Interictal electroencephalographic findings in a family of golden retrievers with idiopathic epilepsy

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ABSTRACT

This study investigated how far electroencephalographic (EEG) testing may help in the confirmation of idiopathic epilepsy (IE) in dogs. We found significantly constant ($P < 0.05$) and similar values of amplitude and frequency under medetomidine/propofol anaesthesia. The baseline pattern of healthy and the background activity of the epileptic dogs were characterised by an homogeneous high voltage slow activity and low voltage fast activity pattern with no significantly different values between tracings. However, we frequently found spindles in all recordings of the epileptic dogs. They impressed by asymmetries as well as significant variation in amplitude and duration. We concluded from these observations that, despite deep anaesthesia, the EEG abnormalities were consistent and extremely important for the confirmation of IE in the dog. In addition, 10 per cent of the offspring in our golden retriever family were positive for spindles, if the EEG was taken at the age of maximal expression. We concluded that this does not mean that this factor is genetically dependent, but that its interaction may increase the liability to contract seizures in the golden retriever. We believe that EEG combined with pedigree analysis may be very helpful in risk assessment of IE in the dog.

INTRODUCTION

The most common cause of recurrent seizures in dogs is idiopathic epilepsy (IE) (Schwartz-Porsche 1994). The clinical properties of IE have recently been studied in different breeds (Bernardini and Jaggy 1996), including the labrador retriever population in Switzerland. Moreover, it has been shown that a multifactorial mode of inheritance including both genetic and some environmental factors is responsible for the transmission and expression of IE in retriever dogs (Srenk and others 1994).

Despite recent data improving diagnostic reliability, a clinical diagnosis of IE still remains a challenge in many cases. It is often difficult, even for an experienced neurologist, to distinguish clinically between idiopathic and secondary epilepsy (Bernardini and Jaggy 1996), especially if an animal is presented for the first time. Therefore, the use of electroencephalography (EEG) as an additional diagnostic tool may be helpful in such cases (Klemm 1989).

A relatively small number of clinical and pathological papers describing different EEG patterns as a result of IE have been published in the veterinary literature (Klemm and Hall 1970, Chen 1976, Breitschwert and others 1979, Crowell-Davis and others 1989). Generally, it has been impossible to identify EEG abnormalities that are specific and diagnostic for IE in the dog (Klemm 1989). EEG tracings were often described as paroxysmal activities including either high voltage slow activity (HVSA), slow or spike and, or, sharp waves, spindles as well as 25 Hz rhythms.

In addition, few systematic studies have been made on EEG patterns correlating with hereditary (Weiderholt 1974,Wallace 1975) and only one, to our knowledge, on experimentally-induced epilepsy in dogs (Gastaut and others 1982).

The incidence rate of abnormal interictal EEG recordings is still controversial. It has been stated that 28 per cent of epileptic dogs have normal interictal EEGs (Holliday and others 1970), whereas Wallace (1975) found no relationship between seizure incidence and abnormal EEGs in dogs with IE.

The purpose of this study was to investigate the usefulness of EEG testing in the screening and confirmation of IE in a golden retriever population.

MATERIALS AND METHODS

Animals

Five idiopathic epileptic dogs (group A) and 10 healthy golden retrievers (group B) of both sexes

and ranging in age from four to eight years were studied. All dogs derived from a genetic study which has been published by Srenk and others (1994). All the healthy dogs were submitted to the University of Berne's Small Animal Department for a routine work-up which included a physical and neurological examination, haematology (red and white cell count, differential cell count and platelet count), a serum chemistry panel including ammonia concentration and fasted bile acids and urine and cerebrospinal fluid (CSF) analysis, the results of which were all normal.

Anaesthesia

All the dogs were submitted to the anaesthetic protocol for EEG recordings as previously established at our clinic. Briefly, the animals were premedicated intravenously with 0·025 mg/kg bodyweight (BW) of medetomidine (Domitor; Orion) and general anaethesia was induced with propofol (Disoprivan; Stuart Pharmaceutical) as an intravenous bolus of 2 mg/kg BW. Depth of anaesthesia, defined by an absence of palpebral reflexes and no response to nociceptive stimulations was maintained with a continuous propofol drip (0·05 to 0·1 mg/kg BW/minute). After 20 minutes, atipamezole (Antisedan; Orion) at a dosage of 0·125 mg/kg BW was given intravenously. Lactated Ringer's solution was given intravenously at a rate of 10 ml/kg BW/hour during the whole procedure and body temperature, heart and respiratory rate were recorded every five minutes.

