SYRINGOMYELIA NEWS

Summer 2005

A research update

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RECENT EVENTS

Clare's talks to ACKCSC National Specialty in Lancaster, Pennsylvania and the National Meeting/Show of the Cavalier King Charles Spaniel Club USA Charlotte North Carolina in early May were very well received. She was very grateful for the clubs' invitation to present up-to date information about the condition and tackle the variety of misconceptions and misquotes that abound. At the Lancaster show a taskforce was set up linking the human syringomyelia support group – ASAP (The American Syringomyelia Alliance Project) with breeders and pet owners willing to help investigate the condition and prevent suffering.

Cavalier Committee of ASAP'
Their hands are full!

Some of the committee can be seen here with Clare.
Annabelle Glover (secretary) Sandra Morgan (cavalier owners)
Anne Eckersley-Robins, Kathy Conrad (breeders)
Dorothy Poppe (National Director of Medical Development ASAP)
Not in photo, Susan Shidler (Chairwoman.) and Mary Maly
Dr Jim Cupery (MD, Radiologist). See http://www.asap.org/

The group have already generated many exciting initiatives and fundraising events

such as “ASAP Paws for a Cause”. Collaboration between veterinary surgeons is advancing surgical technique e.g. Dr Curtis Dewy is starting trials into the use of titanium mesh plates (used in human surgery) in an attempt to limit postoperative scarring and redevelopment of signs of syringomyelia.

The Canadian Cavalier King Charles Spaniel Club, Ontario hosted a seminar on Syringomyelia on May 29th 2005. It was a very special event described as 'a meeting of minds'. Pat Barrington and her colleagues achieved a substantial coup in securing the participation of Dr Berge Minassian (our collaborator from Sick Kids Hospital in Toronto) and Melanie Bernard (the project co-ordinator from Dr Guy Rouleau’s lab at CHUM, Montreal). Not content with bringing together neurology specialists from the veterinary and human fields, Pat also invited Barbara Forrestall. Barbara was responsible for establishing the Canadian Syringomyelia Network support group. As she is a syringomyelia sufferer herself she was able to provide a valuable insight into the disorder and the challenging issues that surround it. Participants to the seminar included breeders, pet owners and veterinarians. As at the CKCS Club USA, the Canadian hospitality was outstanding and Clare was much pampered with a mix of tourism and professional visits to Guelph University and the Genome lab at the Sick Kids Hospital.

Clare also gave seminars at University of Pennsylvania and the American College Veterinary Internal Medicine; Neurology Forum in Baltimore. This was particularly valuable because she was able to talk to other colleagues conducting research into Syringomyelia such as Dr Marsh and Dr Abramson from Ohio State University, Dr Olby from North Carolina SU and Dr Dewey from Long Island who is now on the committee of ASAP ‘Paws for a Cause’ with Clare.

DNA Research Team Update

Marie Pierre Dube has completed a preliminary analysis of the initial scan and the good news is that the chosen markers are sufficiently informative enough to justify a whole genome scan in the CKCS breed. This first stage of gene mapping will involve around 500 markers and 200 dogs. Marie Pierre, a genetics epidemiologist, has recently taken on a position at the Montreal Heart Institute where she heads a research team in genetics of cardiology. She has a particular interest in MVD.

Zoha Kibar has been appointed as the molecular geneticist in charge of fine mapping and identification of the gene(s) defective in SM in the CKCS breed. Zoha pursued her postdoctoral studies at McGill University working on a mouse model for neural tube defects (NTDs) in humans. She is interested in identification and characterization of the molecular basis of congenital malformations of the central nervous system, particularly NTDs and Chiari malformations and she is planning to pursue her career as an independent researcher in this field.

She says: ”Genetic analysis is more definitive and accurate and of course cheaper than MRI. I have to stress the fact that we don't need to wait for identification of the gene for genotyping the dogs. Once we map the gene to a genomic region, we can select a few informative polymorphic markers that are tightly linked to the segregating phenotype (and hence the gene) and we can develop a genetic test that will give a probability value of carrying the defective gene. Of course identification of the gene and the underlying mutation will give a more clear-cut answer where sequencing the

DNA will give a definitive genotype."

