Epilepsy

Holger A. Volk  DVM, DipECVN, PhD, FHEA, MRCVS
Head of Department CSS & Professor of Veterinary Neurology & Neurosurgery
Royal Veterinary College
Similarities
OneHealth

Technical

Institutional

Social
1+1=3 Synergy

Technical

Social

Institutional

OneHealth
Unpredictable & Uncontrollable
Impact

Dogs with epilepsy (poorly controlled, high seizure frequency) -> increased risk of¹-⁴
• premature death
• behaviour changes
• reduced quality of life (QoL).

Seizures not only affect QoL for affected dogs, but also for owner³-⁴.

Quality-of-life aspects in idiopathic epilepsy in dogs

A. Wessmann, H. A. Volk, R. M. A. Packer, M. Ortega, T. J. Anderson

Veterinary Record (2016) doi: 10.1136/vr.103355

• **Carer-perceived dog’s QoL impacted by**
  • High seizure frequency
  • Receiving 3rd antiepileptic drugs

• **Owner’s QoL impacted by**
  • Sedation level
  • Ataxia level

Reductions in perceived canine QoL scores associated with reductions in carer QoL, and vice versa
Physiological reactivity to spontaneously occurring seizure activity in dogs with epilepsy and their carers

R.M.A. Packer\textsuperscript{a}, H.A. Volk\textsuperscript{b}, R.C. Fowkes\textsuperscript{b}

(A) Dog

(B) Owner

![Graphs showing cortisol levels in dogs and owners during non-seizure and seizure states at 20 and 40 minutes post-seizure.](image-url)
Evaluation of the Impacts of Epilepsy in Dogs on Their Caregivers

Julie A. Nettifee, BS, RVT, VTS (Neurology), Karen R. Munana, DVM, MS, DACVIM (Neurology), Emily H. Griffith, PhD

- QoL significantly associated with
  - Seizure type (cluster)
  - Seizure frequency
  - Side-effects
  - No additional medication

- QoL not associated with the number of antiepileptic medications or average monthly cost of treatment
• Median expenditure for antiepileptic medication was $51–75.
  • Cost not associated with quality of life score.
• Support
  • 80% reported receiving veterinary support
    • veterinarian (reported by 89% of owners),
    • online educational materials (26%),
    • veterinary technician (24%),
    • printed educational materials (10%),
    • and client-to-client interactions (8%).
  • 68% online support groups for owners of pets with epilepsy

• Regular contact with and easy access to veterinarian important in reducing anxiety associated with their dog’s epilepsy. (Berendt et al. 2007)
Neurobehavioural comorbidities

- Epilepsy characteristics
  - Seizure severity
  - Seizure frequency

- Underlying cause

- Epilepsy treatment
  - Seizure control
  - Side-effects

- Brain development and ageing

- Nutrition

Quality of life
Idiopathic epilepsy ≠ One disease
<table>
<thead>
<tr>
<th>Early terminology</th>
<th>Terminology currently in use</th>
<th>Suggested veterinary terminology 2015</th>
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<tbody>
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<td>Primary Epilepsy</td>
<td>Idiopathic Epilepsy</td>
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<td>Symptomatic Epilepsy</td>
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<td>- A suspected symptomatic cause, which however remains obscure</td>
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Belgian shepherd
Late onset epilepsy (mean 3.3 years) with focal onset seizures
ADAM23 gene
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<td>Symptomatic Epilepsy</td>
<td>2. Suspected genetic background</td>
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<td>- Epilepsy caused by identified cerebral pathology</td>
<td>- Epilepsy caused by identified cerebral pathology</td>
<td>3. Unknown cause and no indication of</td>
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ADAM23 is a common risk gene for canine idiopathic epilepsy

Lotta L. E. Koskinen, Eija H. Seppäla, Jutta Weiss, Tarja S. Jokinen, Ranno Viitmaa, Reetta L. Hänninen, Pascale Quignon, Andrea Fischer, Catherine André and Hannes Lohi

Abstract

Background: Idiopathic or genetic adult-onset epilepsy is a common neurological disorder in domestic dogs. Genetic association has been reported only with ADAM23 on CFA 37 in few breeds. To identify novel epilepsy genes, we performed genome-wide association (GWA) analyses in four new breeds, and investigated the association of the previously reported ADAM23 haplotype with the epilepsy phenotype in eight breeds.

