Section 8

Summarising discussion and appendixes

Chapter 8.1

English Summary

Introduction

Chiari-like malformation (CM) is a condition characterised by a mismatch between the caudal fossa (skull) volume and its contents, the cerebellum and brainstem **(Section 2.1)**. The neural structures are displaced into the foramen magnum obstructing cerebrospinal fluid (CSF) flow. A consequence of this is syringomyelia (SM) where fluid filled cavities develop within the spinal cord. The primary clinical sign of CM/SM is pain, either due to obstruction of the CSF pulse pressure and/or a neuropathic pain syndrome due to damage to the spinal cord dorsal horn. This disease has also been referred to as *occiptial hypoplasia* (**Section 3.1 and 7.1**) and *caudal occipital malformation syndrome* (COMS) (Dewey et al 2005). CM/SM is sometimes erroneously confused with *Arnold Chiari malformation* (cerebellar and medulla herniation associated with myelomeningocele- **Section 2.2**) and *occipital dysplasia* (incomplete ossification of the supraoccipital bone – **Section 3.1**).

Pathogenesis

The pathogenesis of canine CM/SM is not fully understood (**Section 2.2**). An important contributory factor is thought to be an inadequate small caudal fossa volume which early observations suggested is due to a relatively short basioccipital bone i.e. inappropriately short skull base. However it is likely there are other unidentified anatomical or environmental factors. A study comparing intracranial dimensions did not demonstrate a significant difference between the size of the caudal fossa in cavalier King Charles spaniels (CKCS) with and without syringomyelia (**Section 4**). CKCS with syringomyelia did have a significantly wider vertebral canal at the C2/C3 junction and mid C3, however the distance was so small that it was not measurable with standard techniques and further studies are required to determine if this is in fact related to the development of a syrinx (**Section 4**).

The precise pathogenetic mechanism by which syringomyelia develops is much debated (**Section 2.1**). There is, however, increasing agreement that the syrinx fluid is not CSF, but most likely extracellular fluid that accumulates within the central canal or spinal cord substance as a consequence of abnormal pressure differentials between the spinal cord and subarachnoid space. Early proposals for the pathogenesis of SM, such as the *water-hammer* and *suck effect* theory, now seem unlikely because these rely on there being a connection between the fourth ventricle and central canal as well as a lower pressure system within the syrinx relative to the ventricle and subarachnoid space. The *intramedullary pulse pressure* theory of syringomyelia postulates that the obstruction of CSF flow results in relative increase in intrathecal pressure and decrease in subarachnoid pressure, the consequence of which is repeated mechanical distention of the spinal cord. This in turn results in dilatation of the central canal and accumulation of extracellular fluid which eventually coalesces into cavities (**Section 2.2**).

Incidence

The CKCS is overwhelmingly overrepresented for cases of CM/SM. An estimated 95% of the population have CM and as many as 50% have CM/SM with the proportion of affected dogs increasing with age **(Section 7)**. There is no colour or sex predisposition. As shortened skull is a risk factor, any breed with a degree of brachycephalism and/or miniaturization could potentially be predisposed to CM/SM. To date the condition has been also reported in King Charles spaniels, Brussels griffons, Yorkshire terriers, Maltese terriers, Chihuahuas, Miniature dachshunds, Miniature/toy poodles, Bichon Frise, Pugs, Shih Tzus, Pomeranians, Staffordshire bull terriers, a Boston terrier, a Pekingese, a miniature Pinscher, and a French bulldog. (**Section 7.4**). Recent studies suggest 35% of SM-affected dogs have clinical signs of the condition **(Section 5.1)**. The youngest reported dogs with SM have been 12 weeks old. Dogs may be presented at any age although the majority are young. Approximately 45% will develop first signs of the disease within the first year of life and approximately 40% of cases have first signs between 1 and 4 years old. As many as 15% develop signs as mature dogs and the oldest reported case first developed

signs of disease when aged 6.8 years (**Sections 5.1, 6.1, 6.2**). Due to the vague nature of clinical signs in some cases and lack of awareness of the disease there is often a considerable time period (mean 1.6 years) between the onset of signs and confirmation of a diagnosis (**Sections 5.1, 6.1, 6.2**).

Clinical Signs

The most important and consistent clinical sign of CM/SM is pain **(Section 5 and appendix 1 –SM pain score)** however this may be difficult to localise on clinical examination and, because it is often intermittent, may be dismissed by owners or veterinary surgeons. Therefore, historical signs of pain should be considered seriously in predisposed breeds. Owners may describe postural pain. For example, affected dogs may suddenly scream and/or lie with their head on the ground between the paws after jumping up or during excitement. It is also common for affected animals to sleep with the head in unusual positions, for example elevated. Discomfort often appears worse in the evening and early morning or when excited and can be associated with defaecation and may vary with weather conditions. Some of the signs of syringomyelia, such as posture-related pain, could be explained by obstruction to CSF flow but syringomyelia also results in a neuropathic pain syndrome probably due to damage to the spinal cord dorsal horn **(Section 5.1).** Affected dogs behave as if they experience allodynia, i.e. pain arising in response to a non-noxious stimulus, for example they appear to dislike touch to certain areas of skin (ear, neck, forelimb or sternum) and may be unable to tolerate grooming or a neck collar. Pain is positively correlated with syrinx width; i.e. dogs with a wider syrinx are more likely to experience discomfort, and dogs with a narrow syrinx may be asymptomatic, especially if the syrinx is symmetrical and not deviated into the dorsal horn. Dogs with a wide syrinx may also scratch, typically on one side only, while walking and often without making skin contact. Such behaviour is often referred to as an “air guitar” or “phantom” scratching. This sign is highly suggestive of dysaesthesia - i.e. a spontaneous or evoked unpleasant abnormal sensation. Humans with syringomyelia associated dysaesthesia describe painful burning itching and/or an intense sensation suggesting insects crawling on the skin.

Dog with a wide syrinx are also more likely to have scoliosis **(Section 5.1)**. This is likely to relate to damage to the dorsal grey column and a unilateral loss of proprioceptive information. Scoliosis is more common in dogs less than one year old and may be the first clinical signs of SM, appearing before signs of neuropathic pain develop. In many cases the scoliosis slowly resolves despite persistence of the syrinx.

SM may result in other neurological deficits such as thoracic limb weakness and muscle atrophy (due to ventral horn cell damage) and pelvic limb ataxia and weakness (due to white matter damage or involvement of the lumbar spinal cord by the syrinx). Seizures, facial nerve paralysis and deafness may also be seen however no direct relationship has been proven and this association may be circumstantial **(Section 2)**.

