Lafora’s Disease and Epilepsy – Clare Rusbridge

Scope of Lecture:

- What is a seizure?
- Idiopathic epilepsy vs. Lafora’s disease
- What is Lafora’s disease?
- Genetics of Lafora’s disease
- Preventing Lafora’s disease
- Genetics of idiopathic epilepsy
- Preventing idiopathic epilepsy

**Slide 1: What is a seizure?**

Abnormal brain electrical activity

**Normal electrical activity is random. Seizures cause:**

Sudden episodic transient signs

- Involuntary muscle movements
- Sensory disturbances
- Altered consciousness. *No recollection of the seizure. Just because they appear to be ‘there’ they might not be normal*

(image: graph showing Spike in Paroxysmal discharge)

**Slide 2:**

(images of EEGs: ‘Normal’ showing random activity,’ Focal Seizure’ showing organised activity on some lines , ‘Generalised tonic clonic’ showing organised, regular, large activity spikes on all lines, ‘Petit mal (3 per sec spike wave) ‘ showing organised, regular, small activity spikes on all lines.)
It is difficult to gather an EEG recording on a dog as they have thicker muscle, thicker skulls, smaller heads. Therefore, the only practical way is to insert needles directly into the brain, and the only way to do that safely is to anaesthetise. Anaesthesia suppresses seizures and the animal would have to be admitted to the veterinary hospital for an unspecified amount of time whilst waiting for a seizure to happen, which is distressing for the animal and expensive for the owner. The ultimate reason for using EEG on humans is to identify the loci of the epilepsy and ‘cut it out’. That is unlikely to be an option in a dog.

Generalised tonic clonic seizures affect the whole of the brain, focal seizures only certain parts of the brain and therefore may only be apparent outwardly in certain parts of the body. Petit Mal is a series of very small seizures that affect

**Slide 3: What is a seizure?**

Film clip of dog (not dachshund) experiencing a seizure.

**Slide 4: Seizure type depends source**

Images: light hearted cartoon of dachshund brain; diagram showing 4 lobes of brain: frontal, parietal, occipital, temporal

The seizure type is related to source of the disturbance: frontal lobe (altered consciousness, generalised seizures); parietal lobe (motor activity); temporal lobe (motor, language); occipital lobe – relatively rare for this lobe to be affected, but it appears to be the main area affected by Lafora: jerking back in response to sudden movement, flashing lights, black/white patterns, temporary or permanent blindness, visual hallucinations causing panic attacks etc.

**Slide 5: Causes of Seizures**

Image: flow chart breaking down different causes:

When a dog presents at clinic with a seizure, a vet try to identify whether the cause is:
1. **Intracranial**: (in the brain) This is broken down into:
   a. primary (idiopathic or genetic) or
   b. secondary epilepsy acquired/seizure focus), either as a result of
      b.i. static brain disease (e.g. after trauma) or
      b.ii. progressive brain disease, (e.g. brain tumour)

2. **Extracranial**: (in the blood) due to:
   a. Toxins, either:
      a.i. external toxins (e.g. poison, slug pellets,)
      a.ii. or internal toxins (as a result of liver, kidney or other metabolic disease
      b. excess or deficit (e.g. of glucose, electrolytes etc.)

A blood sample may help identify toxins and their source or excess/deficit. Lafora is a form of primary epilepsy.
Slide 6 Idiopathic/Inherited epilepsy

Image: photo of mini long:

- Increased prevalence in mini longs?


The DBC 2012 survey gathered evidence that suggests that mini long dachshunds may have an increased prevalence in mini longs.

Slide 7 Idiopathic epilepsy

- Definition:
  - 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 1-2% suggests an inherited tendency.
  - Dachshund 1.2%?
    - Dachs-Life May 2012 page 24
    - 17 dogs – 12/17 mini long

The evidence from the Dachs-life survey seems to suggest that there might be an inherited tendency. 1.2% of health reports mentioned epilepsy and anything greater than a 1-2% prevalence suggests inherited. Of the 17 reports of epilepsy, 12 were from mini longs.

Slide 8: Top epilepsy “breeds”(UK) (ranking in number registrations KC 2011)

(Characteristics of epileptic episodes in UK dog breeds, an epidemiological approach, Veterinary Record 2011)

- Labrador retriever (1)
- Border Collie
- German Shepherd (4)
- Staffordshire Bull Terrier (8)
- Crossbreeds
- Cavalier King Charles Sp. (6)
- Cocker Spaniel (2)
- Springer Spaniel (3)
- Boxer (11)
- Jack Russell Terrier
- Golden Retriever (5)
- Border Terrier (7)
- Yorkshire Terrier (18)
- Dalmatian

Also in top 10 for epilepsy Sweden

**Slide 9: Dachshund 18/1260 (1.4% epileptic dog population)**

Image: Table 1: Breed Distribution of a cohort of 1260 dogs with epilepsy, showing Dachshund ranked 18th with 1.4% of dogs from the whole epileptic population of 1260 dogs tested. The top 14 breeds accounted for more than 75% of the epileptic cohort, top 5 breeds accounted for more than 50% of the epileptic cohort (Veterinary Record 2011).

