks of premature death are not known.

Hypothesis: Dogs with epilepsy have an increased risk of premature death as compared to a general population of dogs.

Animals: Sixty-three dogs diagnosed with epilepsy between 1993 and 1996 were included in this study.

Methods: A prospective longitudinal study of the population was performed from the diagnosis of epilepsy until the time of euthanasia, death, or a maximum of 12 years to investigate mortality and risk factors. Information about sex, onset, type, frequency, and control of seizures, remission of epilepsy, death, cause of death, and owner's perspective was collected and analyzed.

Results: The median age at death of dogs was 7.0 years. The life span of dogs in which euthanasia or death was directly caused by their epileptic condition was significantly shorter as compared with epileptic dogs that were euthanized because of other causes ($P = .001$). The median number of years that a dog lived with epilepsy was 2.3 years. Females lived longer with epilepsy than males ($P = .036$). Seizure type (primary generalized versus focal seizures) was not significantly associated with survival time. The remission rate of epilepsy (spontaneous remission and remission with treatment) was 15%.

Conclusion and Clinical Importance: The diagnosis of epilepsy implies an increased risk of premature death. The prognosis for dogs with epilepsy is dependent on a combination of veterinary expertise, therapeutic success, and the owner's motivation.

Key words: Canine; Convulsions; Mortality; Seizures; Survival analysis.

Epilepsy is a common neurologic disorder in dogs and is often associated with dramatic clinical signs. The clinical picture widely varies, but recurring seizures with tonic-clonic convulsions and loss of consciousness are common. Daily treatment with antiepileptic drugs can, in many cases, reduce the frequency, the severity, or both of seizures, but complete freedom from seizures is difficult to achieve.[1] Status epilepticus can be fatal, and in chronic epilepsy, euthanasia may be the only alternative to medical treatment when the seizure frequency cannot be reduced to an acceptable level.[2]

Direct comparisons between human and veterinary studies of fatality in subjects with epilepsy are impossible because rarely are dogs allowed to die spontaneously. However, epilepsy in dogs shares many clinical and epidemiologic features with human epilepsy,[3–8] including prognosis and mortality. An increase in the overall standard mortality ratio (SMR, calculated as the observed number of deaths in the study cohort divided by the expected number of deaths in the control population) was shown in several studies of human epilepsy.[9–12] This increase is primarily due to an increased SMR in people with remote symptomatic epilepsy, in which tumor disorders and cerebrovascular diseases particularly contribute to the raised mortality.[9–11,13] An investigation of the mortality in a population of 2,928 purebred and mixed-breed dogs revealed the median age at death to be 7 years for the 51 dogs diagnosed with epilepsy.[14]

The authors know of no survival analysis published in the field of canine epilepsy. The objective of the present study was to investigate whether the risk for premature death in dogs is associated with epilepsy. Also, possible risk factors, including sex, weight, seizure diagnosis, medical therapy, and the direct cause of death as stated by the owner, were investigated. Furthermore, it was the aim to characterize epilepsy as it develops with time by reporting data on seizure control, possible remission, and how owners cope with having a dog with epilepsy.

Material and Methods

Study Population

Sixty-three dogs diagnosed with epilepsy between 1993 and 1996 at The Royal Veterinary and Agricultural University, Copenhagen, Denmark, were followed until the time of death, euthanasia, or for a maximum of 12 years. The study population included from 1993 to 1996 was described in detail by Berendt and Gram in 1999[5] and consisted of 25 intact females, 37 intact males, and 1 neutered male. Twenty dogs (32%) suffered from primary generalized seizures, and 41 dogs (65%) suffered from focal (partial) seizures with or without secondary generalization. In 2 dogs (3%) the seizure type could not be classified. The classification was established for each dog at the time of inclusion in the study (1993–1996). Seizure control was attempted with either phenobarbital alone or a combination therapy with phenobarbital and potassium bromide. In dogs known to have cluster seizures or long lasting seizures, diazepam was administered rectally during seizure episodes to prevent prolonged or forthcoming seizures.

Study Design

A longitudinal study was designed to follow the epileptic dogs from inclusion between 1993 and 1996 until the time of death or euthanasia or to end of the study period in February 2005.