CM alone appears to cause facial pain in some dogs with owners describing ear and facial rubbing/ scratching. It has been proposed that CM and direct compression of the medulla can result in a disorder of sensory processing and a pain syndrome **(Section 5.2)**. In this circumstance it can be difficult to be certain that the CM, as apposed to ear, oral or skin disease, is the cause of the distress especially as CM is a common incidental finding in the CKCS breed.

Clinical course

Progression of disease is variable. Some dogs remain stable or deteriorate minimally. Other affected dogs can be severely disabled by pain and neurological deficits within 6 months of the first observed signs **(Section 2.2)**.

Diagnosis

Magnetic resonance imaging (MRI) is essential for the diagnosis and determination of the cause of SM **(Section 2.1)**. In the instance of CM/SM the cerebellum and medulla extend into or through the foramen magnum which is occluded with little or no CSF around the neural structures. The size of the cerebellar herniation is not correlated with severity. There is typically ventricular dilatation. SM is indicated by fluid-containing cavities within the spinal cord. The upper cervical and upper thoracic segments are typically the most severely affected. The shape of the cavity may be complex with septations (i.e. haustra) and generally involves a portion of the central canal at some level. Maximum syrinx width is the strongest predictor of pain, scratching behaviour and scoliosis; 95% of CKCS with a maximum syrinx width of 0.64cm or more will have associated clinical signs **(Section 5.1)**.

Laboratory tests such as haematology, serum biochemistry and urinalysis are only useful in eliminating other differentials or to establish that there is nothing precluding surgical or medical management. Radiographs have limited value. In severe cases cervical images may suggest widening of the vertebral canal especially in the C2 region and/or scoliosis. Flexed and extended images of neck can be used to rule out vertebral abnormalities such as atlantoaxial subluxation and for an indication of the likelihood of intervertebral disc disease **(Section 1.3)**. Ultrasonography through the cisterna magnum may confirm cerebellar vermis herniation. However, as CM is so common in the CKCS this information has limited value. Ultrasound examination can also detect a syrinx if within the cranial cervical segment however failure to detect a syrinx does not eliminate the possibility of one more caudally. CSF analysis may be useful to rule out inflammatory diseases. Sampling requires experience as there is a high risk of inaccurate needle placement. Myelography is contraindicated for same reason. CM/SM does not appear to increase risk associated with anaesthesia.

Differential Diagnosis

The most important differential diagnoses **(Section 1.3)** are other causes of pain and spinal cord dysfunction such as intervertebral disc disease; CNS inflammatory diseases such as granulomatous meningoencephal

omyelitis; vertebral abnormities such as atlantoaxial subluxation; neoplasia; and discospondylitis. When scratching or facial/ear rubbing is the predominant clinical sign, ear and skin disease should be ruled out. The scratching behaviour for SM is classically to one discrete area of skin. It is a common *incidental* finding for CKCS to have a mucoid material in one or both tympanic bullae and in the majority of cases this is *not* associated with clinical signs. Some cases with scoliosis appear to have a head tilt which could be confused with vestibular dysfunction. If in doubt cervical radiographs can confirm scoliosis.

Treatment and Prognosis

The main treatment objective is pain relief. The most common surgical management is *cranial cervical decompression* (also described as foramen magnum or suboccipital decompression) establishing a CSF pathway via the removal of part of the supraoccipital bone and neural arch of C1 **(Section 6.1)**. This may be combined with a durotomy (incision of the dura with/without incision of subarachnoid meninges) with or without patching with a suitable graft material such as biocompatible collagen matrix (Vet BioSIST ™, Cook/Global Veterinary Products, SurgiVet, Smiths Medical Pm inc N7 W22025 Johnson Road, Waukesha, WI USA 53186). Cranial cervical decompression surgery is successful in reducing pain and improving neurological deficits in approximately 80% of cases and approximately 45% of cases may still have a satisfactory quality of life 2 years postoperatively. However surgery may not adequately address the cause of syringomyelia and most importantly the syrinx is persistent. The clinical improvement is probably attributable to improvement in CSF flow through the foramen magnum. In many cases scaring and fibrous tissue adhesions over the foramen magnum will result in re-obstruction and as many as 50% of cases can eventually deteriorate. This can be as early as 2 months postoperatively. Due to the persistence of SM and dorsal horn damage it is likely that the patient will also require continuing medical management for pain relief **(Section 5.2)**.

There are three main drugs used for treatment of SM: drugs that reduce CSF production; analgesics; and corticosteroids **(Section 2.2 and 5.2).** If the dog's history suggests postural pain or discomfort relating to obstruction of CSF flow then a trial of furosemide is appropriate. A furosemide trial is also very useful if it is difficult to determine if the cause of discomfort is CM versus, for example, ear disease. Furosemide may be sufficient to control signs in some dogs, but additional analgesics are likely to be necessary for an individual with a wide syrinx. In this circumstance it is suggested that non steroidal anti-inflammatory drugs are the medication of first choice partly because there are several licensed products. However, for dogs with signs of neuropathic pain, i.e. allodynia and scratching behaviour (suspected dysesthesia); a drug which is active in the dorsal horn is more likely to be effective. Because gabapentin has established use in veterinary medicine it is suggested that this is the drug of first choice but amitriptyline or pregabalin may also be suitable. Corticosteroids are an option if pain persists or where available finances prohibit the use of other drugs. Because the mechanisms of development of neuropathic pain are multifactorial, appropriate polypharmacy is likely to be more effective than treatment with single agents **(Section 5.2)**. Anecdotally, acupuncture and alphasonic treatments have been reported to be useful adjunctive therapy in some cases. The dog's activity need not to be restricted but owner should understand that dog may avoid some activities and grooming may not be tolerated. Simple actions, for example raising the food bowl and removing neck collars, can also help.

Prognosis is guarded especially for dogs with a wide syrinx and/or with first clinical signs before 4 years of age. In a small case series **(Section 6.2)** managed conservatively for neuropathic pain, 36% were eventually euthanatized as a consequence of uncontrolled pain. However 43% of the group survived to be greater than 9 years of age (average life expectancy for a CKCS is 10.7 years). Most dogs retain the ability to walk although some may be significantly tetraparetic and ataxic.