Slide shows total dogs from each breed in the sample. Crossbreeds represented 250 of the 1260 dogs, there were 139 Golden Retrievers, 142 Border Collies, 82 German Shepherds, 66 Staffies, 63 Jack Russells, 58 Golden Retrievers, 39 Yorkshire Terriers, 27 Border Terriers, 19 Dalmatians, 18 Dachshunds. N.B. – note to self: does it take any consideration of relative popularity – e.g. Crossbreeds far more numerous than dachshunds etc.?

**Slide 10: What is idiopathic / inherited epilepsy?**

**Ion channel disorders?**

Images:

- Battery like box showing negative and positive ions inside and two channels into box, one allowing positive (+) ions and one negative (-) colours. Excitation (more positive charge) – nerve cell more likely to fire
- Graph showing spike in activity

**Slide 10: To MRI or not to MRI**
• Advantage
  o Rules out the “nasties”
  o Can help with making decision for treatment

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

Slide 11: Lafora’s disease
Images:

• 7th January 2005 BBC website article on the story of the research into the gene by the Hospital for Sick Children in Toronto and the discovery of the test that could help owners breed out the disease http://news.bbc.co.uk/1/hi/sci/tech/4149179.stm.
• Video clip of dog showing myoclonic jerks in response to clapping
• Polyglucoside platelets in the brain.

Lafora was identified with the help of the Dachshund Club in the 1990’s. Clare was treating a number of mini wires from the same family and spotted similarities between their symptoms and those described in work by Berge Minassian, so emailed him. Within 5 minutes, she received a reply: please tell me everything you know, send dogs over! Berge came over, tested dogs and in Jan. 2005 announced that the gene had been found.

Slide 12: Lafora’s disease – dog

<table>
<thead>
<tr>
<th>Early</th>
<th>Late</th>
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<tbody>
<tr>
<td>• Myoclonus (jerks)</td>
<td>• Panic attacks</td>
</tr>
<tr>
<td>o Photosensitive</td>
<td>o Visual hallucinations?</td>
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<tr>
<td>o Sudden movement/noise</td>
<td>• Dementia</td>
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<tr>
<td>o Manifestation of cortical irritability</td>
<td>• Incontinence</td>
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<tr>
<td>• Seizures</td>
<td>• Blindness</td>
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<tr>
<td></td>
<td>• Deafness</td>
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<td></td>
<td>• Walking difficulty</td>
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<td>o Stiffness</td>
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n.b. Clare referred to it being late onset, with no known incidence earlier than 5 years. At the time, one member of the audience mentioned that there is one tested affected dog showing symptoms age 3.5 years. On 30th January 2014 another dog, tested affected under WHDC
was also reported as showing symptoms age 3.5 years… Just after weaning a litter of puppies.

Slide 13: Lafora’s disease – human

<table>
<thead>
<tr>
<th>Initial</th>
<th>Progressive</th>
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<tbody>
<tr>
<td>- Myoclonus (jerks)</td>
<td>- Cognitive decline</td>
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<tr>
<td>- Seizures</td>
<td>- dementia</td>
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<tr>
<td>- Myoclonic</td>
<td>- Walking difficulty</td>
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<tr>
<td>- Occipital</td>
<td>- Wobbly – plastic</td>
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<tr>
<td>- Transient blindness</td>
<td>- Emotional disturbance and confusion</td>
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<tr>
<td>- Visual hallucinations</td>
<td>- Die within 10 years</td>
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<tr>
<td>- Photoconvulsion</td>
<td>- Status epilepticus and complications (e.g. pneumonia)</td>
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<tr>
<td>- Tonic Clonic</td>
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<tr>
<td>- Atypical absence</td>
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<td>- Atonic</td>
<td></td>
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<tr>
<td>- Complex Partial Seizures</td>
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<td>- Photosensitive</td>
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Slide 14: Berge Minassian Research Lab “Sick Kids” Hospital Toronto

The team are scientists and they have had to come out of their ‘comfort zone’ to get involved with the testing programme for mini wires as they are not set up to be a commercial lab. The technology has been expensive to set up and the testing takes a lot of time out their research. They have had to re-invent an older testing method as that is the most reliable test they have found. The Money they raise is put towards the research.

Slide 15: Management

Images of the two different types of Lafora genes, courtesy of Berge Minassian:

- EPM2A gene showing Laforin and
- EPM2B, the dog Lafora Gene.

Deficiency of Malin results in accumulation of malformed glycogen (Lafora bodies) in the brain.

