New developments in CMSM research

Talk given CKCS club
7th October 2010 - Leicester

(some images removed)
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Lecture synopsis

- What causes Chiari-like malformation?
- Why do some dogs with CM get SM?
- Genetics of CM/SM
- What is the incidence of SM in the CKCS?
- The breeding guidelines – do they work?
- Treatment – anything new?
- Other questions to be answered
What is Chiari malformation
Overcrowding of the skull

Normal  CM
Chiari-like malformation

Overcrowding of the FM

large cerebellar herniation not required

Be cautious before declaring a dog safe to breed on the basis of appearance of the brain

Which dog will get SM?
Chiari-like malformation
most common cause SM in dog

Mismatch between brain and skull size
CM – characteristics
changes in proportions of the skull

Griffon with no CM or SM
Griffon with CM and SM

basicranium (skull base) shortens
parietal bone lengthens
supraoccipital bone is shorter and straighter
smaller frontal sinuses
A theory for CM in the GB

Hypothesis for CM Bone insufficiency or craniosynostosis?

Embryological origin skull bones
White – membrane bone
Stippled – cartilaginous neurocranium
Hatched – visceral arches

From The Life of Mammals
Young, Oxford University Press, 1957
CKCS with CM
Comparison of brain and skull volume

Cross H. R., Cappello R, Rusbridge C Comparison of cerebral cranium volumes between CKCS with chiari-like malformation, small breed dogs and Labradors JSAP 2009 50 399-405
CKCS with CM

• Similar skull volume to other toys
• More brain tissue within skull
  – Statistically similar volume to Labradors

Cross H. R., Cappello R, Rusbridge C Comparison of cerebral cranium volumes between CKCS with chiari-like malformation, small breed dogs and Labradors *JSAP 2009  50 399-405*
CKCS with SM

• Skull (caudal fossa) volume
  – No difference between CKCS with & without SM in a mixed age group
  – Significantly smaller for CKCS with early onset SM (<2y) compared to clear CKCS (> 5y)

• Volume of brain within skull
  – significantly greater for CKCS with SM
  – Especially in CKCS with early onset SM

• SM associated with brain / skull mismatch
• Early onset SM greater disparity

C.J. Driver C. Rusbridge H.R. Cross I. McGonnell H.A. Volk Volumetric Comparison of Brain Parenchyma within the Caudal Cranial Fossa of Cavalier King Charles Spaniels with and without Syringomyelia (unpublished)
CKCS with SM

• Larger brain within skull = larger syrinx (Pearson r=0.437)

• Larger syrinx = larger ventricles (Pearson r=0.592)
  – i.e. dogs with SM tended to have ventriculomegaly and big syringes were associated with big ventricles

C.J. Driver et al Volumetric Comparison of Brain Parenchyma within the Caudal Cranial Fossa of Cavalier King Charles Spaniels with and without Syringomyelia (publication pending)
Inherited CMSM in humans

• Tartar population
• Work of Enver Bogdanov (Kazan Tartarstan)
• Typical appearance
  – Flat face (brachycephalic)
  – Short neck
• Variation in presentation and progression
  – Large syrinx progresses quicker
  – Mild cases may be asymptomatic
• Genome work in progress
Inherited CM/SM in dogs

- CMSM has moderately high hereditability in the Cavalier
  - SM = 0.37 (maximum is 0.64)
- It is a complex inheritance involving more than one gene.
  - Initial results suggest genes at two or more loci interact to give disease
Canine CM/SM genome project - 2 parts

Search for syringomyelia genes in Cavaliers

Search for chiari genes in Griffon Bruxellois
Canine SM genome project
Where are we now?
DNA samples taken after a MRI scan (saliva sponges)
Canine SM genome project

• Recent progress
  – Identification of locus for SM associated with CM in the CKCS
  – Identification of a haplotype that infers protection against SM

• Next steps
  – Wider dense SNP coverage
  – Candidate gene sequencing
Canine SM genome project

red triangle indicates significant region on the chromosome!

Block 1

$P$ value = $3.2 \times 10^{-15}$

Linkage disequilibrium in fine-mapping region analyzed by Haploview v4.2 with R squared method

10-SNP window spans 1.3 Mb.

Genome wide linkage studies identify a novel locus for syringomyelia associated with Chiari-like malformation in the Cavalier King Charles Spaniel

Quoc-Huy Trinh, Penny Knowler, Alexandra Thibault, Marie-Pierre Dubé, Guy A. Rouleau, Clare Rusbridge and Zoha Kibar
Canine CM genome project

• Recent progress
  – Identification of 2 candidate loci (i.e. small areas of a chromosome) for CM

• Next steps
  – Fine mapping
  – Candidate gene sequencing

Trinh VQH 1, Knowler P 2, Dubé MP 3, Blott S 4, Rusbridge C 2, Rouleau GA 5, Kibar Z 1

1 Centre de recherche CHU Sainte-Justine, Université de Montréal; 2 Stone Lion Veterinary Centre, Wimbledon; 3 Institut de Cardiologie de Montréal, Université de Montréal; 4 Department of Genetics, Animal Health Trust, UK; 5 Centre de recherche du CHUM, Université de Montréal.
Prevention of CM/SM

• EBV
  – Currently only CKCS
  – Ultimately GBV?