Genetics and Breeding recommendations

CM/SM in the CKCS can be traced backed to two UK bitches from the post-WWII era, which were foundational dogs for the modern breed "created" from the shorter-nosed King Charles spaniel (**Section 7.1 and 7.2**). A CKCS genome scan is currently underway with the hope of identifying the causal genes. Preliminary results have suggested six interesting regions on six associated chromosomes which warrant further investigation **(Section7.3 and 7.4)**. However, because of the ubiquity of the condition within the CKCS breed this is a complex task and focus is now centring on comparison with sporadic cases in other breeds. The mode of inheritance, including the number, identity and relative contribution of the causative genes is not yet determined. The etiology of both conditions could be further complicated by variable penetrance of the various genotypes and the involvement of environmental factors. Current breeding recommendations for CKCS concentrate on removal of dogs with early onset SM (i.e. within the first 2.5 years of life) from the breeding pool (**appendixes 2-4**). This involves MRI screening of potential breeding stock and is therefore a costly process. The aim of current breeding recommendations is to limit the number of severely affected dogs rather than eliminate the disease from the CKCS population. Due to the number of affected dogs there is a danger that very restrictive breeding practices will further narrow the gene pool and other diseases will emerge. It should also be borne in mind that absence of SM in a young dog does not exclude the possibility that it will develop with time.

Future research

This study into Chiari-like malformation and syringomyelia addressed three hypotheses. Some answers were provided however it is not surprising that many more questions were generated and work into this fascinating disorder continues

Hypothesis 1

Syringomyelia in the cavalier King Charles spaniel occurs secondary to obstruction of cerebrospinal fluid flow through the foramen magnum which is due, at least in part, to bony abnormalities, in particular an inappropriately small caudal fossa

This hypothesis is neither proven nor unproven. Although the MRI appearance of CM is characterised by a small volume caudal fossa with foramen magnum overcrowding, a link to the development of SM has not been proven. The work detailed in Section 4 found no difference between the volume of the caudal fossa between CKCS with and without SM. A recent study (Sgouros and others 2006) investigated whether children with symptomatic CM had smaller posterior fossas than healthy controls, and whether a small posterior fossa was linked to the presence of syringomyelia. They did *not* find a significant difference between the sizes of the posterior fossa of children with symptomatic CM versus healthy controls; however, they did find that patients with CM/SM had significantly smaller posterior fossa measurements. This difference was more pronounced in children under 10. As a natural model of CM and CM/SM the CKCS is an important resource for further understanding this disease and further research is continuing as follows

1) Investigation into how miniaturisation and brachiocephalicism alters caudal fossa MRI dimensions. This is a comparative study involving many dog breeds with the aim of establishing i) whether the CKCS has a smaller caudal fossa volume than dogs of a similar body weight and ii) if selecting for certain head shapes has a disproportional effects on certain skull bones compared to others
2) CT study of ancient and modern King Charles spaniels and CKCS skulls (in collaboration with the Natural History Museums of London and Berne). This study is with the aim of establishing if over time selection has resulted in a change in caudal fossa dimensions.
3) Investigation in subluxation of the atlantoaxial joint in the CKCS (in collaboration with Cambridge University). This study is with the aim of looking for other anatomical factors which could influence the development of syringomyelia.
4) Comparative study of cervical and intracranial dimensions in young CKCS (less than 2 years of age) with and without syringomyelia (in collaboration with Cambridge University). In this study we aim to compare skull and cervical dimensions to establish if there are any risk factors for the early development of syringomyelia. We are particularly interested to establish whether, like humans, there may be a more disproportionate difference in caudal fossa volume between young healthy dogs and dogs with CM/SM.
5) One important question that is yet to be addressed is whether cerebrospinal fluid abnormalities influence the development of syringomyelia for example abnormally high CSF pressure. We are looking at ways that this hypothesis could be investigated.

Hypothesis 2

The clinical signs of scratching and pain in CM/SM are a manifestation of a neuropathic pain syndrome.

The work in Section 4 strongly supported this hypothesis however greater understanding is needed in particular what anatomical and neurochemical changes, in the spinal cord dorsal horn are associated with the neuropathic pain At the present time we are focusing on

1) How the clinical signs are related to the pathology: a histological study of SM (in collaboration with Cambridge University).
2) Prospective clinical trial assessing which medical management is most appropriate (in collaboration with Cambridge University).
3) Improving surgical technique

Hypothesis 3

CM/SM is a hereditary disease in the cavalier King Charles spaniel.

The work in Section 7 strongly supported this hypothesis and work continues in this area (in collaboration with Centre for the Study of Brain Diseases, Notre Dame Hospital and Cambridge University). Recent studies on (human) families with multiple members affected by CM found that small posterior fossa volume was a heritable trait and that size of cerebellar herniation was not. The researchers identified significant areas on chromosomes 9 and 15 which may be implicated in the disease. There are over 300 genes in these regions, however it is interesting to note that there is one gene, Fibrillin-1, already associated with three genetic conditions which involve mis-shaped skulls. Identification of the genes responsible for CM with or without SM will improve understanding of the pathogenesis for better diagnosis, prognosis and clinical management of this devastating condition. These studies will also help unravel some of the complexity involved in this malformation and in the embryonic development of the affected structures.

This study was beset by many problems in establishing the hereditary nature. The most important difficulties were

1) **Defining the phenotype -** This has been an evolving process which is still unresolved. There is still no clear definition of “normal” i.e. what degree of caudal fossa overcrowding is acceptable in a dog. For this reason and, because studies in this thesis and elsewhere suggest that the pathogenesis of SM involves more than a small caudal fossa, it is recommended that future research concentrate on the heritable traits in the dog that lead to SM. It is also the recommendation that breeders concentrate on eliminating dogs with SM from their breeding program and that for the present time less priority is given to the presence / apparent severity of CM until it is better established what heritable features are associated with SM.
2) **Working with the dog breeding community -** This project would not have been possible without the considerable assistance of many dog breeders across Europe, North America, Australasia and South

Africa however not all breeders or breed club officials place dog health and welfare as a high priority and many are more concerned about reputation, puppy sales and value of breeding stock. This meant that we faced the problem of misleading information, non cooperation and attempts at discrediting the research findings (mostly in on-line chat-rooms). It is has also taken time to develop knowledge and contacts and if we had the foundation in 2000 that we have now then we would have been able to approach some of the studies differently especially the early genetic research in Section 7 that followed the discovery of the disease. As a consequence we can make the following recommendations in the set up of future studies.

a. Well defined phenotype that is easy to confirm with a simple inexpensive test (unfortunately because SM is diagnosed by MRI a simple inexpensive method of diagnosis has not been possible)
b. Simple and accurate method of DNA collection and storage (Unfortunately DNA collection is made more complicated in the UK because collection of canine blood for research is prohibited, even after owner consent, and all UK samples were obtained from left over blood following an appropriate diagnostic test).
c. Comprehensive database where it is easy to retrieve and add information and compare relationships between family groups.
d. Dedicated person(s) able to enter information into database, statistically analyse it and coordinate DNA collection and other research.
e. Maintenance of a high level of communication of the project findings and progress to breeders so that the study remains high profile.
f. It is also important that the molecular geneticists have some understanding of dog breeding and the motivations and passions of dog breeders and owners.

