IS IT REALLY EPILEPSY?

And if not……..

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AGENDA

- "Classical" Epilepsy (Bob)
- Paroxysmal dyskinesia (Bob)
- *Benign Juvenile Epilepsy (Caroline)*
- *Head tremors (Caroline)*

BUT FIRST…

- We all have to….
  - come to the same conclusion from what we see or evaluate
  - count on reliable sources of information and speak the same language
  - share these findings and collaborate, in order to support research and reduce the frequency of neurologic problems in our population over time
- Source of information
  - Evidence based (as much as possible)
  - Up to date
  - No gut feeling or emotional decision making
  - International Veterinary Epilepsy Task Force

AND REMEMBER…

SOURCE OF INFORMATION

- International Veterinary Epilepsy Task Force: since 2014!!!
  - Who?
    - 26 veterinary practitioner, neuropharmacology, neuropathology and neurology experts from around the world (Australia, Austria, Belgium, Denmark, Germany, Netherlands, Spain, United Kingdom, United States)
    - Special thanks to Dr. Sofie Bhatti, DVM, PhD, Head of the Clinical Neurology Department at Ghent University, who is a member of the IVETF, and provided all the video's for this lecture
  - What?
    - produced seven 'consensus statements'
    - recommendations and classifications on all aspects of the condition
    - It is the first time this many veterinary neurology clinicians and neuroscientists have formally agreed on the key aspects of canine and feline epilepsy
  - Where? Open access: https://pubmed.ncbi.nlm.nih.gov/

SOURCE OF INFORMATION

- International Veterinary Epilepsy Task Force:
  - 7 Consensus statements
    - Report on epilepsy definition, classification and terminology in companion animals
      - https://bmcvetres.biomedcentral.com/articles/10.1186/s12917-015-0461-2#Tab1
    - Proposal on the diagnostic approach to epilepsy in dogs
      - https://bmcvetres.biomedcentral.com/articles/10.1186/s12917-015-0462-1
    - Current understanding of idiopathic epilepsy of genetic or suspected genetic origin in purebred dogs
      - https://bmcvetres.biomedcentral.com/articles/10.1186/s12917-015-0463-0
    - *Medical treatment of canine epilepsy in Europe*
    - *Outcome of therapeutic interventions in canine and feline epilepsy*
    - *recommendations for a veterinary epilepsy-specific MRI protocol*
    - *recommendations for systematic sampling and processing of brains from epileptic dogs*

TERMINOLOGY

- Seizures
  - any sudden, short lasting and transient event
  - It does not imply that the "event" is epileptic!!!
- Epileptic seizures
  - excessive or synchronous, usually self- limiting epileptic activity of neurons in the brain
  - short episodes with convulsions or focal motor, autonomic or behavioural features
- Reactive seizures
  - occurring as a natural response from the normal brain to a transient disturbance in function (metabolic or toxic in nature)
- Epilepsy
  - disease of the brain characterized by an enduring predisposition to generate epileptic seizures (at least 2 or more unprovoked epileptic seizures >24 h apart)

VETERINARY TERMINOLOGY AND ITS MOST COMMON AMENDMENTS OVER TIME

	Early terminology	Terminology currently in use	Suggested veterinary terminology 2015
EPILEPTIC SEIZURES			
An epileptic seizure with clinical signs indicating activity which starts in a localised area in the brain	Petit Mal	Partial/focal seizure	Focal epileptic seizure[a]
-Will present with focal motor, autonomic or behavioural signs alone or in combination	Aura	- Simple partial/focal seizure (consciousness unimpaired[a])	
		- Complex partial/focal seizure (consciousness impaired[a])	
An epileptic seizure with clinical signs indicating activity involving both cerebral hemispheres from the start. -In dogs and cats the seizure presents predominantly as immediate 'convulsions' and loss of consciousness. Salivation, urination and/or defecation often also occur during convulsions. May also (but rare) present as atonic or myoclonic seizures	Grand Mal (always implicating convulsions)	Primary generalized seizure	Generalized epileptic seizure
An epileptic seizure which starts in a localized area in the brain and spreads subsequently to involve both hemispheres. -In dogs and cats the seizure starts with localized motor, autonomic and/or behavioural signs rapidly followed by convulsions. Salivation, urination and/or defecation often also occur during convulsions.	Partial seizure with secondary generalization (secondary generalized seizure)	Focal seizure with secondary generalization	Focal epileptic seizure evolving to become generalized