What the investigation into the disorder has shown so far:
* A number of dogs have a mild malformation but do not have syringomyelia
* Clinically affected offspring often have affected (clinically or sub-clinically) parents
* Clinically affected parents can produce 'clear' offspring
* The signs of syringomyelia can get worse and have an earlier onset with each generation
* Chiari malformation occurs occasionally in other toy breeds (the DNA collection includes 7 different breeds)
* Syringomyelia can be asymptomatic or apparently asymptomatic. Sometimes this is because the signs of pain are not recognised e.g. many dogs show discomfort during the evening and on walks. If the dogs are predominantly penned and not exercised (as in some breeding establishments) then signs of pain may be missed. However some dogs genuinely exhibit few or no signs because of where and how their spinal cord has been affected
* Length and diameter of the syrinx does not necessarily reflect severity and should not be used as a factor in decision making for breeding.
* The inheritance of the disorder is not yet known. The "best guesses" are that it is polygenic or dominant with incomplete or variable penetrance but the influence of another gene cannot be ruled out; affected lines are always found on both sire and dam sides of an affected case.

Some startling statistics: In a sample of 70 'unaffected" CKCS MRI scanned for breeding purposes in Europe and North America:

49 (70%) had syringomyelia
12 (17%) were at risk -young dogs with occipital hypoplasia but no syringomyelia yet
9 (13%) were clear

Other screening studies have reported 'more with than without'. Pedigree analysis confirms this is a worldwide problem and not limited to any particular country, breeding line or kennel.

DNA Collection Project
Again we are indebted to the number of dedicated and unselfish breeders, pet owners and veterinarians who have taken the time and trouble to send blood samples for archiving. Several breeders from the USA, UK and Netherlands have sent their MRI scans to Clare which ensures consistency of diagnosis. 48 owners kindly donated blood at the Malvern Show, UK. We would like to thank the Health Committee and Carol Fowler for making this possible – apparently there was a long queue and not everyone had time to complete the forms correctly during extremely hectic day. The UK DNA Archive has extracted DNA from over 550 samples, with an estimated cost of over £10,000. This is a huge contribution to the project and shouldn't be underestimated. The main focus of the DNA collection now is to identify MRI 'normal' dogs and their siblings. Any owners with such dogs are asked please to get in touch and make available the names of any dogs that do not have the malformation to other breeders. The Cavalier Club now have a 'Clear List' on their website www.thecavalierclub.co.uk.

MRI screening and breeding recommendations
The diagnosis of syringomyelia is easily confirmed by MRI but neurologists have yet to define what is meant by the term 'clear' given that most cavaliers have a degree of skull malformation. The late onset of clinical signs and the number of asymptomatic dogs adds to the complexity of the disease. Not enough is known about long term progression to ascertain the optimum age young dogs should be screened for the disease. The research is an evolving process and hopefully a proven accurate and UNIVERSAL scheme will be developed eventually. Recent studies suggests that in the vast majority of cases the syrinx starts in the upper cervical spinal cord so if this is included then scanning of the entire cord (more expensive) may not ultimately be necessary. Any 'normal' dog without the occipital malformation which makes the skull small has a genetic advantage and should be used for breeding.


This lovely pup belongs to Sue Shidler (SevenWoods) one of a growing number of breeders who are screening dogs before breeding at substantial personal expense. 'Kiera' has MRI normal parents, including a 'clear' line of four generations. Although there is no guarantee her litter will all be SM clear, the chances are considerably increased. Evidence gained from such matings will prove invaluable for the geneticists and our understanding of the condition.

The following breeding recommendations are made using current information and in response to breeder requests for guidelines. It has yet to be proven if this guide is appropriate. The aim of these recommendations is to reduce the incidence of symptomatic syringomyelia in the breed not to create litters of puppies guaranteed not to have SM as the chance of producing an affected dog cannot be predicted without knowing the inheritance. It is recommended that the offspring of any mating is also MRI screened before breeding. As the incidence of syringomyelia is so high in the breed there will be severe depletion of the gene pool if only clear dogs are used (i.e. other problems will develop). Therefore until the genetic defect is determined it is recommended that dogs with syringomyelia be used if they are valuable in another genetic sense e.g. good heart. The general principle of these guidelines is that dogs with code A are more desirable to use than B, etc but that dogs with a higher letter code may still be used in some limited circumstances.