• Breeding guidelines
  – Eliminate early onset SM dogs (E)
  – Only breed young clear (C) to older clear (A)
  – Only breed late onset SM (D) to older clear (A)
  – Identify CM free dogs?
    • June 2009-10 229 MRI from breeding CKCS (CR) - no dogs without CM; 2 dogs with mild CM.
Incidence SM 55%
(slide content removed and replaced with abstract)

FP8. THE INCIDENCE OF SYRINGOMYELIA IN CAVALIER KING CHARLES SPANIELS

John Parker1, Penny Knowler2, Nick Jeffery1, T. J. McKinley1 and Clare Rusbridge2
1 The Queen’s Veterinary School Hospital, Department of Veterinary Medicine, University of Cambridge, Cambridge, Cambridgeshire, United Kingdom; 2 Stone Lion Veterinary Centre, Goddard Veterinary Group, London, United Kingdom

The epidemiology of cervical syringomyelia in a population of 804 Cavalier King Charles Spaniels (CKCS) was investigated using the results of a voluntary MRI screening programme that is ongoing in the United Kingdom (UK) and the Netherlands. The aim of the study was to establish the incidence of disease and to determine the risk factors for its development. The data was analysed using logistic regression to assess the influence of certain variables on the likelihood of detecting syringomyelia and to generate a predictive model for the outcome of screening.

The lifetime risk of developing syringomyelia in the study population was estimated to be 55%. Of the variables investigated, only the age at which a scan was performed significantly predicted the outcome of screening and the likelihood of detecting the disease increased with age-at-scan up to the age of four years. The predictive accuracy of the final model was 62.4% and factors not evaluated by this study are therefore also likely to contribute to the timing of disease manifestation.

It is concluded that syringomyelia is likely to be one of the most common disease conditions of the CKCS. The age at which an MRI scan is performed predicts the likelihood of disease detection and a susceptible individual may not express the diagnostic phenotype until the age of four. Performing screening before this time may give a false negative result for the lifetime risk of disease development.

Parker J. et al 2010 presented 23rd Annual Symposium ECVN and ESVN
Using breeding guidelines - Incidence of “A” (>2.5y clear) dogs
(Slide contents removed and replaced with abstract)

Knowler et al 2010 presented 23rd Annual Symposium ECVN and ESVN
Using breeding guidelines - Incidence of “A*” (>5y clear) dogs

Knowler et al 2010
Conclusions

• To increase number SM free dogs
  – at least 1 parent should be ascertained to be free of SM by MRI at 2.5 years of age.
  – the true SM status of the grandparents at least 5 years old should be established.
  – Using dogs of unknown status is risky - all breeding dogs should be MRI screened.
  – all results should be sent to a recognised central database (EBV).
Conclusions continued

• If SM affected dog is used then ideally the chosen mate would either be selected on the basis of its EBV and/or would be a older SM clear dog (>5 years).
• The offspring of the proposed mating should also be scanned and ideally bred to older SM clear dogs.
Conclusions continued

- “D” status (or equivalent) will only be appropriate if the dog was first proved to be SM free before 2.5 years of age.

- Future breeding recommendations will also take account of dogs with central canal dilatation less than 2mm.
### Proposed new guidelines

<table>
<thead>
<tr>
<th>SM Grade</th>
<th>Age (years)</th>
<th>Breed to</th>
</tr>
</thead>
<tbody>
<tr>
<td>0a</td>
<td>&gt; 2.5</td>
<td>SM grade 0a,b, 1, 2, 3a*</td>
</tr>
<tr>
<td>0b</td>
<td>&lt; 2.5</td>
<td>SM grade 0a, 1</td>
</tr>
<tr>
<td>1</td>
<td>&gt; 5</td>
<td>SM grade 0a,b, 1, 2, 3a*</td>
</tr>
<tr>
<td>2</td>
<td>&lt; 5</td>
<td>SM grade 0a, 1</td>
</tr>
<tr>
<td>3a</td>
<td>&gt; 2.5</td>
<td>SM grade 0a, 1</td>
</tr>
<tr>
<td>3b</td>
<td>&lt; 2.5</td>
<td>Do not breed</td>
</tr>
<tr>
<td>Any clinical signs</td>
<td>Any</td>
<td>Do not breed</td>
</tr>
</tbody>
</table>

**Grade 0**, normal (a = over 2.5 y; b = less than 2.5 y).

**Grade 1**, CCD < 2mm; dog > 5 y.

**Grade 2**, CCD < 2mm; dog < 5 y.

**Grade 3**, SM or pre-SM (a = over 2.5 y*; b = less than 2.5 y)

* Must have been clear of SM b4 2.5y
The need for estimated breeding values!