From the Department of Small Animal Clinical Sciences, The Royal Veterinary and Agricultural University, Denmark (Berendt, Gredal); the Department of Large Animal Sciences, Veterinary Epidemiology, The Royal Veterinary and Agricultural University, Denmark (Ersbøll); and the Danish Epilepsy Center, DK-4293 Dianalund, Denmark (Alving).

Reprint requests: Mette Berendt, DVM, PhD, Associate Professor, Department of Small Animal Clinical Sciences, The Royal Veterinary and Agricultural University, Copenhagen, Dyrlaegevej 16, DK-1870 Frederiksberg C, Copenhagen, Denmark; e-mail: mbe@life.ku.dk.

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The study population was followed through control visits and in two follow-up studies performed as telephone interviews using a standardized questionnaire. Data were collected regarding seizure onset, seizure frequency, medication and seizure control, remission of epilepsy, and cause and time of death. Available postmortem reports were used in the investigation.

The first follow-up study was done in February 1997 and the second follow-up in February 2005. In 2005, only owners of dogs still alive in February 1997 were contacted. The 1997 and 2005 telephone surveys followed an identical design. The owners were interviewed about the disease status of their dogs. The investigators used a standardized questionnaire addressing seizure frequency, seizure control, medication, medication adverse effects, and if family life had been influenced by having a dog with epilepsy. If the dog had died or had been euthanized, owners were questioned about the time and cause of death.

In this study, "spontaneous remission of epilepsy" was defined as freedom from seizures for >3 years without antiepileptic medication. "Epilepsy in remission with treatment" was defined as seizure freedom for >3 years while being administered medication.

Statistical Analysis

A descriptive analysis was initially performed for the age at seizure onset, age at death, and number of years from seizure onset until death by calculating 25%, 50%, and 75% quantiles.

The median age at death of dogs in the present study was compared with the estimated median age at death of 7 and 10 years, respectively, from Proschowsky et al (2003).[14] A median test was performed by using Wilcoxon's signed ranks test[15] and a 5% significance level.

The influence of seizure type (primary generalized seizures and focal [partial] seizures with or without secondary generalization), sex, body weight and therapy at the age of seizure onset, the age at death, and the number of years with epilepsy (ie, from seizure onset until death) were evaluated using a Kaplan-Meiers procedure in a survival analysis.

The causes of death were assigned to 1 of 2 main groups. The first group included deaths related to epilepsy or in which euthanasia was directly motivated by the dog's epileptic condition. This group included dogs with primary Central Nervous System (CNS) disease, status epilepticus, and unacceptable seizure control (suffering from no other medical or surgical problems than epilepsy). The second group included dogs in which euthanasia or death was due to other causes than epilepsy (Table 1). The effect of the cause of euthanasia/death on the age at death and the number of years with epilepsy was evaluated using a Kaplan-Meiers procedure in a survival analysis.

When performing survival analysis, Cox's proportional hazards regression is often used. Cox's proportional hazards regression assumes proportional hazard functions,[16] which were not fulfilled when evaluating scatterplots of the log of the negative log of survival probabilities versus the log of time. Instead, the survival analyses were performed using the Kaplan-Meier procedure for calculating the survival probabilities. The effect of seizure type, sex, therapy, and cause of euthanasia/death, respectively, were tested using the Log-rank test in univariable analyses. To adjust for the large number of tests performed (in total, $p = 13$ individual tests), Bonferroni's method[17] was used to adjust the significance level. The comparison-wise error rate was set to $\alpha/p = 0.05/13 = 0.0038$ with $\alpha = 0.05$ as the experiment-wise error rate (the overall Type I error rate) and p as the number of tests performed. The comparison-wise error rate is the significance level used for the individual tests performed using the Log-rank test. For each of the significant risk factors, the median value of the outcome and the corresponding 95% confidence interval was calculated, stratified by the significant risk factor. All data analyses were performed using Statistical Analysis System (SAS, version 9.1).

Results

Statistical Data

At the first follow-up in 1997, 26 dogs (41%) had died, and 31 dogs (49%) were alive. Six dogs (10%) were lost to follow-up because the owners could not be located. At the second follow-up in 2005, the owners of the 31 dogs alive in February 1997 were contacted. Two dogs were lost to follow-up, leaving 29 dogs, of which 28 had died. Eight of 63 dogs (12%) were lost to follow-up.