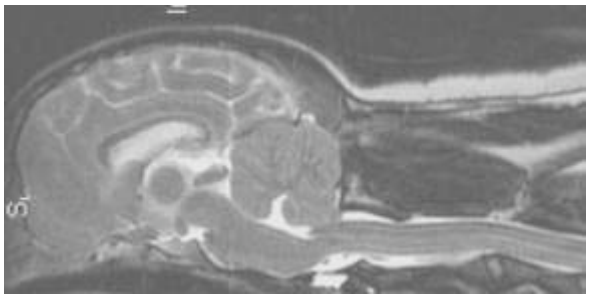
Current breeding recommendations (August 2005) (NB these have been revised and current guidelines are available HERE).
Note- The age cut off at 2.5years has been decided so as to tie in with MVD recommendations and because most dogs with symptomatic syringomyelia will show signs before 3 years of age. > =greater than; < less than

Colour code red = under 2.5 years blue = over 2.5 years, **purple = any age**

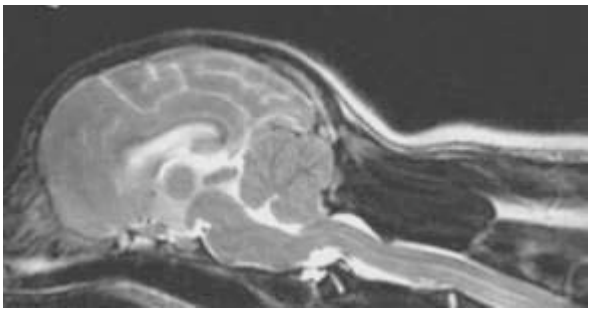
Code	AGE (years)	Syringomyelia	Occipital Hypoplasia	MVD[1]	Breed to
A*	Any	Absent	Absent	Fail/Pass	A, B, C, D,
A	> 2.5	Absent or central canal dilatation in the C2-C4 region only	Present [2]	Pass	A, B, C, D
B	< 2.5	Absent	Mild [2]	Dam and sire pass	A, B, C, D Consider rescan after 2.5 years to clarify status, monitor heart
C	< 2.5	Absent	Present [2]	Dam and sire pass	A , B Consider rescan after 2.5 years to clarify status, monitor heart
A , B	> 2.5	Present but asymptomatic	Present [2]	Pass	A, B
E[4, 5]	< 2.5	Present but asymptomatic	Present [2]	Dam and sire pass	Wait until 2.5y to clarify status
F	> 2.5	Present but asymptomatic	Present [2]	Fail	NO
F	Any	Present and symptomatic	Present[2]	Fail/Pass	NO

Notes : These recommendations will only work if cavaliers are actually MRI scanned!!

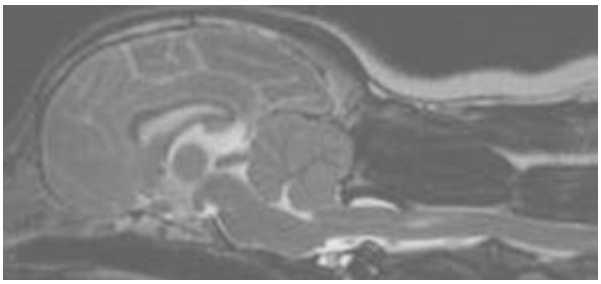
1. MVD - to pass a dog must be free of systolic murmur over 2.5 years old with systolic murmur-free parents over 5 years old
2. Occipital hypoplasia can be difficult to define because, in comparison to other toy breeds, the back of the CKCS skull is smaller – i.e. “normal” is very hard to find and there are few CKCS that are A*. In addition the term ‘too small’ has not been defined neither is there a consensus on how to measure the occipital bone. Basically there are 3 classic features of the malformation i) loss of the normal round shape of the cerebellum which can appear indented by the occipital bone ii) displacement of the cerebellum into and through the foramen magnum i.e. herniation iii) kinking of the medulla. Mild occipital hypoplasia is defined as a displacement cerebellum into the area of the foramen magnum and slight kinking of medulla and indentation of the cerebellum (see diagrams below).



Mild occipital hypoplasia – the cerebellum is very slightly indented, the kinking of the medulla is normal for a toy breed and there is displacement of the cerebellum into and just out of the foramen magnum. The ventricular system is slightly dilated. This dog is graded B. If he was older than 2 ½ he would be graded A.



Although the cerebellum is not coming through the foramen magnum this dog has a greater degree of occipital hypoplasia than the dog above. See how the cerebellum is indented and the medulla is kinked. The central canal is dilated above the first disc space – this is the first sign of syringomyelia developing. There is also mild ventricular dilatation. **This dog would be graded C if less than 2 ½ years**



This dog has descent of the cerebellum towards the foramen magnum and the cerebellum is indented. The medulla is normal for a toy breed; there is mild ventricular dilatation and a small syrinx/central canal dilatation in the upper cervical spinal cord. However he is 8 years old with a clear heart. He is graded as A.