Conclusions

The main conclusions from this thesis were

1) Syringomyelia has a high incidence in the cavalier King Charles spaniel breed and the tendency for it is suspected to be inherited. Preliminary results from a genome scan suggested six interesting regions on six associated chromosomes which warrant further investigation
2) Syringomyelia is seen in association with a Chiari-like malformation in this breed however a definite link between small caudal fossa volume and fluid cavitation within the spinal cord has yet to be established
3) It is hypothesised that syringomyelia occurs secondary to cerebrospinal fluid obstruction and abnormal pressure differentials between the spinal cord and subarachnoid space. It is further hypothesised that the syringomyelic fluid is extracellular rather than cerebrospinal in origin
4) Syringomyelia can result in a neuropathic pain syndrome and this is more likely with a wide syrinx and damage to the spinal cord dorsal horn.
5) Scoliosis is also likely with a wide syrinx and damage to the spinal cord dorsal horn
6) Medical treatment of syringomyelia associated pain should be directed at agents active at the level of the spinal cord dorsal horn. Drugs that reduce cerebrospinal fluid pressure may also be helpful
7) Surgical cranial cervical decompression can improve clinical signs of pain however the syringomyelia is generally persistent.

References

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Chapter 8.2

Samenvatting

The author is very grateful to Paul Mandigers for translating this summary into Dutch

Introductie

Chiari-like malformatie (CM) is een aandoening die gekarakteriseerd wordt doordat het volume van de fossa caudalis (schedel) en zijn inhoud, het cerebellum en de hersenstam niet in verhouding zijn **(Hoofdstuk 2.1)**. Hierdoor kunnen onderdelen van het centraal zenuwstelsel naar causaal verplaatst worden, door het foramen magnum, en zo de cerebrospinale vloeistof (CSF) stroom blokkeren. Als gevolg hiervan kan syringomyelie (SM), met vocht gevulde holtes in het ruggenmerg, zich ontwikkelen. Het primaire klinische symptoom van CM/SM is pijn. Dit ontstaat of ten gevolge van obstructie van de CSF en de aanwezig puls druk, en/of een neurogeen pijn syndroom ten gevolge van beschadiging van de spinale dorsale hoorn.

Naar deze ziekte wordt ook verwezen als *occiptiale hypoplasie* (**Hoofdstuk 3.1 and 7.1**) en *caudaal occipitaal malformatie syndroom* (COMS) (Dewey et al 2005). CM/SM wordt soms ten onrechte verward of gezien als een *Arnold Chiari malformatie* (cerebellaire en medullaire herniatie welke geassocieerd is met een myelomeningocele - **Hoofdstuk 2.2**) en *occipital dysplasie* (incomplete ossificatie van het supraoccipitale been - **Hoofdstuk 3.1**).

Pathogenese

De pathogenese van canine CM/SM is niet volledig bekend (**Hoofdstuk 2.2**). Een belangrijke factor is mogelijk een inadequaat smal caudaal fossa volume wat volgens eerdere waarnemingen mogelijk veroorzaakt wordt door een relatief kort basioccipitaal been dan wel onaangepaste korte schedel basis. Het is waarschijnlijk zo dat er nog andere niet geïdentificeerde anatomische en omgevingsfactoren een rol spelen. Een studie waarbij de intracraniale verhoudingen werden vergeleken liet een significant verschil zien voor de grote van de caudale fossa bij de cavalier King Charles spaniels (CKCS) met en zonder syringomyelie (**Hoofdstuk 4**). CKCS met syringomyelia hebben een significant wijder vertebraal kanaal bij de C2/C3 overgang en het midden van C3 hoewel meer studies nodig zijn om vast te stellen of dit gegeven gerelateerd is aan de ontwikkeling van een syrinx. Vergelijkbaar zijn CKCS met syringomyelie geassocieerde pijn significant nauwer bij C1/C2 hoewel een ware associatie nog niet bewezen is (**Hoofdstuk 4**).

De exacte pathogenese van de ontwikkeling van een syringomyelie is aan debat onderhevig (**Hoofdstuk 2.1**), hoewel er in toenemende mate gedacht wordt dat de syrinx niet is gevuld met CSF maar waarschijnlijk met een extracellulair vocht dat zich verzameld binnen het centraal kanaal en het ruggenmerg als een consequentie van een abnormaal drukverschil tussen het ruggenmerg en de subarchanoidale ruimte. Eerdere pathogenetische voorstellen van SM zoals de water-hamer en zuig effect theorie lijken inmiddels onwaarschijnlijk doordat deze afhankelijk zijn van een verbinding tussen de vierde ventrikel en het centraal kanaal naast een lage druk binnen de syrinx relatief ten opzichtte van de ventrikel en de subarachnoidale ruimte. De *intramedullaire puls druk* theorie van SM postuleert dat de obstructie van CSF stroom resulteert in een relatief hoge intrathecale druk en verlaagde subarachnoidale druk, resulterend in herhaalde mechanische verwijding van het ruggenmerg. Dit op zijn beurt resulteert in een verwijding van het centraal kanaal en de ophoping van extracellulaire vloeistof welke uiteindelijk uitmondt in holtes (**Hoofdstuk 2.2**).

Incidentie

De CKCS is overtuigend over gerepresenteerd voor wat betreft CM/SM. Naar schatting heeft 95% van de populatie CM en zoveel als 50% heeft CM/SM waarbij de fractie van aangedane honden toeneemt met de leeftijd **(Hoofdstuk 7)**. Er is geen kleur of sexe predispositie. Een verkorte schedel is een risico factor. Elk ras met een zekere mate van brachycephalie en/of dwerggroei is potentieel gepredisponeerd voor CM/SM. Heden ten dage is de aandoening beschreven bij King Charles spaniëls, Brusselse griffons, Yorkshire terriërs, Malteser leeuwtjes, Chihuahuas, dwergtekkels, Staffordshire bull terriërs, een Boston terriër, een mopshond en een Franse bulldog (**Hoofdstuk 7.4**). Recente studies suggereren dat 35% van de door SM aangedane honden ook klinische beelden hebben **(Hoofdstuk 5.1)**. De jongst beschreven hond met SM was een puppy van 12 weken oud. De aandoening kan op iedere leeftijd voorkomen

hoewel de meerderheid van de honden (ongeveer 45%) de eerste klinische beelden gedurende het eerste levensjaar laten zien. Ongeveer 40% van de honden heeft de eerste klinische beelden tussen de leeftijd een en vier jaar. Ongeveer 15% van de honden vertonen pas verschijnselen tijdens volwassenheid. De oudst beschreven hond was 6.8 jaar oud (**Hoofdstuks 5.1, 6.1, 6.2**). Deels door de soms vaagheid van de symptomen maar ook deels door het zich niet bewustzijn van de ziekte kan het soms lang duren voordat de diagnose gesteld wordt. De gemiddelde duur tussen het opmerken van symptomen en het stellen van de diagnose is gemiddeld 1.6 jaar (**Hoofdstuks 5.1, 6.1, 6.2**).