The median age at seizure onset was 2.0 years (25–75% range, 1.0–3.5 years). The median age at death was 7.0 years (25–75% range, 3.0–11.0 years). The median number of years a dog lived with epilepsy (from seizure onset until death/euthanasia) was 2.3 years (25–75% range, 0.9–8.0 years) (Table 1). It should be noted than when using medians, the estimates of median age at seizure onset and the median number of years with epilepsy do not sum up to the median age at death. This is because of a highly skewed distribution, particularly in the number of years a dog was affected with epilepsy.

The median age at death in the present study (7.0 years) was significantly different ($P < .001$) from the estimated median age at death of dogs in a Danish study of 2,928 dogs (10 years).[14] As compared with the median age at death of 7.0 years in dogs with epilepsy found in the study of Proschowsky et al (N = 51), no significant difference was found ($P = .70$).

The causes of death/euthanasia had a significant effect on age at death ($P < .001$). The estimated age at death for causes of death directly related to epilepsy was 4.5 years (95% CI: [3.0–7.0 years]). The estimated age at death from other causes was 12.0 years (95% CI: [9.0–13.0 years]) (Fig 1). There was also a significant association between the causes of death and the number of years the dog lived with epilepsy ($P < .001$). The estimated number of years with epilepsy was 1.3 years (95% CI: [0.7–2.0 years]) for the causes of death directly related to epilepsy and 8.1 years (95% CI: [6.2–10.0 years]) for other causes of death, respectively (Fig 2).

No statistical difference was found between the two sexes with regard to age at seizure onset (median ages for males and females were 2.2 and 1.6, respectively, $P = .26$), age at death (median ages for males and females were 6.0 and 8.0, respectively, $P = .22$), or number of years with epilepsy (median numbers of years with epilepsy for males and females were 2 and 6, respectively, $P = .021$).

No statistical difference was found between the 3 weight groups with regard to age at seizure onset (median ages for the 3 weight groups <10, 10–30, and >30 were 3.3, 2.3, and 1.6, respectively, $P = .32$), age at death (median ages for the 3 weight groups <10, 10–30, and >30 were 12.5, 7.0, and 6.0, respectively, $P = .033$), and number of years with epilepsy (median numbers of years with epilepsy for the 3 weight groups <10, 10–30, and >30 were 8.8, 1.0, and 2.3, respectively, $P = .15$).

Table 1. Descriptive analysis of dog's age at seizure onset, age at death, and number of years with epilepsy given as the median (25–75% quantiles). The analysis is performed overall and stratified by cause of death/euthanasia, seizure type, therapy, and sex. A longitudinal study of epilepsy in dogs in Denmark, 1993–2005. Because of missing values in the cause of death, seizure type, therapy, and body weight variables, N do not add to the total number of the overall study population.

	Age at seizure onset		Age at death		Number of years with epilepsy	
Variables	N	Median (25–75%)	N	Median (25–75%)	N	Median (25–75%)
Overall	60[a]	2.0 (1.0–3.4)	55[b]	7.0 (3.0–11.0)	53[c]	2.3 (0.9–8.0)
Cause of death/euthanasia						
Motivated by epilepsy	33	2.2 (1.3–3.5)	35	4.0 (3.0–8.0)	33	1.4 (0.5–2.5)
Other causes	19	2.0 (1.0–4.0)	19	12.0 (8.0–13.0)	19	8.2 (3.0–10.5)
Seizure type						
Primary generalized	19	2.0 (1.0–3.6)	15	7.0 (3.0–11.0)	15	2.3 (1.0–8.2)
Partial seizure onset	39	2.0 (1.3–3.3)	39	7.0 (3.0–11.0)	37	2.0 (0.8–7.0)
Therapy						
With medical treatment	44	2.0 (1.3–3.5)	46	6.5 (3.0–11.0)	44	2.0 (0.6–6.3)
Without medical treatment	7	3.1 (1.0–4.5)	7	10.0 (7.0–12.0)	7	8.0 (2.5–8.8)
Sex						
Male	37	2.2 (1.4–3.5)	33	6.0 (3.0–10.0)	33	2.0 (0.5–4.8)
Female	23	1.6 (1.0–2.8)	22	8.0 (5.0–14.0)	20	6.0 (1.8–9.2)
Body weight (kg)						
<10	7	3.3 (0.8–4.0)	6	12.5 (9.0–14.0)	6	8.8 (2.5–10.0)
10–30	23	2.3 (1.1–5.0)	22	7.0 (3.0–9.0)	20	1.0 (0.3–5.9)
>30	29	1.6 (1.3–2.7)	27	6.0 (1.0–10.0)	27	2.3 (1.0–6.9)