EEG

All the dogs were submitted to a single recording as described by Redding and others (1966) with some minor modifications. Briefly, six subdermal platinum needle electrodes were inserted subcutaneously over the cranium. They were arranged over the left and right frontoparietal, occipital and vertex cranium area. The ground electrode was placed over the external occipital protuberance. An eight-channel electroencephalograph (Schwarz ED 14 Picker) with the following settings was used: paper speed 10, 15 and 30 mm/second; sensitivity 30, 50, 70 and 100 µV; and filter range 0·53 and 70 Hz. A standardisation signal of 50 µV was recorded on the EEG before and after each recording session. The EEG was set for the standard lead system to be used and electrode resistances were tested. Monopolar and bipolar EEG recordings were performed.

Statistical analyses

Each EEG recording was visually examined, and amplitude and frequency of all leads were calculated at regular time intervals manually. The mean, standard deviation (SD) and range of amplitude and frequency of each EEG recording were calculated using a statistical software package (SAS). Statistical comparisons between means of frequency and amplitude of each lead one to another and of pooled EEG tracings between dogs of group A and B were made by the Wilcoxon signed-rank test ($P<0.05$). Reproducibility (R = var (ID)/[Var (ID) + Var]) of all results were evaluated with the restricted maximum likelihood estimation procedure. Homogeneity of all calculations was checked using the Monova Test Criteria and differences between means were considered significant if $P < 0.001$.

RESULTS

Dogs

All the dogs of group A (probands = Pr) had generalised seizures. Clinical details of the seizures are described elsewhere (Srenk and others 1994). Pedigree analyses revealed that Pr 1 and 5 belonged to the same family, whereas Pr 2, 3 and 4 were unconnected to this subpopulation, but were from the same dog population in Switzerland which we studied (Srenk and others 1994). Group B consisted of healthy dogs 6 to 15. Dogs 1 and 7 to 15 were all offsprings in the second generation of the parental animals Pr 5 (group A) and dog 6 (group B, Fig 1). They were all older than three years by the time of the EEG recordings (Table 1).

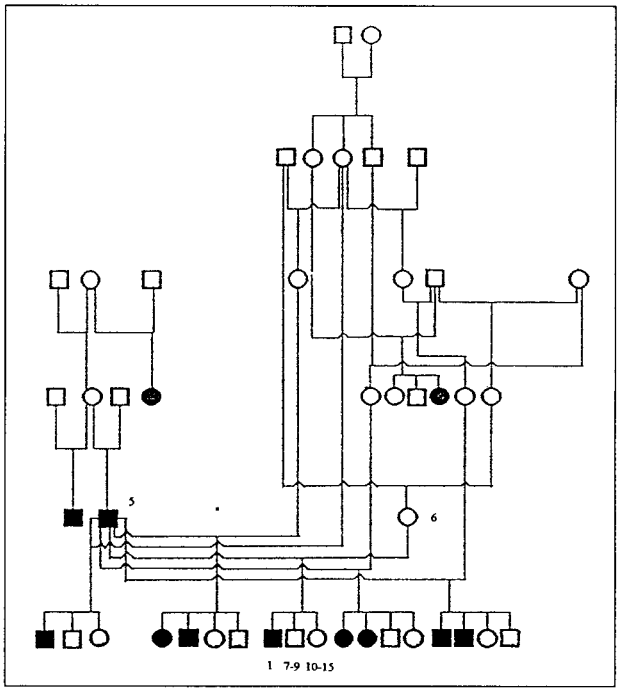

FIG 1. Pedigrees of related families of parental animals (proband 5 and dog 6) and offsprings (dogs 1 and 7 to 15). ○ Female, healthy, ● Female, proband, □ Male, healthy, ■ Male, proband, ❑ Number of dogs

