Chiari-like malformation and Syringomyelia in the Cavalier King Charles Spaniel

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ISBN-10: 90-393-4456-6
ISBN-13: 978-90-393-4456-9

The publication of this thesis was financially supported, which is greatly appreciated, by Novartis, The Goddard Veterinary Group, Royal Canin, Bayer, Pfizer, Intervet, Kruuse, Vetoquinol, Idexx Laboratories, Fort Dodge, Boehringer, Hills, Merial, Centaur Services Ltd, AUV and the Department of Clinical Sciences of Companion Animals

Grafische bewerking: Basement Graphics, Den Haag
Illustraties: Clare Rusbridge and Penny Knowler

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Chiari malformatie en Syringomyelie in de Cavalier King Charles Spaniel

(met een samenvatting in het Nederlands)

Proefschrift ter verkrijging van de graad van doctor aan de Universiteit Utrecht
op gezag van de Rector Magnificus,
prof. dr. W.H.Gispen, ingevolge het besluit van het College voor Promoties in het openbaar
te verdedigen op donderdag 15 februari 2007 des namiddags te 14.30 uur

door

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Geboren 10 January 1970 te Canterbury, England

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Contents

This thesis is dedicated to all the cavalier King Charles spaniels that taught me about this disease, in particular: Beau; Rosie I; Monty; Chester; Amber and Diva A; Sofie and Molly C.; Gypsy-Rose; Amber D; Kizzy; Dan; Phoebe; Max; Emma; Poppy; Oscar; Buttons; Billy; Molly W; Alfie; Bonnie and Rosie F.; Maggie May and Oliver S.; Truffle and Woolloomooloo G; Chicca; Freeway; Chris; Linus; Zack; Tucker; Holly B.

Section 1

Aims and Scope of the Study

Chapter 1.1

Aims and Scope of the Study

In 1995, when a neurology resident at the Royal Veterinary College, I was presented with Beau a cavalier King Charles spaniel with neurological problems. Beau's most striking feature was that when he walked he simultaneously scratched at his right shoulder area giving him an almost comical, bicycling action. Full investigation at the time, including myelography, CSF analysis and electromyography, failed to reveal the cause of his neurological deficits. More importantly I was completely at a loss to explain the scratching behaviour. I presumed that Beau must experience some abnormal sensations but the behaviour wasn't typical for any sensory neuropathy or spinal disease that I had prior experience of. I vowed at that time that I would eventually find an explanation for this and this thesis represents the culmination of over a decade of study. Beau eventually had a diagnosis of Chiari-like malformation and syringomyelia (CM/SM) in 1997 when spinal MRI facilities were finally available for animals. The syringomyelia was managed medically and he died at the age of 10 years old from mitral valve disease.

Syringomyelia is characterised by cavitation of the spinal cord and occurs when there is obstruction to CSF flow. It is often a painful condition which in severe cases results in a disabling neuropathic pain syndrome for which there can be an unsatisfactory medical or surgical solution. In this thesis 3 hypothesis are investigated.

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

Hypothesis 2

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

Hypothesis 3

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

In order to investigate these hypotheses several questions were asked.

1) What is the possible pathogenesis of syringomyelia?
2) Do CKCS with syringomyelia have smaller a caudal fossa than CKCS without syringomyelia?
3) Are there other anatomical variations which influence the condition?
4) How does syringomyelia cause the clinical signs that it does?
5) What is the natural history of the disease and what is the most appropriate treatment – medical and surgical?
6) What is the evidence for a hereditary nature for the condition?
7) If it is an inherited condition what are the implications in a breed with a small gene pool and a high incidence of other inherited conditions?

