Causes of seizures

Extracranial causes

Intracranial causes

Seizures

Primary epilepsy (idiopathic/genetic)

Secondary epilepsy (Acquired / Localised Focus)

Autoimmune brain disease (e.g. brain tumour)

Progressive brain disease (e.g. brain tumour)

Poisons

Liver disease

Kidney disease

Other metabolic disease

Glucose

Electrolyte

Triglycerides

Prevalence of canine epilepsy

- 92 primary vet clinics (VetCompass project)
- Prevalence of epilepsy 0.62%
- ♂ > 1.5x more likely to have epilepsy
- Border terriers and GSD increased risk (2.7x & 1.9x crossbreed)
- WHWT reduced risk
- Neuter status, colour, weight - no associ
Idiopathic epilepsy
unknown cause other than possible hereditary predisposition; not in consequence of some other disease or injury

- Majority genetic (i.e. inherited) in the dog
  - Breed epilepsy prevalence greater than 1% suggests inherited tendency
  - Akbash Dog, Alaskan (Racing) Husky, Alaskan malamute, American Water Spaniel, American Shepherd Dog, Australian Shepherd, Russell Terrier, Rough Hair Collie, Rough Collie, Shepherd (Border), Basset Hound, Bloodhound, Brussels Griffon, Brussels Griffon (bouledogue), Bullmastiff, Cocker Spaniel, Chinese Crested, Chihuahua, Chihuahua (American), Collie, Corgi, Coton de Tulear, Dalmatian, English Setter, English Springer Spaniel, Entlebucher Mountain Dog, Finnish Lapphund, German Shepherd, German Shepherd (Schnauzer), Great Dane, Great Pyrenees (Pyrenean Mountain Dog), Greyhound, Great Pyrenees (Pyrenean Mountain Dog), Greyhound, Greyhound (Ibizan Hound), Gordon Setter, Irish Setter, Irish Water Spaniel, Irish Wolfhound, Italian greyhound, Irish wolfhound, Italian Spinone, Italian Spinone (Spinone Italiano), Irish Terrier, Irish Wolfhound, Japanese Akita, Japanese Spaniel, Japanese Shiba Inu, Saint Bernard, Saint Bernard (Italian Greyhound), Saint Bernard (Italian Greyhound), Saint Bernard, Saint Bernard (Irish Wolfhound), Saint Bernard (Irish Wolfhound), Saint Bernard (Italian Greyhound), Saint Bernard (Italian Greyhound), Saint Bernard (Irish Wolfhound), Saint Bernard (Irish Wolfhound), Saint Bernard (Italian Greyhound), Saint Bernard (Italian Greyhound), Saint Bernard (Irish Wolfhound), Saint Bernard (Irish Wolfhound), Saint Bernard (Italian Greyhound), Saint Bernard (Italian Greyhound), Saint Bernard (Irish Wolfhound), Saint Bernard (Irish Wolfhound), Saint Bernard (Italian Greyhound), Saint Bernard (Italian Greyhound), Saint Bernard (Irish Wolfhound), Saint Bernard (Irish Wolfhound), Saint Bernard (Italian Greyhound), Saint Bernard (Italian Greyhound), Saint Bernard (Irish Wolfhound), Saint Bernard (Irish Wolfhound).}

Top epilepsy “breeds” (UK)
(ranking in number registrations KC 2011)

- Labrador retriever (1)
- Border Collie (2)
- German Shepherd (4)
- Staffordshire Bull Terrier (8)
- Crossbreds
  - Cavalier King Charles Spaniel (6)
  - Cocker Spaniel (2)
  - Springer Spaniel (3)
  - Boxer (11)
- Jack Russell Terrier (5)
- Golden Retriever (15)
- Border Terrier (21)
- Yorkshire Terrier (18)
- Dalmatian (23)
To MRI or not to MRI

• Advantage
  – Rules out the “nasties”
  – Can help with decision making for treatment

• Disadvantage
  – Expensive
  – Not a specific test for inherited epilepsy
  – For animals with inherited epilepsy does not necessarily help with prognosis or treatment
  – Requires general anaesthetic
Idiopathic / Inherited epilepsy

Myth busters

- Dogs with IE have generalised tonic clonic sz

What is a seizure?
What is a seizure?

English Bulldog

Bulldog 2
French Bulldogs

Idiopathic / Inherited epilepsy

Myth busters

• Age of onset between 6 month and 6 years

Age of Onset of Epilepsy

Belgian Shepherds

mean 3.3 years (range 0.5 – 8.0 years)
**Juvenile epilepsy**

- Lagotto Romagnola
  - 1st focal K9 epilepsy gene
  - Mutation LGI2
    - Also childhood epilepsy gene
    - Involved synapse remodelling (pruning?)
- “grow out of it”
  - Sz starts 7wks stops 4 months

**Juvenile epilepsy - Boerboel**

- Seizures characterised by
  - periods of anxiety
  - vocalisations
  - impaired consciousness
  - spasms
- Mutation
  - mitochondrial membrane protein
- DNA test available
- Other epilepsy exists

**Idiopathic / Inherited epilepsy**

**Myth busters**

- Animal is normal between seizures
Unfortunately not always …

- 71% have at least one behavioural change e.g.
  - Fear/Anxiety
    - Anxious/ fearful with unfamiliar dogs, people, surroundings, sudden / unpredicted movements
  - Aggression
    - When handled, other dogs, unfamiliar people
  - Abnormal Perception
    - Aimless barking / pacing, chasing shadows or light spots, aimless, staring into space.