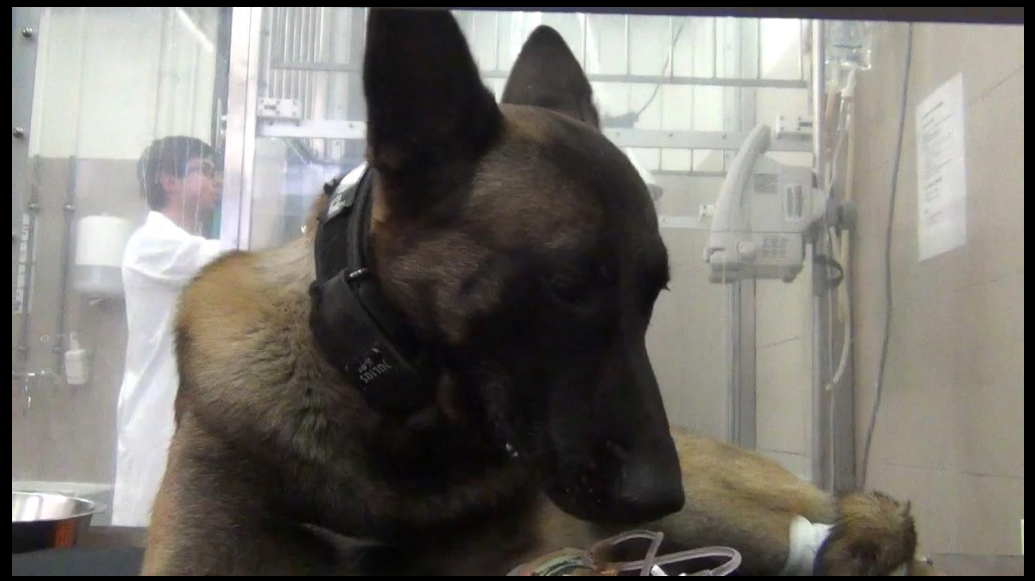
CLASSIFICATION: SEIZURE TYPE

- Focal epileptic seizures
  - episodic focal ***motor*** activity e.g. facial twitches, repeated jerking head movements, rhythmic blinking, repeated rhythmic jerks of one extremity
  - AND OR ***autonomic activity*** (dilated pupils, hypersalivation or vomiting)
  - AND OR short lasting episodic change in ***behaviour*** such as e.g. anxiousness, restlessnesss, fear reactions, abnormal attention seeking
- Generalized epileptic seizures
  - bilateral involvement
  - tonic, clonic or tonic-clonic epileptic seizures
  - lose consciousness, but….
  - Salivation, urination and/ or defecation often also occur
- Focal epileptic seizures evolving into generalized epileptic seizures

GENERALIZED IDEOPATHIC EPILEPSY

video's courtesy of Dr Sofie Bhatti

Focal Epilepsy: brain tumor



Focal Epilepsy encefalitis 4m

Focal Ideopathic epilepsy

video's courtesy of Dr Sofie Bhatti

VETERINARY TERMINOLOGY AND ITS MOST COMMON AMENDMENTS OVER TIME

	Early terminology	Terminology currently in use	Suggested veterinary terminology 2015
EPILEPSY			
Epilepsy classified by aetiology	Primary Epilepsy	Idiopathic Epilepsy	Idiopathic Epilepsy
	- Epilepsy where no structural cerebral pathology is suspected	- Epilepsy where no structural cerebral pathology is suspected. A genetic component may be involved	1. Proven genetic background
			2. Suspected genetic background
			3. Unknown cause and no indication of structural epilepsy
Epilepsy classified by aetiology	Secondary or Acquired epilepsy	Symptomatic Epilepsy	Structural epilepsy
	- Epilepsy caused by identified cerebral pathology	- Epilepsy caused by identified cerebral pathology	- Epilepsy caused by identified cerebral pathology
Epilepsy classified by aetiology	Cryptogenic	Probably or possibly symptomatic epilepsy	Unknown cause
	- Meaning hidden	- A suspected symptomatic cause, which however remains obscure	

CLASSIFICATION: AETIOLOGICAL

- Idiopathic epilepsy (overarching term)
  - Genetic epilepsy
  - Suspected genetic epilepsy, involving multiple genes and interactions between genes (epistatic) and between genes and the environment (epigenetic)
  - (yet) unknown cause, and no indication of structural epilepsy
- Structural epilepsy
  - intracranial/cerebral pathology
  - vascular, inflammatory/infectious, traumatic, toxic, anomalous/developmental, metabolic, neoplastic and degenerative diseases
    - Ex: Lafora disease progressive myoclonic epilepsy, a storage disease