[a] In 3 dogs, the owner did not know the exact age at seizure onset because the dog at that time belonged to another owner. One of these dogs was later lost for follow-up.

[b] Eight dogs were lost for follow-up and the age at death was therefore not known.

[c] For 10 dogs, information on the age at seizure onset, age at death, or both was not available. The number of years with epilepsy could therefore not be calculated.

With regard to medical treatment, there were no significant differences between treated and untreated dogs in age at death (median ages for treated and untreated dogs were 10.0 and 6.5, respectively, $P = .32$) and in number of years with epilepsy (median ages for treated and untreated were 2.0 and 8.0, respectively, $P = .33$).

There was no significant difference in the age at seizure onset between the 2 groups of seizure types (primary generalized seizures versus partial seizures with or without secondary generalization) ($P = .78$), or in the age at death ($P = .72$), or in the number of years with epilepsy ($P = .70$) for the 2 groups.

Fig 1. Survival probability plot of age at death by cause of death. Broken line, death related to epilepsy (N = 35); solid line, death related to other causes than epilepsy (N = 19).

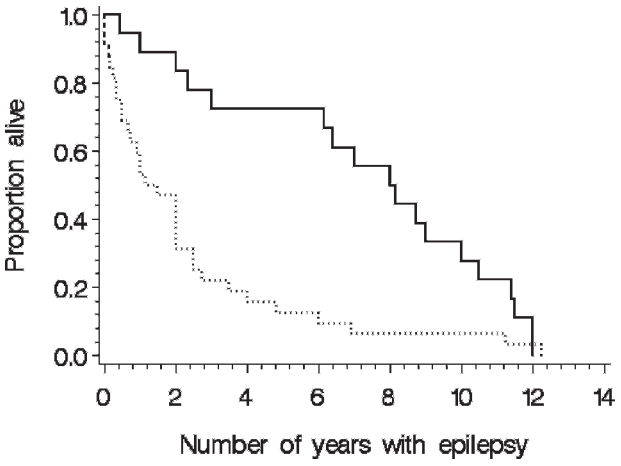

Fig 2. Survival probability plot of number of years with epilepsy by cause of death. Broken line, death related to epilepsy (N = 33); solid line, death related to other cause than epilepsy (N = 19).

Table 2. Causes of death/euthanasia in dogs with epilepsy.

Causes of death	Follow-up 1997 (from 1st contact–1997)	Follow-up 2005 (1997–2005)
Total number of deaths	26	28
Unacceptable seizure control	13	8
Status epilepticus	5	1
Sudden unexpected death[a]	0	1
Considered unfit for breeding	0	1
CNS pathology[b]	6	0
Age related and other disease	2	17

[a] The dog died suddenly and with no known preceding disease other than epilepsy. This death occurred immediately after a single seizure that did not differ from any other seizures in this dog's life. At the time of death, the dog had lived with epilepsy and a seizure frequency <4/y on antiepileptic medication for 7 years. Postmortem examination was not performed.

[b] The 6 dogs suffered from symptomatic epilepsy caused by astrocytoma (3 dogs), canine distemper (1 dog), granulomatous meningioencephalitis (GME) (1 dog), and meningoencephalitis (1 dog).

Seizure Control, Remission of Epilepsy, and Death Related to Epileptic Condition

1997 Follow-Up. Euthanasia was performed in 13 of the 26 dogs because of unacceptable seizure control. These dogs had frequent seizures and often cluster seizures despite intensive antiepileptic combination therapy. Serious adverse effects of the treatment contributed to the decision to euthanize in some of these cases. The reasons for euthanasia in the remaining dogs are given in Table 2.