“but I know what is at the back of my dogs”
Conversation with breeder

• “I am worried about using ……Dog X who was …. scanned A but …..has fathered several progeny with SM”

• Only the vet and breeder of Dog X know that when younger Dog X was indeed an A … however since rescanned and is a D

• The MRI results of Dog X are confidential - i.e. vet cannot comment

• The breeder of Dog X keeps quiet

• EBV will help to protect breeders
Rupert’s Fund

Funds MRI scans for CKCS >5 years and GB

- Applicants to penny.knowler@ntlworld.com
- participating vet centres
- Aims to identify CKCS clear of SM and GB clear of CM
Treatment / prevention?

Before medication

After medication

Pain face
“Fear and aggression related behaviour traits have a positive correlation to clinical severity of CM/SM”

BEHAVIOUR ANALYSIS OF CKCS DIAGNOSED WITH SYRINGOMYELIA

L Rutherford et al ECVN Annual Symposium 2010
When they are gone……

Your Gift of Love
Freedom from Syringomyelia
The Syringomyelia Cavalier Collection Scheme

Be a part of saving the beautiful
Cavalier King Charles Spaniel

The Cavalier King Charles Spaniel, as a breed, is prone to the painful and debilitating disease Syringomyelia or 'SM'. It is a disease which can hugely affect the quality of life for your dog.
Currently, there is no cure.
The Syringomyelia Cavalier Collection Scheme is working to eliminate SM through genetic research.
If you have a Cavalier that has been diagnosed with SM then we would be extremely grateful if you would give consideration to agreeing to your dog taking part in this Scheme.
In the sad event of your dog passing away, the scheme will fund transport costs to the nearest suitably equipped veterinary centre. Here, they will take DNA samples which will also benefit five other research projects. On completion, your dog’s ashes will be safely returned for you to decide on the final resting place.
We realise that this would be a sad and distressing time. Participation in this scheme needs careful thought while you are still enjoying the loving friendship that your dog brings you.
If you would like to help, please contact Margaret Carter by using the details below.

Please help us save this beautiful breed.
Tel: 01707 262 035
Email: mareve-ckcs@ntlworld.com

“My sunshine doesn’t come from the skies, it comes from the love in my dog’s eyes.”
Unknown poet.
Thank you for listening!

Any questions?

www.veterinary-neurologist.co.uk
Acknowledgments

Funding
Syringomyelia DNA research
For the Love of Ollie fund
Rupert’s Fund
Cavalier Friends
Ann Conroy Trust
American Kennel Club Health Foundation
CKCS club of USA Health Foundation
DNA archive for Companion Animals Manchester
Marshfield Clinic (NIH)
UK CKCS & Griffon Bruxellois clubs
The Cavalier Club of the Rand
French Cavalier Club
Cavalier Club of Canada
Frank and Lee Pieterse

Couldn’t have done it without……..
Stone Lion Veterinary Hospital
Diaconessenhuis Meppel CMSM screening program
Paul Mandigers and Utrecht University
Simon Platt and Georgia University
Natasha Olby and North Caroline State University
Margaret Carter
Lee Pieterse
Carol Fowler
Dana Schuller-Kuypers
Rachel Harvey, Maria Oliver

Genome scan

SM project
Vincent Quoc-Huy Trinh

CM project
Philippe Lemay

Overseen by
Penny Knowler
Zoha Kibar
Guy Roleau

Greatly assisted by
Alexandra Thibault
Karine Lachapelle
Annie Levert
Daniel Rochefort
Melanie Benard
Isabelle Thibault
Claude Marineau
Yan Yang

Statistical analysis
Marie-Pierre Dube
Sarah Blott
Sylvie Provost
Slides which might have been required in question and answer session
“General anaesthesia, narcosis or deep sedation required”

General Anaesthesia

- Dexdomitor & butorphanol premedication
- Propofol induction
- Isoflurane & oxygen maintenance
Wrong sequences

Head slightly flexed
Transverse images not perpendicular to spinal cord and not though widest part of syrinx.
Correct positioning and images

King Charles spaniel with head in extension
4mm slices perpendicular to the spinal cord with 1 slice though the widest part of the syrinx
Microchip artefact
Microchip artefact
CM associated pain

Signs of pain

No Clinical Signs
Why T2W? – confirmation suspicious lesion
Clinical signs of SM

• Not all dogs with SM have signs
• Depends on width and location of syrinx
  – Wide syrinx = pain +/- scratching
• Many dogs with SM have no / subtle signs
  – a “problem in waiting”
  – May produce offspring with SM
  – May produce offspring with pain from SM

MRI from 16 month CKCS in severe pain
  Wide asymmetrical syrinx
  White = fluid; light grey = spinal cord