CONCLUSIONS

- (Canine) epilepsy is a complex brain disease with sudden and abnormal activity in neuronal networks
- It causes clinical signs of seizures, characterised by
  - Motor features
  - autonomic features
  - and/or behavioural features
- Epileptic seizures are episodic and brief (in most cases less than 2–3 min)
- Possible impairment of consciousness during seizures
- Can rise from a plethora of causes

CONCLUSIONS

- A high epilepsy prevalence in a specific breed or dog families are strong indicators of inherited epilepsy, BUT

- are the genetic defects the sole cause of the epilepsy?
- the epilepsy might be multifactorial
  - provoking environmental & developmental influences
  - AND genetic factors

EPILEPSY VS EPISODIC DISORDERS

- Is it really (ideopathic) epilepsy?
  - Dog usually normal during a classical consultation
- Diagnoses based on:
  - Anamnese: what happens?
    - When: during efforts, rest, or “in between”?
    - How often
    - How long: don’t estimate, time it!
    - how does the “seizure” looks like?
  - video’s
  - EEG (electro encephalogram): not routinely used

EPILEPSY VS EPISODIC DISORDERS

- Many conditions can trigger seizure-like events, so how do you differentiate among them?
- If a dog is presented with "episodic disorders", showing abnormal (involuntary) movements
  - First determine if it is really epilepsy or something else
  - What are the clinical characteristics of episodic disorders
    - See https://bmcvetres.biomedcentral.com/articles/10.1186/s12917-015-0462-1/tables/1
  - Look for the underlying etiology!

CLINICAL CHARACTERISTICS OF EPISODIC DISORDERS

Discriminator	Syncope	Narcolepsy/ Cataplexy	Neuromuscular weakness	Paroxysmal behaviour changes (compulsive disorder)	Vestibular attack	Paroxysmal Dyskinesia	Idiopathic head tremor	Seizure
Clinical status between episodes	Normal or arrhythmia, pulse deficits, heart murmur, cyanosis, abnormal lung auscultation	Altered sleep/wake cycle, normal clinical examination	Normal or generalised weakness, muscle atrophy, pain, decreased reflexes	Normal	Normal	Normal	Normal	Normal or forebrain signs
Precipitating event or trigger	Exercise, excitement	Excitement, eating	Activity, exercise	Behavioural triggers (*e.g.*, fear)	None	None or activity, exercise, excitement, stress	None or stress, fatigue, overstimulation	None or flashing lights, anxiety, stress
Pre-event changes	None	None	None	None	None	None	None	Pre-ictal signs may be observed including: anxiety, restlessness, increased affection, contact-seeking, withdrawal, hiding, aggressiveness, and vocalization

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Event description	Brief, sudden collapse and rapid recovery	Sudden collapse	Stiff, stilted gait prior to collapse	Pacing, barking, licking, chasing imaginary objects or tail, chewing objects	Head tilt, nystagmus, vestibular ataxia, collapse towards side of head tilt	Dystonia, chorea, ballismus, athetosis, tremors, impaired posture, inability to stand or walk	Vertical or horizontal rhythmic head movement	Depending on seizure focus, focal or generalized, tonic-clonic movements most common
Level of consciousness	Reduced to absent	Normal if only cataplexy. Absent (asleep) in narcolepsy	Normal	Normal	Normal or disorientated	Normal	Normal	Often impaired
Autonomic signs	Possible abnormalities of heart rate and rhythm	None	None	None	None	None	None	Possible: hypersalivation, defaecation, urination
Muscle tone	Flaccid (all body)	Flaccid (all body)	Often flaccid (can appear spastic with certain myopathies)	Normal	Unilateral decrease in extensor muscle tone	Hypertonicity (focal or generalised)	Normal	Typically increased: tonic (hypertonicity) or alternating tonic-clonic movements