Klinische beeld

Het meest belangrijke en steeds terugkomend symptoom van CM/SM is pijn **(Hoofdstuk 5 en appendix 1 –SM pijn score)** hoewel het moeilijk kan zijn deze pijn bij een klinisch onderzoek te lokaliseren en, omdat het vaak intermitterend optreedt, kan het gemist worden door zowel eigenaar als dierenarts. Daarom is het belangrijk eerdere signalen van pijn serieus te nemen bij gepredisponeerde rassen. Eigenaren kunnen houdings-gerelateerde pijn beschrijven; een voorbeeld is het plotseling schreeuwen van aangedane honden en/of gaan met hun hoofd tussen de beide voorpoten op de grond liggen na springen of na beweging. Zo is het ook gewoon dat de honden met hun hoofd in een ongewone, bijvoorbeeld opgeheven, positie slapen. Ongemak blijkt vaak ‘s avonds of in de vroege ochtend erger te zijn als ze opgewonden zijn en kan ook geassocieerd zijn met ontlasten of bij vernaderde weer omstandigheden. Sommige symptomen van syringomyelie, zoals houdings-gerelateerde pijn, kan mogelijk verklaard worden door de blokkade van de CSF stroom maar syringomyelie kan ook resulteren in een neurogeen pijn syndroom wat vermoedelijk veroorzaakt wordt door beschadiging van de spinale dorsale hoorn **(Hoofdstuk 5.1).** Aangedane honden gedragen zich alsof ze allodynia ervaren. Dit is het als pijnlijk ervaren van een niet pijnlijke stimulus. Een voorbeeld is dat ze het niet fijn vinden aangeraakt te worden op bepaalde plaatsen van hun lichaam (oor, nek, voorbeen of borstbeen) en soms laten ze het borstelen of bijvoorbeeld een halsband niet toe. De pijn is positief gecorreleerd met de syrinx breedte; honden met een wijdere syrinx ervaren meestal meer ongemak en honden met een nauwe syrinx kunnen asymptomatisch zijn. Dit zien we met name indien de syrinx symmetrisch is en zich niet uitbreid in de dorsale hoorn. Honden met een wijdere syrinx kunnen ook krabben, typisch is krabben aan een zijde terwijl de hond loopt. Hierbij wordt vaak geen contact met de huid gemaakt. Naar dit gedrag wordt vaak verwezen onder de noemers ‘lucht gitaar’ of ‘fantoom’ krabben. Dit symptoom is vaak suggestief voor een dysaesthesie: een spontane of opgewekte onaangename abnormale sensatie. Mensen met syringomyelie geassocieerde dysaesthesie beschrijven een pijnlijk brandende jeuk en/of een intens gevoel alsof er insecten op de huid kruipen. Honden met een wijdere syrinx hebben vaak ook een scoliosis **(Hoofdstuk 5.1)**. Deze is waarschijnlijk gerelateerd aan beschadiging van de grijze dorsale kolom en het unilaterale verlies van proprioceptische informatie. Scoliosis is meer gewoon bij honden jonger dan een jaar oud en kan het eerste klinische beeld van SM zijn wat zelfs eerder gezien wordt dan dat de neurogene pijn zich ontwikkeld. In veel gevallen verdwijnt de scoliosis langzaam ondanks het aanwezig blijven van de syrinx.

SM kan zich in andere neurologische afwijkingen ontwikkelen zoals een krachtsvermindering in de voorpoten en spieratrofie (ten gevolge van beschadiging van de ventrale hoorn) en ataxie en parese van de achterhand (ten gevolge van beschadiging van de witte stof en betrokkenheid van het lumbale ruggenmerg bij de syringomyelie). Aanvallen, nervus fascialis paralyse en doofheid kunnen ook gezien worden hoewel er geen directe relatie is bewezen en mogelijk berust dit op toeval **(Hoofdstuk 2)**.

Alleen aangezichtspijn bij CM blijkt bij sommige honden uit de beschrijving van eigenaren die de hond zien wrijven of krabben aan oor of aangezicht. Directe compressie van de medulla kan mogelijk resulteren in een afwijking van het verwerken van sensibele prikkels en een pijn syndroom **(Hoofdstuk 5.2)**. In dit geval kan het moeilijk zijn om zeker te zijn dat CM, bij oor, mond of huid ziekte, de oorzaak is van het ongemak, zeker daar het vinden van CM een veelvoorkomende afwijking is bij de CKCS.

Klinisch verloop

Het verloop van de ziekte varieert. Sommige honden blijven stabiel of verslechteren beetje bij beetje in de loop van de jaren. Sommige honden zijn echter binnen een tijdsbestek van 6 maanden sterk gehandicapt door de pijn en de neurologische uitval **(Hoofdstuk 2.2)**.

Diagnose

Magnetische resonantie imaging (MRI) is essentieel voor het stellen van de diagnose en voor het vast stellen van de oorzaak van de SM **(Hoofdstuk 2.1)**. Bij CM/SM gaan zowel het cerebellum als de medulla in of door het foramen magnum wat hierdoor geblokkeerd raakt. Er bevindt zich weinig tot geen CSF rond deze neurale weefsels. De mate van cerebellaire herniatie is niet gecorreleerd met de ernst van de klinische beelden. Meestal is ventriculaire dilatatie. Bij SM zien we de met vocht gevulde holtes binnen het ruggenmerg. Het eerste deel van het cervicale en thoracale deel van het ruggenmerg zijn het meest afwijkend. De vorm van de holte kan complex zijn met bijvoorbeeld septa (haustra) en in de regel is een deel van het centraal kanaal in zekere mate erbij betrokken. Maximale syrinx wijdte is de beste voorspeller van pijn, het krabben en de scoliosis; 95% van de CKCS met een maximale syrinx wijdte van 0.64cm of meer zullen de geassocieerde klinische beelden hebben **(Hoofdstuk 5.1)**.