4. Dogs may develop signs of syringomyelia at any age e.g. a dog can be free of pain until 7 years old i.e. dog's status may change as it gets older.
5. Any dog not MRI scanned is assumed to be grade D or E depending on their age
6. Breed clubs should consider whether to recommend that stud dogs are MRI scanned. Males have most influence on the gene pool (popular champions sire hundreds) and by the time it is known that a dog may pass on the tendency his genes may be widespread. It would be sensible that if a male dog to be used more than twice then, for the safety of the breed, he should be A or B. It would perhaps be a good use of research funds to use them to subsidise testing of stud dogs and publish a clear list. A salient fact is that 93% of top stud dogs in the UK are closely related to 1 or more dogs with SM and the pedigrees of these dogs are similar to Champions worldwide.

Funding

We have received a magnificent gift of $1,000 from Christi Scarpino who owns a Boston terrier called Hope diagnosed with SM. Christi used an extremely imaginative array of fundraising ideas including selling cherished collectables from Boston terrier lovers on Ebay!

Clare's investigation of CT of the occipital bones in CKCS with and without Chiari malformation and syringomyelia is drawing to a close and data analysis will start in

the near future. This project is funded by the Cavalier Club UK and Cavalier KCS Club of Victoria, Australia

Recent Publications

We recommend Karlin Lillington's SM website http://www.cavaliertalk.com/SM This website is easy to navigate and contains lots of useful information and support. There's also a discussion board: www.cavaliertalk.com: 'A community for Cavalier King Charles Spaniel fans'

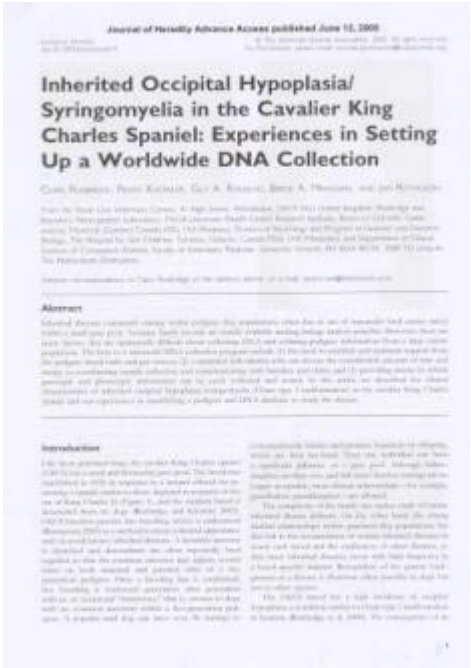
Journals

REVIEW

Neurological diseases of the Cavalier King Charles spaniel

Several neurological syndromes have been described in Cavalier King Charles spaniels and many of the conditions have similar clinical signs. The current knowledge of these syndromes is reviewed in this article, with the aim of enabling the general practitioner to formulate a differential diagnosis and plan for diagnostic tests and treatment. Specifically, the article discusses and contrasts the most common conditions seen, including occipital hypoplasia/syringomyelia, episodic collapse, epilepsy and vestibular disorders.

Contact jacqueline@bva-edit.co.uk for PDF (cost £30 entitling 50 copies)
Journal of Small Animal Practice, 46 (6) June 2005 p265-272



Journal of Heredity Advance Access published June 10, 2009

Inherited Occipital Hypoplasia/ Syringomyelia in the Cavalier King Charles Spaniel: Experiences in Setting Up a Worldwide DNA Collection

PDF:http://jhered.oxfordjournals.org/cgi/reprint/esi074?ijkey=VB0Rz2zSdiW0o1L&keytype=ref
For those wishing to make commercial use of the article, please obtain permission from journals.permissions@oupjournals.org Journal of Heredity published Online June 15

DVD Seminar on Syringomyelia in May 2005
Three copyrighted versions of Clare's presentation will be available soon. They are non profit making and the cost includes a donation to DNA research. Be generous and buy one for your vet or breeder! The programme includes clinical signs; diagnosis; treatment; breeding recommendations; current research; DNA program; and Questions and Answers.

Full details and how to order can be found at the websites below.

http://www.cavaliertalk.com/phpBB2/viewtopic.php?t=355 for details of all versions Karlin has very kindly agreed to produce and distribute UK editions for around £15

http://www.pawsitivelyvideo.com/cavalier2005_showvideo.html for details for ACKCS Lancaster, PA edition$25

http://www.candog.com/cavaliers/ for details of Canadian edition Contact Pat Barrington by email at: harley2@sympatico.ca or by phone: (905-382-0092) Cost: $25.00 (Canadian $) for the Edited Version (Dr. Rusbridge presentation only) or $35.00 (Canadian $) for the Unedited Version with Q and A session.