Section 1 is a general introduction to the cavalier King Charles spaniel and the neurological diseases of the breed. Section 2.1 encompasses the first description of the disease and its proposed pathogenesis. As knowledge and understanding has improved this description is refined in section 2.2 and a novel hypothesis for the pathogenesis is presented. Section 3 compares and contrasts canine Chiari-like malformation (occipital hypoplasia) with the other common developmental defect of the occipital bone – occipital dysplasia. Section 4 details a study investigating intracranial and cervical dimensions and their relationship to the development of syringomyelia. Section 5.1 and 5.2 discuss how CM/SM results in the clinical signs that it does, with particular regard to pain. Section 5.2 also postulates the most appropriate medical treatment. Section 6 discusses the surgical management of the condition and describes a brief pilot study investigating conservative management. Section 7 discusses the possible hereditary nature of the condition and details the work in progress to investigate the causative genes. In section 8 the thesis is summarized and future plans for continuing this research are detailed.

Chapter 1.2

History of the Cavalier King Charles Spaniel

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"Spaniell gentle, or the comforter, a chamber companion, a pleasant playfellow, a pretty worme, generally called Canis delicatus" "These puppies the smaller they be the more pleasure they provoke, as more meet playfellows for mincing mistresses to bear in their bosoms, to keepe company withal in their chambers, to succour with sleep in bed, and nourish with meat at board, to lay in their laps and lick their lips as they ride in their wagons; and good reason it should be so, for coarseness with the fineness hath no fellowship, but featness with neatness hath neighbourhood enough" ***Dr Johannes Casius,*** **1576.**

That, at the present day, dogs have been considerably modified there can be no doubt; ideas of what constitute beauty changes and dogs, like ladies' bonnets, have to be made to suit the prevailing fashion, although some people seem, by persistent dinning into the ears of the unthinking, to achieve ephemeral success in making or adopting a dog and then bringing fashion to smile up it, much to their own benefit, both in praise and profit ***Hugh Dalziel 1897***

The Toy Spaniels, favoured by royals and aristocrats and depicted in many portrait pictures of the 17th and 18th century, have been subjected to many phenotypic changes, mostly dictated by fashion (Dalziel 1897). Their origins are unknown but they were thought to be imported into Spain (spaniel – *espagneul*) from Japan and are possibly connected genetically to the Maltese and Japanese spaniel / chin. In the 19th century four varieties were described, distinguishable by their coat colour (Drury 1903). The **King Charles**, to which Charles II gave his name, is considered to be the oldest variety. It had a long nose and very long ears and was typically black and tan but could also be black and white (Drury 1903). The coat was occasionally curly (Dalziel 1897). Crossing the two colour varieties together, it is rumoured, with the Pug, resulted in the **Prince Charles** or **Tricolour** spaniel which had shorter ears and muzzle (Drury 1903). The **Blenheim** spaniel (Figure 1) was believed to be imported from Spain in the reign of Charles II by the first Duke of Marlborough and bore the name of their home, Blenheim Palace. It was described by a contemporary writer as ''invariably red and white, with very long ears and short noses, and black eyes" (Drury 1903). Mr J.W. Berrie a breeder of Blenheims in the 19th century wrote "The modern Blenheim is undoubtedly made up of the old Marlborough breed, crossed with the King Charles, by reason of which we get the short nose, square muzzle, and large bold skull" (Drury 1903). A characteristic of the Blenheim is the red ears and white blaze down the centre of the forehead with a red spot or "lozenge" in the centre (Dalziel 1897).

Figure 1 Rose, a Blenheim spaniel born around 1847 and illustrating the typical appearance of Toy spaniels at the middle of the 19th Century. Note that in comparison to later King Charles spaniels the muzzle is long.
Specimen and image from the collections of the Natural History Museum, London and the Walter Rothschild Zoological Museum, Tring.

A fourth type, the **Ruby** Toy spaniel was rare until the early part of the twentieth century. Previous to selective breeding they would occasionally appear in a litter of pure bred black and tan Toy Spaniels. There was also variety with deep chocolate and bright tan markings. However this was rare and not as popular as the Ruby and subsequently did not become established as a variety (Drury 1903).