Laboratoria testen zoals haematologie, klinische chemie en urine analyse zijn alleen behulpzaam voor het uitsluiten van andere differentiaal diagnoses of om vast te stellen dat er geen uitsluitende reden is voor de chirurgie of medicamenteuze behandeling. Routine röntgenfoto’s hebben beperkte waarde. Bij sterk aangedane patiënten kunnen bij cervicale opnames een suggestief wijder vertebraal kanaal in de regio van C2 gezien worden en/of scoliosis. Gebogen en gerekte opnames van de nek kunnen gebruikt worden om vertebrale afwijkingen zoals een atlantoaxiale subluxatie en eventuele disk problematiek uit te sluiten

(Hoofdstuk 1.3). Echografie via de cisterna magnum kan een cerebellaire herniatie bevestigen hoewel CM komt zovaak voor bij de CKCS zodat deze informatie beperkte waarde heeft. Vergelijkbaar kan een syrinx gevonden worden in het craniale deel van de cervicale wervelkolom maar het niet aanwezig zijn van zo'n syrinx sluit niet het voorkomen meer caudaal uit. CSF analyse kan behulpzaam zijn bij het uitsluiten van inflammatoire ziekten. Het verzamelen van deze monsters vraagt om ervaring in verband met het risico op verkeerde plaatsing van de naald. Myelographie is gecontraindiceerd voor dezelfde reden. CM/SM lijkt echter geen verhoogd anesthesie risico te introduceren.

Differentiaal Diagnose

De meest belangrijke differentiaal diagnosis **(Hoofdstuk 1.3)** zijn andere oorzaken van pijn en spinale problemen zoals disk problemen. Andere voorbeelden zijn inflammatoire ziekten van het CZSTL zoals een granulomateuze meningoencephalomyelitis; vertebrale abnormaliteiten zoals een atlantoaxiale subluxatie; neoplasie; en discospondylitis. Wanneer krabben of het wrijven over de grond met oor of aangezicht een predominant klinisch beeld is moeten huidziekte uitgesloten worden. Het krab gedrag beperkt zich klassiek tot een specifieke gebied. Het is een veelvoorkomend incidentele afwijking om bij CKCS mucoide materiaal een of beide bulla tympanica bullae te vinden en de meerderheid van deze honden heeft geen geassocieerde klinische beelden. Sommige honden met scoliosis blijken een scheve kophouding te hebben wat verward kan worden met vestibulaire problemen. Bij twijfel moeten er cervicale röntgenopnames gemaakt worden om de scoliosis eventueel te bewijzen.

Behandeling en prognose

Het belangrijkste behandelingsdoel is het opheffen van de pijn. De meest voorkomende chirurgische ingreep is een craniale cervicale decompressie (ook beschreven als een foramen magnum of suboccipitale decompressie) door het verwijderen van een deel van het supraoccipitale been en het dorsale deel van C1 waardoor de CSF weer kan stromen **(Hoofdstuk 6.1)**. Dit kan gecombineerd worden met een durotomie (incisie van de dura met of zonder incisie van de subarachnoidale meningen) met of zonder hechten met een geschikt graft materiaal zoals een matrix van biocompatibel collageen (Vet BioSIST ™, Cook/Global Veterinary Products, SurgiVet, Smiths Medical Pm inc N7 W22025 Johnson Road, Waukesha, WI USA 53186). Craniale cervicale decompressie is succesvol in het reduceren van de pijn en het verbeteren van de neurologische afwijkingen in ongeveer 80% van de gevallen. Ongeveer 45% heeft 2 jaar na de operatie nog steeds een redelijke levenskwaliteit. Hoewel de chirurgie niet noodzakelijkerwijs de oorzaak van een syringomyelie adresseert en bovendien is de syrinx daarna nog steeds present. De klinische verbetering is waarschijnlijk toe te schrijven aan de verbetering van de CSF stroom door het foramen magnum. In 50% van de gevallen zal de vorming van littekenweefsel en fibreuze adhesies over het foramen magnum weer resulteren in herhaalde blokkade van de CSF stroom. Soms kan dit al 2 maanden postoperatief optreden.

Verder kan het noodzakelijk zijn om medicamenteuze pijn bestrijding te blijven geven doordat de SM en de beschadiging van de dorsale hoorn aanwezig blijft **(Hoofdstuk 5.2)**.
Er worden drie medicamenten gebruikt voor de behandeling van SM: medicatie die de CSF productie remt, NSAID's en corticosteroïden **(Hoofdstuk 2.2 and 5.2).** Indien de hond zijn voorgeschiedenis suggereert dat er houdings-gerelateerde pijn of ongemak aanwezig is gerelateerd aan de obstructie van de CSF stroom dan kan een test met furosemide geprobeerd worden. Bij een furosemide medicatie test kan het moeilijk zijn om vast te stellen of de oorzaak van het ongemak CM is of bijvoorbeeld oorproblemen. Furosemide kan voldoende zijn in het behandelen van de klinische beelden bij sommige honden maar aanvullende NSAID's zijn waarschijnlijk noodzakelijk voor een individueel geval met een wijdere syrinx. Het is gesuggereerd dat in dit geval het gebruik van een NSAID mogelijk een eerste keuze product is hoewel er meerdere geregistreerde middelen zijn. Hoewel bij honden met neurogene pijn, bijvoorbeeld allodynia en het krab gedrag een medicament wat actief is in de dorsale hoorn mogelijk effectiever is. Gabapentine heeft haar plaats in de diergeneeskunde verkregen maar mogelijk zijn ook amitriptyline of pregabalin ook bruikbaar. Corticosteroïden zijn ook een mogelijkheid als de pijn blijft bestaan of wanneer financiën de mogelijkheden van andere middelen beperken. Omdat de mechanismen van de ontwikkeling van neurogene pijn multifactorieel zijn is mogelijk polyfarmacie meer effectief dan de medicatie met een enkel middel **(Hoofdstuk 5.2)**. Accupunctuur en alphasonische behandeling zijn ook beschreven als mogelijke additieve behandelingswijzen. De hond zijn activiteit behoeft niet beperkt te worden hoewel de eigenaar moet begrijpen dat de hond sommige activiteiten moet vermijden en dat borstelen niet altijd getolereerd wordt. Simpele maatregelen zoals het verwijderen van de riem of het plaatsen van de voerbak op een verhoging kan helpen.
De prognose is gereserveerd en speciaal bij die honden die een wijdere syrinx hebben en/of als de eerste klinische beelden voor 4 jaar optreden. In een klein onderzoek **(Hoofdstuk 6.2)** waarbij de honden conservatief behandeld werden voor neurogene pijn, moest uiteindelijk 36% geeuthanaseerd worden in verband met oncontroleerbare pijn. Drieënveertig % van deze groep behaalde een leeftijd boven de 9. De gemiddelde levensverwachting van een CKCS is 10.7 jaar. De meeste honden verkrijgen weer het vermogen om te lopen hoewel sommige een duidelijke tetraparese en ataxie blijven vertonen.