Table 1. Age, sex, health status and electroencephalographic findings of high voltage slow activity (HVSA), low voltage fast activity (LVFA) and paroxysmal activity in epileptic (n=5) and control dogs (n=10)

Age (years)	Sex	Health status	Electroencephalographic findings								
			Background pattern				Paroxysmal activity (superimposed pattern)				
			HVSA		LVFA		(Freq (Hz)		Amp (μV)		Duration
			Freq (Hz)	Ampl(μV)	Freq (Hz)	Ampl(μV)	Range	Mean	Range	Mean	(seconds)
4·0	M	GS	1·5-2·0	6·6-33	6·0-9·0	3·0-6·6	11-21	12·70	3·3-33	10·98	0·6-1·7
5·0	M	GS	1·5-2·5	7·5-35	7·0-11	2·5-15	13-16	14·51	3·5-30	12·00	0·8-3·5
3·5	F	GS	1·0-2·0	12-66	6·0-11	4·1-17	11-17	14·00	4·1-41	12·80	0·4-1·4
5·0	M	GS	1·5	11-38	12-17	2·7-14	10-20	15·50	2·8-30	11·90	0·3-1·0
9·0	M	GS	2·0-2·5	8·0-28	8·0-11	3·6-8·0	4-8	7·00	14-56	28·00	1·6-2·8
			Basic pattern								
9·0	F	Healthy	1·5-2·0	15-28	13-14	5·1-9·1	No	No	No	No	No
4·0	M	Healthy	1·5-2·0	20-38	7·0-15	5·0-9·0	No	No	No	No	No
4·0	M	Healthy	1·0-2·0	24-48	8·0-15	7·0-12	No	No	No	No	No
4·0	M	Healthy	1·0-2·5	30-50	8·0-15	10-14	No	No	No	No	No
4.0	F	Healthy	2·0-2·5	25-40	10-20	11-12	No	No	No	No	No
4·0	F	Healthy	1·5-2·0	30-60	5·0-12	5·0-16	No	No	No	No	No
4·0	F	Healthy	1·0-2·0	15-70	10-17	4·0-18	No	No	No	No	No
4·0	F	Healthy	1·5-2·5	20-25	15-27	10-20	No	No	No	No	No
4·0	F	Healthy	2·0-2·5	25-35	10-22	5·0-15	No	No	No	No	No
4·0	F	Healthy	1·0-1·5	30-60	10-22	4·0-12	No	No	No	No	No

M Male, F Female, GS Generalised seizures, Freq Frequency, Amp Amplitude, No – No paroxysmal activity

EEG and statistical findings

The results of the EEG findings in group B are summarised in Table 1. For each dog there was no significant difference ($P > 0.005$) in the recorded parameters of amplitude and frequency comparing each lead (I to VIII) one to another. Therefore, these results were pooled for each dog and expressed as mean values. There was neither a statistical difference ($P > 0.05$) between the pooled results of individual or total EEG recordings. The basic pooled EEG pattern was characterised by HVSA with a mean amplitude of 34·7 ± 8·4 μV (range, 15 to 70 μV), mean frequency of 1·7 ± 0·1 Hz (range, 1 to 2·5 Hz), and low voltage fast activity (LVFA) with low amplitudes ranging between 4 and 20 μV (mean 13·2 ± 4 μV), high frequencies (range = 5 to 27 Hz; mean 16 ± 3 Hz).