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Discriminator	Syncope	Narcolepsy/ Cataplexy	Neuromuscular weakness	Paroxysmal behaviour changes (compulsive disorder)	Vestibular attack	Paroxysmal Dyskinesia	Idiopathic head tremor	Seizure
Lateralising signs	No	No	No	No	Yes	Possible	No	Possible
Duration	Seconds	Seconds to minutes	Minutes to hours	Minutes to hours	Seconds to hours	Seconds to hours	Seconds to hours	Seconds to minutes or > 5 min in case of status epilepticus
Post-episodic changes	None	None	None	None	None	None or tiredness	None, tiredness, or restlessness	Post-ictal signs frequently occur including: disorientation, aggressive behaviour, restlessness, pacing, lethargy, deep sleep, hunger, thirst, ataxia, proprioceptive deficits, and blindness
Further comments	May be accompanied by cough, increased respiratory noise	Often occurs in young purebred dogs.	May be accompanied by dysphagia, dysphonia, regurgitation, dyspnoea	History of anxiety disorder	Subtle signs of vestibular disease might persist	Interaction with the owner can alleviate or interrupt the episode. Consider breed specific disorders and age at onset.	Episodes can be interrupted by the owner	Facial muscles often involved during the ictus

DIAGNOSES OF IE

- Detailed history
- Complete a standardised epilepsy questionnaire
  - https://static-content.springer.com/esm/art%3A10.1186%2Fs12917-015-0462-1/MediaObjects/12917_2015_462_MOESM1_ESM.doc
- A complete clinical and neurological examination
- Video-footage
- Differentiate from other **non-epileptic** episodic or paroxysmal events/movement disorders or dyskinesias (for example paroxysmal dyskinesias, head tremor)

IDEOPATHIC EPILEPSY

- improve consistency in the diagnosis of ideopathic epilepsy
  - Both in the clinical and research settings!!

- Criteria for the diagnosis of idiopathic epilepsy (IE)
  - a 3-tier confidence level system

IDEOPATHIC EPILEPSY: 3-TIER

- Tier I confidence level
  - a history of 2 or more unprovoked epileptic seizures occurring at least 24 h apart
  - age at epileptic seizure onset of between 6m and 6y
  - unremarkable inter-ictal physical and neurological examination
  - no significant abnormalities on minimum data base blood tests and urinalysis
- Tier 2 level: tier 1 plus…
  - unremarkable fasting and post-prandial bile acids
  - MRI of the brain and cerebrospinal fluid (CSF) analysis
- Tier 3 level: tier 1 + 2 +
  - Identification of EEG abnormalities characteristic for seizure disorders

DIFF DIAGNOSES

- Differentiate from paroxysmal movement disorders or dyskinesias
  - abnormal, sudden, involuntary contraction of a group of skeletal muscles which recur episodically
  - challenging to differentiate from (focal) epileptic seizures
  - tend to continue to attempt to perform the activity they were previously doing
  - owner intervention may alter the course of the episode
  - Head tremor: owners reported that they could consistently interrupt each head tremor episode

- narcolepsy

- gen mutation myoclonal epilepsy RR

video's courtesy of Dr Sofie Bhatti

PAROXYSMAL DYSKINESIA

- The Veterinary Journal 213 (2016) 33–37
  - Natural history of canine paroxysmal movement disorders in Labrador retrievers and Jack Russell terriers (Mark Lowrie UK, Laurent Garosi UK)
  - https://pubmed.ncbi.nlm.nih.gov/27240912/
  - 36 Labradors with clinically confirmed PD and a follow-up of ≥3 years were retrospectively reviewed
- Journal of Veterinary Internal Medicine, May 2021 May
  - International veterinary canine dyskinesia task force ECVN consensus statement https://pubmed.ncbi.nlm.nih.gov/33769611/

All dogs show an absence of mentation alterations and autonomic signs
Dog 1: left forelimb shows chorea that then progresses to involve the right forelimb.There is also some athetosis of the trunk causing a bending to the left hand side
Dog 3: left pelvic limb is showing signs of ballism with signs of chorea in the left forelimb
Dog 4: dystonia of the tail as well as similar chorea type movements in the limbs to the other dogs featured.

All four dogs show some degree of body tremor with dog 2 and 4 also exhibiting tremors of the head
Tremors are often seen with paroxysmal dyskinesia but are non-specific signs

No post-ictal or abnormal inter-ictal findings were recorded in any dog (not shown on video).