Slide 16: Management

- High protein, low simple carbohydrate diet
  - Decrease glycogen?
- Myoclonus
  - Levetriacetum (drug)
Avoidance triggers (photo of Alfie the MW in Doggles to reduce changes in light levels)

- Seizures
  - Phenobarbital (drug)
  - Bromide (drug)
  - Zonisamide (drug)

Drugs all expensive, have side effects and work better for some dogs than others.

**Slide 17: Message from Berge (23/1/14)**

- “We are making really huge progress towards therapies, these would be viral vector or small molecule. Nothing ready yet for dogs, though we are treating mice."


Berge is developing a therapy that depends on a virus carrying DNA into a nerve cell. May want younger dogs to be involved in trialling programme.

**Slide 18: Genetics of Epilepsy**

Image: photo of neurone

**Slide 19: Inherited CNS disease**

- Simple (single gene)
  - e.g. lafora’s
- Complex
  - E.g. idiopathic epilepsy
- Susceptibility to immune mediated disease
  - E.g. pug encephalitis
- Inherited susceptibility to neoplasia
  - E.g. brain tumour Boxer Dogs

**Slide 20: Lafora’s – Single Gene Disorder (simple autosomal recessive)**

Image: diagram showing average outcome of breeding carrier to carrier pairing, each carrying one Lafora gene. On average, such a mating would produce 25% clear, 50% carrier, 25% affected offspring.

**Slide 21: “no brainer” questions**
“But Lafora’s isn’t a problem for the breed?”
- WHDC screening programme shows ~ 10% “affected” MWHDs
- 40% UK MWHD could be carriers
- “late onset” disease (5-14 y) – dog have been bred before displaying signs.

Image: fast moving active dachshund

Slide 22: “no brainer” questions
- “The test is too expensive!”
  - £150 subsidised – compared to:
    - Cost of attending Championship Show - £100
    - Cost of reasonable (non-Champion) Stud - £400
- “I have never seen this as a problem in my lines – I don’t need to test!”
  - Great! The breed needs known disease free dogs!
  - Great! You are fortunate to be confident about the results (i.e. no excuse)

Slide 23: “no brainer” questions

“Lafora’s isn’t a big problem for the dog?”

“Lafora’s only affects old dogs at the end of their life”
- Age of onset Lafora’s ~ 7 years (average age taken from Progression Survey)
- Age of death Dachshund ~ 12y7m
  - Purebred Dog Health Survey for Dachshunds (UK Kennel Club)
- 45% f life (or more) is spent with debilitating jerking, seizures, confusion, anxiety, possible hallucinations, difficulty walking and blindness
- Do you really think that is OK?

Image: unknown dachshund in doggles

Slide 24: Quotes from owners (Laforadogs Progression survey)

- “We have seldom seen anything in our mini wires more upsetting – both for us and the dog”
- “the impact of Lafora is enormous, both for our dogs (2 with the disease) and ourselves. We have to adopt a different way of living trying at all times to make
adjustments that will reduce the Lafora symptoms as much as possible. We also have to plan any outings or holidays meticulously to ensure the welfare of the dogs”

Slide 25: More difficult questions
My dog is a carrier. Should I breed?
Yes!!
- MW Breed Average COI is 11%
  - Half sibling mating is COI is 12.5%
- Your dog has valuable and vital DNA
- MUST be mated to DNA tested normal
  - Some/all offspring may be carriers
  - All offspring must be tested
  - All carriers must be mated to DNA tested normal (clear)

Slide 26: More difficult questions
My dog is affected should I breed?
Perhaps?
- If it is important to maintain gene pool and
  - Your dog has valuable and vital DNA
  - Group decision made on other factors e.g. COI
- No evidence (yet) that breeding is detrimental to Lafora dog’s health
- Must be mated to DNA tested normal (clear)
- All offspring will be carriers

Slide 26: More difficult questions
Is there a human reason for not testing?
- “It’s better not to know”
  - The results are published
  - Reputation is at risk
  - Risk of lost income from valuable stud
Slide 27: No-one has perfect DNA!

- A breed with COI of 11% cannot afford to stigmatise dogs or breeders with affected or carrier dogs

- Fingers of blame?
  - Should not point at breeders that do test and are unfortunate enough to have affected/carrier dogs
  - Should point at those who don’t test and don’t help to improve the breed

QUESTIONS/COMMENTS FROM DELEGATES

- Recently became aware that a potential buyer who called a breeder was told that pups were tested – but they weren’t. Also heard of breeders saying pups are tested, and they are, but not confirming what the status is. It is difficult for buyers to challenge people who are high up in the breed as it is perceived to be disrespectful, but buyers are within their rights to ask to see the certificates and confirm pedigree.

- Delegate said the Canadian test is not certificated – it is and certificates have been accepted by Kennel Club.

- Comment from owner of dog that had shown signs of dementia as it got older but at the time, wasn’t aware of it. Could it have been Lafora? Potentially, yes but not sure.