Genetica en aanbevelingen voor de fokkerij

CM/SM kan bij de CKCS terug gebracht worden tot twee vrouwelijke voorouders welke direct na de tweede wereldoorlog leefden. Deze twee honden komen uit de groep van honden die gebruikt zijn om vanuit de kort-snuitige King Charles spaniël de 'modernere' CKCS te creëren (**Hoofdstuk 7.1 and 7.2**). Op dit moment wordt gewerkt aan een genoom scan van de CKCS in de hoop een van de causale genen te vinden. Voorlopige resultaten geven zes interessante regionen aan en zes geassocieerde chromosomen zijn onderwerp van studie **(Hoofdstuk 7.3 and 7.4)**. Gezien het veel voorkomen van de afwijking binnen

de CKCS is deze taak complex en wordt ondermeer gefocust op het vergelijken met sporadische gevallen welke bij andere rassen gezien worden. De wijze van verering inclusief het aantal, de identiteit en de bijdrage van de causale genen is nog niet vastgesteld. De etiologie van beide afwijkingen wordt verder nog gecompliceerd door de variabele penetrantie van de verschillende genotypen en de betrokkenheid van omgevingsfactoren. De huidige fokadviezen voor de CKCS concentreren zich het uitsluiten van honden voor de fokkerij welke vroeg SM krijgen (dit is voor de leeftijd van 2.5 jaar) (**appendix 2-4 – MRI gradering en fokkerij adviezen (vertaler: alleen in het Engels)**). Voor deze aanpak is het screenen van potentiële fokdieren noodzakelijk en daarom is het een kostbaar proces. Het doel van de huidige fok adviezen is het aantal zwaar aangedane honden te verminderen en niet zozeer het elimineren van de ziekte. Gezien het hoge aantal aangedane honden bestaat de kans dat een al te strak fok beleid de genen pool verder zal verkleinen en dat andere ziekten de kop op gaan steken. Het is van belang te beseffen dat het afwezig zijn van SM bij een jonge hond geen garantie is dat hij het niet alsnog op latere leeftijd zal ontwikkelen.

Toekomstig onderzoek

Deze studie naar Chiari-achtige malformatie en syringomyelia kent drie hypotheses. Hoewel sommige vragen konden beantwoord worden zijn er vele bijgekomen en zal het onderzoek naar deze fascinerende ziekte door gaan. In de Engelstalige samenvatting worden de hypothesis verder besproken.

Chapter 8.3

Addenda

Appendix 1

CM/SM Pain score and clinical signs

Pedigree Name

Registration number Microchip number

Date of birth: Call name Owner's name

Colour B B/T R T Gender M MN F FN Weight

PAIN SCORE	FREQUENCY VOCALISATION	FREQUENCY SCRATCHING	EXERCISE ABILITY
0	None	None	Normal
1	< 1 / week	< 1 / day	Normal
2	1 / week	**≥ 1 / day**	Normal
3	**> 1 / week**	> 1 / day	Normal
4	> 1 / week	> 1 / day	**Activity compromised**

Dogs scored according to the most severe clinical sign for example a dog vocalising once daily but shoulder scratching less frequently would be scored 3.

Pain score ☐ **No pain or neurological dysfunction** ☐

Possible signs of pain / neurological dysfunction

Signs	Frequency	Age of onset	Signs	Frequency	Age of onset
Shoulder scratching (indicate side)			Scoliosis	N/A	
Scratching elsewhere (indicate site)			Thoracic limb ataxia	N/A	
Rubbing ears			Thoracic limb weakness	N/A	
Rubbing mouth			Thoracic limb lameness		
Cervical pain			Pelvic limb ataxia	N/A	
Thoracic pain			Pelvic limb weakness	N/A	
Lumbar pain			Pelvic limb lameness		
Screaming when scratching			Vestibular dysfunction (indicate side)	N/A	
Screaming when excited			Facial nerve dysfunction (indicate side)	N/A	
Screaming when touched			Seizures		
Screaming when change head position			Fly catching		
Screaming when jumping			Collapse during exercise		
Screaming for no apparent reason			Cramping during exercise		

N/A – not applicable

Appendix 2

Revised CKCS MRI screening and breeding recommendations - 2006

These breeding recommendations are made using current information and in response to CKCS breeder request 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 (SM) 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.

Notes
The age cut off at 2.5 years has been decided so as to tie in with MVD recommendations and because most dogs with symptomatic SM will show signs before 3 years of age.

The following categories from the previous guidelines have been removed because of difficulty in accurately interpreting
Previously A*- now A
Previously B – now C

It is recommended
1) That both the sire and the dam of a proposed mating are screened (any unscreened dog should be assumed to be "D")
2) Offspring of any mating should also be MRI screened before breeding.
3) Any dog screened before 2.5 years old has a second screen when older,
4) That dogs are screened from 6 months of age
5) That if a limited ("mini") MRI screen is performed that
   a) the minimum area covered is from the level of the interthalamic adhesion to cervical vertebrae 5 (C5)
   b) Both TW1 and TW2 sagittal images are obtained in addition to TW1 and /or TW2 transverse images through the upper cervical spinal cord.
   c) An assessment is also made for presence/absence of ear disease and ventricular enlargement.
6) That interpretation of images is made by Diplomate level radiologists, neurologists and, in special circumstances, by orthopaedic surgeons with recognised expertise in this area.

GRADE	AGE (YEARS)	SYRINGOMYELIA		BREED TO
A	Over 2.5	Absent or less than 2mm central canal dilatation in the C2-C4 region only		A, C, D
C	Under 2.5	Absent		A Re scan after 2.5years
D	Over 2.5	Present	Asymptomatic	A
E	Under 2.5	Present	Asymptomatic	NO
F	Any	Present	Symptomatic	NO

Appendix 3

CKCS MRI screening and breeding recommendations

(used prior to November 2006)

GRADE	AGE (YEARS)	SM	CM	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 2.5years to clarify status, monitor heart
C	< 2.5	Absent	Present [2]	Dam and sire pass	A , B Consider rescan after 2.5years to clarify status, monitor heart
D	>2.5	Present but asymptomatic	Present [2]	Pass	A, B
E	< 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

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

Appendix 4

Sample CM/SM MRI screening certificate

GODDARD
VETERINARY
GROUP

Clare Rusbridge BVMS DipECVN MRCVS
European and RCVS and European Specialist In Veterinary Neurology
Stone Lion Veterinary Centre
41 High Street,
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London, SW19 5AU
Tel: +44 (0)208 946 4228
E-mail: neuro.vet@btinternet.com