Results: GWA analysis did not reveal new epilepsy loci. ADAM23 association (p < 0.05) was identified in five breeds. Combined analysis of all eight breeds showed significant association (p = 4.6e-6, OR 1.9).

Conclusions: Our results further support the role of ADAM23 in multiple breeds as a common risk gene for epilepsy with low penetrance. The lack of findings in the GWA analyses points towards inefficient capture of genetic variation by the current SNP arrays, causal variant(s) with low penetrance and possible phenocopies. Future work will include studies on ADAM23 function and expression in canine neurons, as well as whole-genome sequencing in order to identify additional IE genes.

Keywords: Dog, Canis familiaris, Epilepsy, Idiopathic epilepsy, ADAM23, GWA, Association
Generalized myoclonic epilepsy with photosensitivity in juvenile dogs caused by a defective DIRAS family GTPase 1

Franziska Wielandera,b,c,d,1, Riikka Sarviaho, Fiona James,e, Marjo K. Hytönen,b,c,d, Miguel A. Cortezf,g, Gerhard Klugeri,i, Lotta L. E. Koskined,b,c,d, Meharji Arumillib,c,d, Marion Kornbergj, Andrea Bathen-Noethenk, Andrea Tipoldl, Kai Rentmeisterm, Sofie F. M. Bhattin, Velia Hülsmeyer, Irene C. Boettcher, Carina Tästensen, Thomas Flegeln, Elisabeth Dietschip, Tosso Leebp, Kaspar Matiasekoq, Andrea Fischera,2,3, and Hannes Lohib,c,d,2,3
What next in canine epilepsy research?
## What next in canine epilepsy research?

<table>
<thead>
<tr>
<th>Research Area</th>
<th>Primary care vs. Specialist vets</th>
<th>Owner vs. Primary care</th>
<th>Owner vs. Specialist vets</th>
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<tr>
<td></td>
<td>$\chi^2$</td>
<td>p</td>
<td>Who rated higher?</td>
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<tr>
<td>Existing AEDs</td>
<td>1.2</td>
<td>0.876</td>
<td>Owner</td>
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<td>New AEDs</td>
<td>11.8</td>
<td>0.019</td>
<td>Specialist</td>
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<td>Vet education</td>
<td>6.2</td>
<td>0.186</td>
<td>Owner</td>
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<tr>
<td>Side effects of AEDs</td>
<td>2.4</td>
<td>0.692</td>
<td>Owner</td>
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<tr>
<td>Genetic aetiology</td>
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<td>Seizure detection</td>
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<td>Diagnosing epilepsy</td>
<td>2.1</td>
<td>0.709</td>
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<tr>
<td>Lifespan</td>
<td>4.1</td>
<td>0.393</td>
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<tr>
<td>Seizure classification</td>
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<td>0.079</td>
<td>Owner</td>
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<td>Prognosis</td>
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<tr>
<td>Co-morbidities</td>
<td>4.6</td>
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<tr>
<td>Anxiety</td>
<td>1.8</td>
<td>0.880</td>
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<tr>
<td>Hyperactivity</td>
<td>6.6</td>
<td>0.161</td>
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<tr>
<td>Attention</td>
<td>8.9</td>
<td>0.064</td>
<td>Owner</td>
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<tr>
<td>Physical capabilities</td>
<td>3.6</td>
<td>0.463</td>
<td>Owner</td>
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<tr>
<td>Social interactions</td>
<td>5.8</td>
<td>0.213</td>
<td>Owner</td>
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</table>
Assessment of cognitive impairments in canine idiopathic epilepsy