Owing to fashion and selective breeding in the late eighteenth and early nineteenth century, the Toy spaniels "lost their nose" and became more dome-headed (Figure 2). In addition they were considered one breed, The Toy Spaniel Club was founded in 1886 and the dogs are recognised today as the King Charles spaniel in the UK and English Toy Spaniel in the USA

Figure 1b Toy (King Charles) spaniels from the early 19th Century when it had become fashionable to have dog with a domed head and flat face (i.e. brachiocephalic). From left to right; "Sweetheart", "Harford Defender" and "Aston-Moore Michael". "Harford Defender", the black and tan, was born in 1900 and died in 1905. He was the winner of first prizes at Birmingham, Botanicals Gardens, Richmond and Ealing shows in 1903 and 1905. Sweetheart, the Ruby, was the dam of "Sweet English Rose" the winner of numerous prizes including 2 challenge cups. Note the large variation in size of these adult dogs. The black and tan "King Charles" were generally larger and Harford Defender had a shoulder height of 28cm (the modern CKCS is 30-33cm). *Specimens and image from the collections of the Natural History Museum, London and the Walter Rothschild Zoological Museum, Tring.*

In the mid-1920s, an American millionaire named Roswell Eldridge journeyed to England with the intention of finding a spaniel dog typical of those depicted in portraits of the 17th Century. However he was disappointed by the flat-nosed dog the King Charles spaniel had become and offered a £25 prize at Crufts in 1926 for the best dog and best bitch that met the characteristics, "As shown in the pictures of King Charles II's time, long face, no stop; flat skull, not inclined to be domed and with the spot in the centre of the skull." In 1928 a club was founded, and the title "Cavalier King Charles Spaniel" was chosen. At the first meeting, held the second day of Cruft's Dog Show, 1928, the standard of the breed was drawn up, and has altered little since (Figure 3) (The Cavalier King Charles Spaniel Club, 2002). How the longer muzzle of the cavalier King Charles spaniel was "created" is shrouded in secrecy. It was claimed that it was the result of selection of puppies with longer noses. However it is more likely that the King Charles was crossed with a more mesencephalic breed rumoured to be the Papillon and/or Cocker spaniel.

Figure 3 The modern cavalier King Charles spaniel. From left to right Tricolour (Zack), Blenheim (Zoey), and Ruby (Sienna). Zack suffers from syringomyelia. The black and tan variety is not depicted in legend figure 3.

The change in skull shape of the Toy spaniels is illustrated in Figure 4.

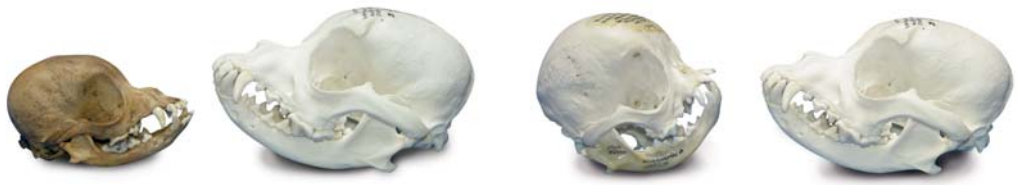

Figure 4a Figure 4b

Figure 4a Comparison between an early King Charles spaniel (left) and modern Cavalier King Charles spaniel (right).
Figure 4b Comparison between a modem King Charles spaniel (left) and a modern Cavalier King Charles spaniel (right).
Specimens: modern King Charles spaniel and cavalier King Charles Spaniel from the collections of the Albert Heim Foundation, Museum of Natural History, Bern. Early King Charles spaniel from the collections of the Natural History Museum, London