Date**: * 2006**

To whom it may concern:

This is to confirm that on the above date magnetic resonance imaging (MRI) was carried out on **Pedigree name** (**call name**)

Colour CKCS,**SEX, DOB**, **not micro-chipped / microchip number**

Owner – **NAME**

These images reveal:

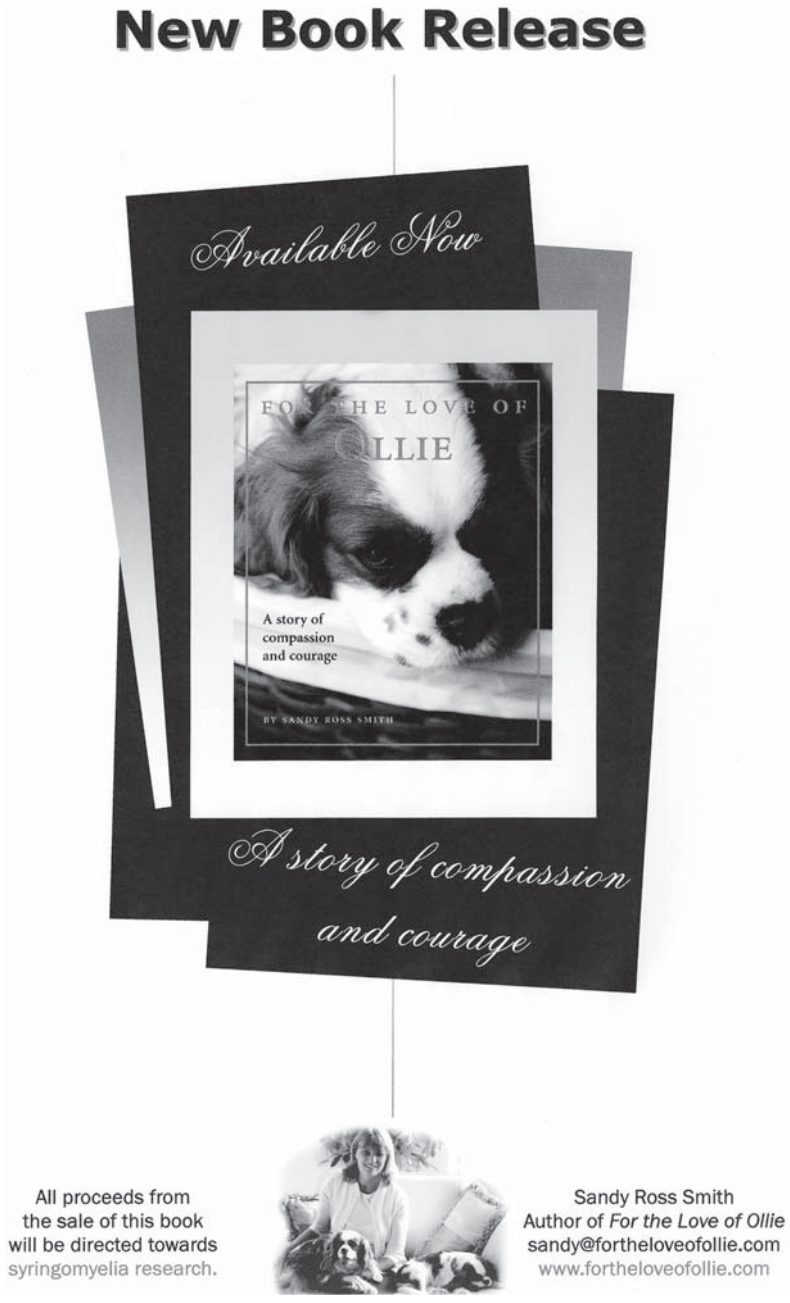
Chiari-like malformation of the caudal skull	**YES / NO**
Dilatation of the central canal	**YES / NO (region)**
Syringomyelia in the cervical spinal cord	**YES / NO (maximum width)**
Ventricular dilatation	**YES / NO**

Mucoid material in **RIGHT / LEFT / BOTH** tympanic bullae

Using the informal CKCS CM/SM classification the grade of ***** would be attributed to this individual.

Clare Rusbridge BVMS DipECVN MRCVS
RCVS and European Specialist In Veterinary Neurology

Appendix 5



Chapter 8.4

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never given up despite many setbacks and I have great admiration for you. Also **Karlin Lillington** owner of a 'clear' and SM affected dog - thank you for providing such an informative and unbiased web site and for defending our cause in the internet chat-rooms. Your website www.sm/cavaliertalk.com and others like www.cavalierhealth.com have provided a reservoir of information to cavalier lovers worldwide. Finally to **Angela Baker**, who established the first support group for this disorder – this was a much needed resource for many desperate pet owners.

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Chapter 8.5

Curriculum vitae

Clare Rusbridge was born on January 10th 1970 in Canterbury. She attended primary and secondary school in Milngavie, Glasgow and started her veterinary training in 1986 at the University of Glasgow. She graduated in 1991 with distinction in Veterinary Medicine and Surgery. She then enjoyed a year in the USA as a small animal intern at the University of Pennsylvania. She was fortunate to have the opportunity to spend some weeks at North Carolina Veterinary School Neurology department and it was here that she met her future mentor Dr Simon Wheeler. She then spent a year in the "real world" of general small animal practice in Cambridgeshire. In 1993 she joined the Royal Veterinary College, completing a BSAVA/Petsavers residency in Neurology under Simon Wheeler and then spent one year as a Staff Clinician in Neurology. In 1996 she was board-certified by the European College of Veterinary Neurology. Since August 1997 she has operated a neurology referral service at the Stone Lion Veterinary Referral Centre in Wimbledon gaining Royal College of Veterinary Surgeons Specialist status in 1999. She became interested in Chiari-like malformation / syringomyelia in 1995 and has continued to research this disease focusing on the genetics, pathogenesis and treatment. Her other professional interests include other causes of neuropathic pain (in particular feline orofacial pain syndrome), feline neurology and epilepsy.

Publications

Books

Chiari-like malformation and Syringomyelia in *Current Veterinary Therapy XIV* (in press)

Chiari-like malformation and Syringomyelia in 5 Minute Veterinary Consultations (in press)

Neurological Infections. In: *BSAVA Manual of Canine and Feline Infectious Diseases* 2001

Illustrations for *BSAVA Manual of Exotic Pets(2nd Edition)* and *BSAVA Manual of Reptiles (1st Edition)*

Refereed journals

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