Of the 31 living dogs, 19 (61%) were seizure-free on antiepileptic drugs, and 9 (29%) experienced acceptable seizure control on antiepileptic drugs. Three dogs (10%) experiencing less than 4 seizures per year were not receiving any medication.

2005 Follow-Up. Euthanasia was associated with the epileptic condition in 11 dogs (Table 3). Eight dogs were euthanized because of unacceptable seizure control. These dogs had experienced a progression of seizure frequency with time and frequent seizures at the time of euthanasia. They had initially achieved acceptable seizure control (seizure reduction but not seizure freedom) on antiepileptic medication for a period of 3–12 months. Subsequently, seizure frequency had increased to multiple weekly or daily seizures. Serious adverse effects had also influenced the decision to euthanize. The most common reason for euthanasia for the remaining dogs was osteoarthritis (Table 2).

In the 17 dogs euthanized for other reasons than epilepsy, 10 dogs had remained on antiepileptic treatment until their death. Six of these had acceptable seizure control (in 5 dogs, <2–6 seizures/year). One dog had 2–4 seizures/month. This dog had only received phenobarbital, because the owner rejected combination therapy with potassium bromide. The dog lived >7 years after the first seizure and was euthanized because of progressing coxofemoral osteoarthritis. No decrease in learning skills or awareness was observed. and the dog served as a hunting dog until its death.

Eight dogs had a remission of epilepsy: 3 dogs had spontaneous remission of epilepsy, whereas 4 dogs achieved seizure freedom with antiepileptic treatment (epilepsy in remission with treatment), and one female dog that had suffered from catamenial epilepsy achieved remission after an ovariohysterectomy.

One dog had liver failure after 7 years on phenobarbital. Postmortem examination was not performed.

Influence of the Dogs Epileptic Condition on Family Life

Thirty-three owners (60%) stated that having a dog with epilepsy had a negative influence on their daily life. The most common complaints were: ''feeling restricted and stressed by the fear of the dog having a seizure while being unattended,'' ''fearing coming home and finding the dog dead after a seizure,'' and ''fearing that the dog could drown during a seizure while swimming.'' The owners would hurry home from work, avoid participating in social events if this meant leaving the dog alone at home, bring the dog along whenever possible, and reject vacations where they could not bring the dog. Owners also reported that their sleep was affected because they feared seizures during night. Overall, concerns about the dogs' life quality and ongoing discussions among family members pro and contra medication and euthanasia influenced the daily life of these families.

All but 8 of the owners stated that support from, regular contact with, and easy access to the investigators was important and necessary with respect to motivation and anxiety reduction. Thorough information regarding epilepsy, seizure types and possible prognosis, instructions with regard to handling the animal during a seizure, therapeutic regime, and active involvement from the investigators at times with increased seizure frequency helped to reduce emotional stress associated with the dogs' epileptic condition.

In the 2005 follow-up 2 owners reported that they had decided against introducing a new dog into the family because of sad memories of the epileptic dog they had lost. One owner chose a cat as her next pet for the same reasons.

Discussion

We found the median age at death for dogs with epilepsy to be 7.0 years. A previous study of 2,928 purebred and mixed-breed dogs reported a median age

at death of 10.0 years.[14] Comparing these 2 studies, the difference in median ages at death was found to be statistically significant, thus supporting the hypothesis that the life span of dogs with epilepsy is shorter than for dogs in general. This is also the case in humans with epilepsy.[9,11,13,18]

The dogs in the present study were all patients referred to the Royal Veterinary and Agricultural University, Denmark. As these referrals may have been slightly skewed toward more severe cases of epilepsy, a small bias could be present in these results. However, a median age at death for dogs with epilepsy of 7 years is in accordance with the results from Proschowsky et al (2003), who also found the median age at death to be 7 years for dogs diagnosed with epilepsy.

We found a significantly shorter median age at death (4 years) for dogs euthanized because of reasons directly caused by their epileptic condition than for dogs living with epilepsy and being euthanized for other reasons (12 years). The number of years a dog survived with epilepsy was also significantly different between the 2 groups. The 6 dogs with provoked seizures (symptomatic epilepsy), in which prognosis primarily reflected the underlying disorder (active CNS pathology), considerably contributed to this finding. This is in accordance with the findings in humans.