Spatial Working Memory

Problem Solving Abilities
Trainability is affected by epilepsy

<table>
<thead>
<tr>
<th>Question</th>
<th>Epilepsy</th>
<th>Control</th>
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</thead>
<tbody>
<tr>
<td>Easily distracted by sights, sounds, smells</td>
<td>**</td>
<td></td>
</tr>
<tr>
<td>Will fetch sticks, balls or objects</td>
<td>**</td>
<td>**</td>
</tr>
<tr>
<td>Listens closely to everything you say/do</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Obeys sit immediately</td>
<td>**</td>
<td></td>
</tr>
<tr>
<td>Obeys stay immediately</td>
<td>**</td>
<td>**</td>
</tr>
<tr>
<td>Returns when called off leash</td>
<td>**</td>
<td>**</td>
</tr>
<tr>
<td>Slow to learn new tricks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Slow to respond to punishment</td>
<td>**</td>
<td>***</td>
</tr>
</tbody>
</table>
Cognitive Dysfunction (CCDR)
A holistic approach...

- Removing potential triggers
- Reducing stress factors
- Antiepileptic drug
- Nutrition
- Epilepsy control
Have you ever cooked spaghetti?
Therapy – Mode of action

Excitatory Nerve Terminal
- Carbamazepine
- Phenytoin
- Valproate
- Lamotrigine
- Gabapentin?
- Felbamate?

Presynaptic neuron
- Glutamate
- Na⁺, Ca²⁺
- NMDA receptor
- Glycine
- K⁺
- Depolarization

Inhibitory Nerve Terminal
- GABA
- SSA
- GABA-T
- GABA receptor
- Benzodiazepines
- Phenobarbital
- GABA-A receptor
- Cl⁻
- Vigabatrin
- Tigabine

Presynaptic neuron
- Glutamate
- GAD
- GABA

Glia cell
What do we treat?

Initiating event (e.g. head trauma, febrile seizures, stroke, infections, gene defects)

- Repair (or control)
- Failure to repair

No consequence

Onset of epileptic cascade (e.g. by 'second hit', polymorphisms, susceptibility genes, crucial modulators)

Epileptogenesis

Role of neurodegeneration?

Spontaneous seizure (onset of epilepsy)

- No progression
- Progression of epilepsy

Chronic epilepsy

Often pharmacoresistant

Pharmacological intervention

Antiepileptogenic

Anticonvulsant

Disease-modifying

Reversal and/or prevention of multidrug resistance

Neurobehavioural changes

TRENDS in Pharmacological Sciences

Löscher, Trends in Pharmacological Sciences, 2002
Seizure begs another seizure?

A. Progression of epilepsy in previously untreated dogs:
   Number of baseline seizures prior to treatment

\[ r^2 = 0.64 \]

B. Number of baseline seizures prior to treatment,
   averaged over 2 month periods

\[ r^2 = 0.91 \]

Lösch et al., 2004
Responses to successive anti-epileptic drugs in canine idiopathic epilepsy


10.1136/vr.102934 | Veterinary Record

The magic one Third - two Third

 Patients receiving AEDs (n=196)

  - PB non-responsive (n=123) 62.8%
  - PB responder (n=73) 37.2%
    - n=28 seizure free 14%

phenobarbitone

phenobarbitone + potassium bromide

phenobarbitone + potassium bromide + third line drug

- PB and KBr responder (n=21) 26.3% of 80 dogs receiving 2nd line AED
- PB and KBr non-responder (n=59) 73.8% of 80 dogs receiving 2nd line AED
  - No extra AEDs added (n=28)
    - Lost to follow up (n=15)
  - No extra AEDs added (n=26)
    - Lost to follow up (n=1)

- PB, KBr and third line drug responder (n=21) 37.5% of 32 dogs receiving 3rd line AED
- PB, KBr and third line non-responder (n=20) 62.5% of 32 dogs receiving 3rd line AED
  - No extra AEDs added (n=26)
    - Lost to follow up (n=1)
A prospective observational longitudinal study of new-onset seizures and newly diagnosed epilepsy in dogs

N. Fredsoe, N. Toft, A. Sabers and M. Berendt

Fig. 2 Seizure recurrence in 24 untreated dogs with idiopathic epilepsy. Open circles = seizure. Black circles = end of study. Gray circles = cluster seizure. Gray squares = Death/euthanasia
Drug-resistant epilepsy

Environment?