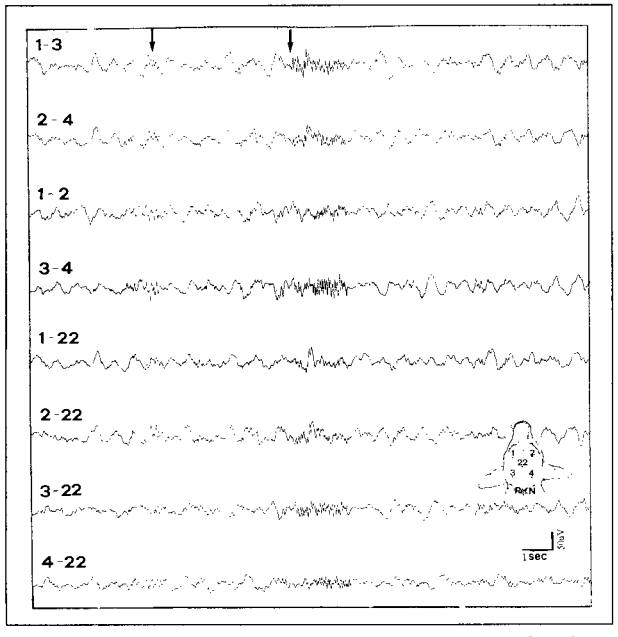

FIG 2. Electroencephalographic findings of proband 1. Arrows denote generalised paroxysmal activities in all leads

The results of the EEG findings in group A are summarised in Table 1. There were no statistical differences ($P > 0.05$) between amplitude and frequency of the individual EEG tracings. Therefore, these results were pooled. The background activity consisted of HSVA with a mean amplitude of 29·5 ± 4·5 μV (range, 6·6 to 66 μV) and mean frequency of 1·6 ± 0·1 Hz (range, 1 to 2·5 Hz) as well as LVFA with a mean amplitude of 5·2 ± 1·4 μV (range, 2·5 to 17 μV) and mean frequency of 10 ± 2·0 Hz (range, 6 to 17 Hz).

In addition, we found in all probands paroxysmal activity which was characterised by spindles with a mean frequency of 12 Hz (range, 4 to 21 Hz) and an amplitude ranging between 3·3 and 56 μV. These random isolated events lasted between 0·3 and 3·5 seconds (Table 1) and had a generalised transient distribution in the EEG tracings (Fig 2).

The mean values between HVSA in dogs of groups A and B were not significantly different ($P > 0.05$). However, the mean values of both low amplitude and fast activity of dogs of group A were significantly different ($P < 0.05$) from B.

The reproducibility (R) of the results ($R = 0.60$) was significantly high for all measured parameters, as was the homogeneity of the calculated values ($P < 0.001$).

DISCUSSION

In the present study, EEG recordings from a family of 10 healthy dogs and five dogs with IE under standardised medetomidine/propofol anaesthesia were performed. Our objective was to

assess the usefulness of EEG for screening and confirmation of IE in the dog.

Our study demonstrated significantly constant ($P < 0.05$) and similar values in amplitude and frequency of EEG recordings. The baseline EEG pattern in group B dogs and the background activity of group A were characterised by an homogeneous HVSA and LVFA pattern with no significantly different values between tracings.

A variety of interictal EEG abnormalities associated with epilepsy has been published over the past decades (Klemm and Hall 1970, Chen 1976, Breitschwert and others 1979, Crowell-Davis and others 1989). They included asymmetry, sharp waves, spike, HVSA, slow or fast frequency and spindles, while EEG findings in hereditary IE were mainly characterised by generalised spike discharges (Weiderholt 1974, Bernardini and Jaggy 1995). Visual examination of EEG recordings from our probands did not reveal spikes but spindles, which are believed to be induced by either the anaesthetic agent (Klemm 1989) or may be the result of behavioural and psychomotor seizures (Breitschwert and others 1979). We found in the present study that the EEG abnormalities had some characteristic features of seizure activity (Klemm 1968). Indeed, they were frequently observed as transient patterns in all our probands and additionally impressed by an asymmetrical distribution. Moreover, these isolated EEG events had a typically high variation in amplitude and duration. Therefore, we concluded that spindles in our epileptic dogs reflect neuronal discharges caused by IE itself, rather than hypoactivity induced by our specific anaesthetic agents.

Some aspects of the EEG findings deserve attention. We found that the mean amplitude of the transient activity from Pr 5 had a wider range and slower frequency when compared with other epileptic dogs. One reason may be that the amplitude/frequency ratio increases with age (Klemm 1989) and therefore, older dogs with IE will show different spindle activities similar to dogs with psychomotor seizures (Breitschwert and others 1979). Although the waveforms of the EEGs were characterised by HVSA and LVFA (Fig 2), we found that the mean amplitude of the low voltage (LV) pattern and the mean frequency of the fast activity (FA) were significantly smaller in probands. A likely explanation is that spindles may mask some of the LV background and therefore the frequency of FA may increase progressively and dominate background activity (Mühlau 1990).