LOWRIE & GAROSI PUBLICATION

- 36 Labradors with clinically confirmed PD and a follow-up of ≥3 years were retrospectively reviewed
- young onset, triggered by startle or sudden movements
- male bias (81%)
- No concurrent disease
- The median age of the 36 Labradors at episode onset was 2 y 3 m (range, 9 months to 10/11 years)
- Triggers: sudden movements - being startled - excitement
- episodes always at home and never when sleeping or during exercise

PAROXYSMAL DYSKINESIA

- hyperkinetic paroxysmal movement disorders
- main feature is involuntary sustained muscle contraction
- recurrent episodes are assumed to be the result of a molecular or structural abnormality
- Known causes of PD in dogs are thus far limited to:
  - genetic (Forman et al., 2012; Gill et al., 2012; O'Brien et al., 2015) in CKCS
  - drug-induced (Kube et al., 2006; Mitek et al., 2013) in epileptic Chow (by phenobarb)
  - dietary factors (Lowrie et al., 2015) in Border Terrier with canine epileptoid cramping syndrome, a manifestation of gluten sensitivity
  - most commonly of idiopathic or familial aetiology

CLINICAL SIGNS OF 'DYSKINESIA'

- **Chorea:** abrupt, unsustained contraction of different muscle groups
- **Athetosis:** prolonged, slow contraction of the trunk muscles resulting in bending and writhing of the body and precluding maintenance of a stable posture
- Choreoathetosis: Involuntary movements that have characteristics of both chorea and athetosis
- **Ballism:** abrupt contraction of the limb muscles which results in flailing movement of the limb, often unilateral
- **Dystonia:** sustained involuntary contraction of a group of muscles producing abnormal postures

DIAGNOSIS OF PD

- Is suspected when dogs had “episodes”
- absence of mentation alterations
- Absence autonomic signs
- Absence abnormal interictal signs and post-ictal behaviour.
- core movement had to be dyskinesia that is, involving movement of the limb(s)
  - Chorea
  - Athetosis
  - dystonia
  - ballism

DIAGNOSIS OF PD

- unremarkable haematology and biochemistry
- Normal serology for toxoplasma or neospora, US, X-ray, Thyroid, cardiac exam, CSF, MRI……..
- Gluten sensitivity is a causal agent or trigger in Border Terriers
  - Cfr J Vet Intern Med (Lowrie et al., 2015): Border Terrier with **canine epileptoid cramping syndrome**
  - Does this exist in other breeds?

DIFFERENTIAL DIAGNOSIS OF PD

- considerable confusion and disagreement concerninig the distinction from epilepsy
- strong evidence to suggest that similar pathogenic mechanisms may be involved in generating epileptic seizures and PD
- The phenotype and clinical approach is distinct
  - Simple partial seizures
    - can occur while consciousness is maintained and lack of autonomic signs
  - PD
    - generalised nature of the dyskinesia
    - long duration of episodes

CANINE EPILEPTOID CRAMPING SYNDROME

- paroxysmal gluten-sensitive movement disorder in Border Terriers
- triggered and perpetuated by gluten
- responsive to a gluten-free diet
- tested for anti-transglutaminase 2 (TG2 IgA) and anti-gliadin (AGA IgG) antibodies
- In labradors??

CASE

Labrador, born 28/12/2020
Female
First attack april ‘22 (16m)
In general 1 attack/month
On gluten free diet since 4m

Gluten Sensitivity

Modified Gliadin IgG 0.57

Interpretation:
Ratio < 0,6 = negative
Ratio 0,6 - 0,8 = questionable
Ratio > 0,8 = positive

Transglutaminase-2 IgA 0.80

Interpretation:
Ratio < 0,6 = negative
Ratio 0,6 - 0,8 = questionable
Ratio > 0,8 = positive

A positive ratio for Modified Gliadin Peptide IgG or Tissue Transglutaminase-2 IgA or both speaks for gluten sensitivity.

PD & GENETICS

- The first genetically mapped PD was that associated with episodic falling in Cavalier King Charles spaniels (Forman et al., 2012; Gill et al., 2012
- Genetic studies have not yet been performed in Labradors
- A dominant mode of inheritance seems unlikely given the limited pedigree data obtained from Labradors in the Lowrie & Garosi study

PROGNOSIS OF PD

- The natural history is self-limiting with 32% entering remission and an improvement in 75%
  - Labradors: episodes reduced in terms of frequency & duration
- Remission was lower in dogs with cluster episodes than those without
  - (Cluster episodes were defined as more than one episode in a week)
  - The presence of cluster episodes is of predictive value for the prognosis
- progression of the disease remains uncertain
- The overall tendency is for the episodes to stabilise in the first few years following onset, at which point they may improve in the ma jority with clinical remission in the minority

THANK YOU!


YEAH THE VASECTOMY WENT GREAT
OF COURSE I STILL HAVE MY BALLS HA HA
YEAH IT'S ACTUALLY A FAIRLY SIMPLE PROCEDURE. I FEEL GREAT