Diet?

- Impact of
  - genetic Factors (epistatic, epigenetic)
  - disease-associated factors
  - drug-induced factors

Seizure density

- ? Changes in drug targets
- ? Changes in local brain uptake of anticonvulsant drugs
Is there a magic wand?
Loscher and Schmidt 2011
Education prior to treatment

Life-time commitment - “your dog may always have a seizure”

Chart for seizure frequency

Side effects

A holistic approach:

- Removing potential triggers
- Reducing stress factors
- Antiepileptic drug
- Nutrition
- Epilepsy control
What is the role of diets?
• General dietary considerations
• Specialised nutrition
  – Hypoallergenic diet
  – Omega-3 fatty acid supplementation
  – Ketogenic diet (KD)
A randomised trial of a medium-chain TAG diet as treatment for dogs with idiopathic epilepsy

Tsz Hong Law¹,², Emma S. S. Davies¹, Yuanlong Pan³, Brian Zanghi³, Elizabeth Want² and Holger A. Volk¹*  
¹Department of Clinical Science and Services, Royal Veterinary College, Hatfield AL9 7TA, UK  
²Section of Computational and Systems Medicine, Imperial College, London SW7 2AZ, UK  
³Nestlé Purina Research, St Louis, MO 63164, USA  

(Submitted 20 April 2015 – Final revision received 16 July 2015 – Accepted 21 July 2015)
Medium chain triglycerides diet (MCTD) study design

- 6-month prospective, randomised, double-blinded, placebo controlled crossover dietary trial
- Idiopathic epilepsy
- ≥1 Antiepileptic drug (AED) chronically treated (steady state)
- ≥3 seizures in last 3 months
Seizure frequency per month

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Test</th>
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<tbody>
<tr>
<td>Minimum</td>
<td>0.33</td>
<td>0.00</td>
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<tr>
<td>Median</td>
<td>2.67</td>
<td>2.31</td>
</tr>
<tr>
<td>Maximum</td>
<td>22.92</td>
<td>9.89</td>
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Wilcoxon’s matched pairs signed rank test

P=0.0195 (2-sided)

3 become seizure free
7 responders (>50% reduction in seizures)
5 reduction in seizures
6 no response
Results

• No significant change between both diets in:
  – Phenobarbital serum levels (26.50μg/ml, 23.50-34.00μg/ml v. 32.50μg/ml, 25.00-36.75μg/ml, p=0.4233)
  – Potassium bromide serum levels (1.23mg/ml, 1.09-1.89mg/ml v. 1.29mg/ml, 1.02-1.61mg/ml, p=0.4037)
  – Weight (29.79, ±15.16kg v. 29.61, ±15.51kg, p=0.2997)

• There was a significant increase in blood level hydroxybutyrate (BHB) on MCTD
A NOVEL MECHANISM OF ACTION

- Typical antiepileptic drugs (phenobarbital and potassium bromide) are GABAergic enhancing inhibitory neurotransmission.
- Experts believe MCTs (C10:0 – decanoic acid) may have direct anti-seizure effects via blockage of AMPA receptors inhibiting excitatory neurotransmission; enhancing typical antiepileptic therapy.¹⁰

![Diagram showing the mechanism of action of MCT oil on AMPA receptors](image-url)
Epilepsy beyond seizures: a review of the impact of epilepsy and its comorbidities on health-related quality of life in dogs

Rowena M. A. Packer, Holger A. Volk

Veterinary Record (2015), 306-315  doi: 10.1136/vr.103360