Why?

- More widespread brain disorder ?
  - Neurotransmitter imbalance?
- Treatment?
  - Anti-epileptic drugs may affect mood
  - Some dogs restless and agitated on Phenobarbital
    - Owners think their pets have poorer quality of life if they show this behaviour
  - Many dogs have behavioural change prior to medication

Epilepsy in Irish Wolfhounds

- In some dogs behavioural change months b4
  - Males hyperactive and hard to control
  - Females withdrawn and unable to relax
  - sound and touch sensitivity
  - submerging entire head when drinking
  - shyness of doors or other barriers
  - exaggerated flight distance
  - shyness approaching perceived threat.
**Heritability of epilepsy**

- Most epileptic dogs do not have epileptic parents and epilepsy can skip generations
  - Autosomal recessive
  - Unaffected dogs may be carriers
- Often high e.g. Irish Wolfhounds = 0.87
  - if one knew what to select for it could be "bred out"
  - Expression of disease may be influenced by other as yet unknown factors
  - Likely more than one gene

**Finding generalised IE genes so how is that going?**

- **Lupa** [http://www.eurolupa.org/](http://www.eurolupa.org/)
  - Dog genetics to understand human diseases
  - Collaboration of 20 veterinary schools from 12 European countries
    - Large DNA collections from many breeds
  - Investigation many disease including IE
    - Lagotto Romagnola (Finland – Hannes Lohi)
    - Finnish Spitz (Finland – Hannes Lohi)
    - Border Collie (AHT, UK)
    - Norwich Terrier (AHT, UK)

**Finding generalised IE genes - USA**

Work in progress for many breeds
[http://www.canine-epilepsy.net/](http://www.canine-epilepsy.net/)

- 9909 DNA samples (28/1/11)
  - 108 different breeds
  - 1578 affected dogs
- University of Missouri
- University of Minnesota
  - Australian Shepherds, Beagles,
  - English Springer Spaniels
  - Greater Swiss Mountain Dogs, Vizslas
What about human IE genes?
What about mouse IE genes?

- None so far
- Looked for candidate genes in Vizslas, English Springer Spaniels, Greater Swiss Mountain Dogs, and Beagles.

Finding generalised IE genes
so is there any progress?

Belgian Shepherds
- Novel Idiopathic Epilepsy Locus identified
  - Small region (1Mb) of chromosome
  - Contains 12 genes
    - No known epilepsy genes
    - None encode ion channels
  - One candidate gene ADAM23 most likely
    - Interacts known epilepsy proteins LG11 and LG12
    - Having 2 copies of SNP variation increases risk epilepsy
- Still need to identify mutation
- DNA test
- Life span not affected

Prognosis and genetics
Do some breeds get it worse?

- ~1/3 epileptic dogs & humans refractory to AED
- Unresponsive to multiple drugs with a wide range of mechanistic actions
- If seizures haven’t controlled on 2 drugs then much less likely to ever get good control
  - Study 49 epileptic Border collies
    - 24/49 treated with >2 AED
    - 17/49 drug resistant epilepsy
      - 71% of those > 2 AED
    - Hülmeyer and others 2010
Prognosis and genetics

Why are some dogs refractory to AED?

- Genetic or disease-related alteration in AED target?
  - Decreased sensitivity to treatment.
- Overexpression BBB drug transport proteins?
  - Limits penetration of AEDs into the brain
    - E.g. P-glycoprotein (ABCB1 gene)
      - Altered expression in Rough/Smooth Collie
      - Severely truncated, non-functional (ivermectin sensitivity)
      - Homozygous for mutation
        - Fewer seizures on less drugs
        - Less adverse effects
      - Epiphenomenon?
        - Less severe phenotype?
- Genetic or disease-related alteration in AED target?
- Overexpression BBB drug transport proteins?
- P-glycoprotein (ABCB1 gene) in Border Collies
  - Mutation noncoding, promoter region
  - Associated resistance to phenobarbital
  - Affect expression of ABCB1 and PGP?
  - Influence the response to AED therapy?

P-glycoprotein (ABCB1 gene) in Border Collies

- Mutation noncoding, promoter region
- Associated resistance to phenobarbital
- Affect expression of ABCB1 and PGP?
- Influence the response to AED therapy?

Seizures before 1 year old

- Prognosis
  - ~1 in 5 (22%) became seizure free
  - ~1 in 3 (37%) died / euthanased seizures
    - Mean survival time 7.1 years.
  - Poorer prognosis
    - History of status epilepticus
    - Border collie

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Paddy
Prognosis

Irish Wolfhounds
• Life expectancy affected; dogs decreased by 2yrs (average age of death 4.7yrs)
  – 50.3% epilepsy was direct or indirect cause
  • 60.8% euthanasia due to uncontrolled seizures
  • 16.1% death during seizure
  • 6.6% hepatotoxicity from phenobarbital treatment
  • 6.6% aspiration during seizures & fatal pneumonia
  • 3.9% non-recovery after a seizure

Belgian Shepherds
• Life expectancy not affected
  – But; epilepsy cause of death in 25% population
  – And 70% of dogs with epilepsy had a epilepsy-related death

Summary
• Genetics plays an important part
  – Tendency for epilepsy
  – Age of onset
  – How bad it is
  – Responsiveness to drugs
• By understanding canine genetics
  – We can prevent epilepsy
  – Find better ways of treating it
  – Better understand & treat human epilepsy

Thank you for listening!

Any questions?

www.veterinary-neurologist.co.uk

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