Several investigations in human epilepsy state an overall increase in the SMR caused primarily by an increase in remote symptomatic epilepsy.[9–12] Tumor disorders and cerebrovascular disease contribute largely to the raised mortality in human epilepsy.[9–11,13]

The mortality risk is highest during the first 2 years after the diagnosis.[11] This was also true in the present study for dogs euthanized for reasons motivated by their epileptic condition (including the dogs with severe active CNS disease causing symptomatic epilepsy).

The median survival time (the number of years an epileptic dog lived with epilepsy from the first seizure to death/euthanasia) was 2.3 years. We found that the owners' psychological resources and personal opinion concerning life quality, not only for the dog but also for the family, strongly influenced the decision of when to euthanize the dog, and thus the time of death.

Acceptable seizure control reflected a reduction in seizure frequency to a level that could be tolerated by the owner. What is considered acceptable or tolerable with regard to seizure frequency, clinical signs, and medication adverse effects depended on the individual owner and, indeed, was not necessarily correlated with the objective professional evaluation of the epileptic condition. However, owners generally tolerated monthly seizures and, for a period of time, weekly seizures, whereas they were less likely to accept cluster seizures, status epilepticus, and antiepileptic drug adverse effects.

We found no statistically significant differences in age at death or number of years with epilepsy between treated and untreated dogs. One would expect that untreated dogs (reflecting a less severe epileptic condition) would have a better prognosis for survival than dogs receiving medical treatment. On the other hand, well controlled epileptic patients may not experience a shorter life span than untreated dogs with a low seizure frequency. However, these results most probably reflect the relatively small sample size ($N = 63$) for a survival analysis evaluating the effect of explanatory variables. Increasing the sample size would probably not make a big difference in the analysis of the factors in relation to the 3 outcome variables, as the median differences of the outcome variables are very small. However, there is a relatively big difference in number of years with epilepsy for therapy (2.0 years for treated dogs versus 8.0 years for untreated). For these analyses, a larger sample size would probably change the significance of the explanatory variables.

One case of spontaneous seizure–related death had occurred. Sudden unexpected death in association with epilepsy (SUDEP) are well known in humans.[11] According to recent studies, SUDEP contributes about 10–15% of the mortality in epilepsy, 2.5 times more common in chronic than in newly diagnosed epilepsy.[19] Young age, male sex, poor seizure control, and occurrence in relation to (especially nocturnal) seizures are hallmarks of SUDEP in humans.[20] The fact that SUDEP in the present series was observed in only one of the epilepsy-related deaths is probably because we did not experience the natural history of epilepsy (these dogs were not allowed to live a full life with epilepsy).

Epilepsy remission (spontaneous and drug induced) is an important outcome measure in epilepsy in humans.[21,22] Remission of epilepsy in dogs has previously only been reported in 1 study and was also documented to have occurred in 15% of the study population in the present study.[23] This finding is important because it documents that epilepsy in dogs is not necessarily a chronic condition.

Phenobarbital therapy is known to have a potential for liver toxicity in dogs.[24] In this study 1 dog had liver failure that might have been related to long-term phenobarbital treatment.

When looking at the emotional stress the owners reported in this study, it is clear that having a dog that is affected by a seizure disorder has many consequences. In particular, the fear of future seizures made the owners decide to restrict their lifestyle to reduce their own anxiety level and to accommodate the needs of their pet. Uncontrolled seizures and adverse effects of antiepileptic medication gave rise to many concerns. Indeed, in a number of dogs, the owner decided for euthanasia, not only because of the severity of the epileptic condition itself, but also because of the psychological burden that was associated with owning an epileptic dog. However, many owners were motivated to preserve the life of their pet, given that the investigators provided thorough information and support whenever needed.

The telephone surveys served to support the information collected in the dogs' files with time, thereby securing information that might otherwise have been lost. The disadvantage of telephone interviews may be interviewer bias and the risk of prejudged categorization by the interviewer.[25] In the present study the owners interviewed and the dogs in question were already well

known to the investigators (interviewers), and we therefore believe that the overall study design helped us to overcome the disadvantages normally associated with telephone interviews.

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