Recently, it has been shown that IE in the golden retriever has a multifactorial mode of inheritance and that the convulsive liability is high, if underlying endogenous characters such as emotional stress coincide with other factors (Srenk and others 1994). Despite the fact that 10 per cent of the offspring in our retriever family were positive for spindles – if the EEG is taken at the age of maximal expression – it does not mean that this factor is genetically dependent, but that its interaction may increase the liability to contract seizures in the golden retriever. However, in terms of genetics, EEG abnormalities represent just an epiphenomenon of a complex genetic background (Doose and Baier 1988). Indeed, there are striking parallels between spike-and-waves (Bernardini and Jaggy 1996) and spindles related to IE in our dogs. They show a similar topography and their age and sex distribution are similar. These descriptive similarities cannot prove, but may suggest, that these types of paroxysms have a common neurophysiological basis, but different degrees and modes of clinical expression.

Our study has clearly demonstrated that EEG is of extreme importance in the verification of a tentative diagnosis of IE in the dog. Therefore, we believe that EEG combined with pedigree analysis may be very helpful in the risk assessment of IE. Further studies are needed to define electroencephalographic characteristics in young dogs of related families to be able to inform breeders and owners whether their dogs will be prone to seizures.

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ABSTRACTS

Diagnostic and therapeutic considerations in a hypercalcaemic dog with multiple endocrine neoplasia

A YORKSHIRE terrier aged 13 years had progressive weakness and disorientation for four months. Initial episodes manifested themselves as 'star-gazing' and loss of directional sense. Physically, the dog was normal and alert. Haematological and serum biochemistry abnormalities included hypercalcaemia and increased total CO_2 concentration. There was rapid deterioration in neurological status 11 days later, when the dog had seizures. A cranial abdominal mass was demonstrated on ultrasonography. This was diagnosed as a phaeochromocytoma. Serum intact parathyroid hormone (iPTH) and ionised serum calcium assays were undertaken to determine if primary hyperparathyroidism was the cause of the hypercalcaemia. Results were consistent with a parathyroid hormone-secreting neoplasm. To support the diagnosis, scintigraphy was performed and results suggested multiple endocrine neoplasia. Adrenalectomy was performed. No obvious metastases or invasion of surrounding tissue was seen. Phaeochrom- ocytoma was confirmed on histology. Total serum calcium concentrations decreased, despite continued high iPTH levels, until the 17th postoperative day. Subsequently, the serum calcium rose, confirming concurrent primary hyperparathyroidism. Scintigraphy also confirmed this. Over a 451 day follow-up period, the dog returned to normal, except for a few periods of weakness. No further episodes of star-gazing or disorientation have occurred.

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Use of diazepam per rectum at home for the acute management of cluster seizures in dogs

ELEVEN dogs (including three German shepherd dogs) with idiopathic epilepsy were treated with diazepam per rectum (DPR) in the home to control generalised cluster seizures. They were evaluated over a 16-month period. Each animal had a prior history of cluster seizures and had been treated with a variety of antiepileptic drugs. All were being treated with phenobarbitone, and 10 were being treated with bromine concomitantly. Owners were instructed to give the DPR by plastic teat cannula, attached to a plastic syringe, inserted approximately 2 cm into the rectum, when the initial generalised seizure/paddling occurred. This was to be repeated if a second or third generalised seizure occurred within 24 hours. The DPR was not to be given if there was a fourth seizure within this time, if the dog was having difficulty breathing, if it was excessively depressed or if there was blood around the rectum from the previous dose. If these conditions arose, veterinary advice was to be sought. Dosage of the DPR was 0·5 mg/kg. All seizures were recorded by the owners in a daily log. Treatment lasted from 57 to 464 days. There was a significant decrease in cluster seizures, and in the number of seizures per cluster, after treatment began. DPR was successful in preventing further seizures after the first occurrence. No significant correlation was found between the type of antiepileptic drug treatment and the change in the number of cluster seizures after DPR. Eight dogs are alive and well following this treatment. Two were euthanased because of intractable seizures, one was killed in a car accident.

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