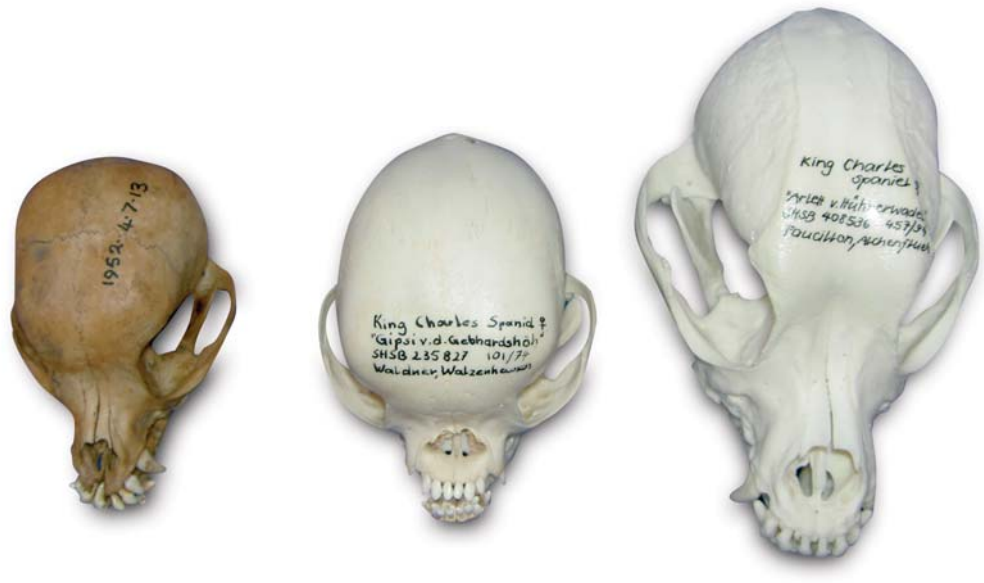

Figure 4c Left to right: early King Charles spaniel, modern King Charles spaniel and cavalier King Charles spaniel

Specimens: modern King Charles spaniel and cavalier King Charles Spaniel from the collections of the Albert Heim Foundation, Museum of Natural History, Bern. Early King Charles spaniel from the collections of the Natural History Museum, London

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Chapter 1.3

Neurological diseases of the cavalier King Charles spaniel

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Journal of Small Animal Practice 2005; 46: 265-272

Introduction

The cavalier King Charles spaniel (CKCS) is a relatively modern breed of dog, developed in the 1920s. Its attractiveness and friendly disposition ensures that it is one of the most popular and numerous toy breeds. However, the available gene pool is small and is decreasing due to the historical popularity of certain champions and breeding recommendations used to reduce the incidence of hereditary mitral valve and eye disease (Rusbridge and Knowler 2004). In recent years, a number of neurological syndromes have been described, some of which have similar signs such as collapse, neck pain, abnormal head position and scratching of the ears or shoulder. This review discusses and contrasts the most common neurological conditions seen in the breed, categorising them according to the predominant first presenting signs of spinal pain, scratching, seizures and seizure-like events, and abnormal head position.

Conditions causing spinal pain

Disc disease

The CKCS is a chondrodystrophic-type breed and as such is prone to Hansen type I disc extrusions. The most common clinical sign is spinal pain, with or without paresis (Table 1).

Table 1 Differential diagnoses of spinal pain in the CKCS

Condition	Characteristics of pain	Age
Disc disease	Single site of pain within C2-C7 or T11-L6 Typically acute onset and persistent although cervical disc disease may present with “spasms” of pain. May be associated with paresis	>2 years
Syringomyelia	Cervical pain typically intermittent at first and may be related to posture e.g. may prefer to sleep with head raised. May be worse at night/ when first getting up / hot or cold temperature extremes / when excited Dog may seem to be overly sensitive to touch on one side of the neck / ear / shoulder / sternum Often associated with scratching at one shoulder/ ear/side of neck	> 6months
GME	Acute onset Cervical pain especially on ventriflexion. May have multiple sites of spinal pain Dog depressed with other central neurological signs especially seizures, paresis, vestibular signs	Any age; 2-6years more common
Atlantoaxial subluxation	Pain on ventriflexion head Tetraparesis, limb proprioceptive deficits.	Typically <3 years
Spinal neoplasia or other space occupying lesion	One focus of pain with corresponding neurological deficits	Typically >5 years
Spinal trauma	One or more focuses of pain with corresponding neurological deficits	Any age
Discospondylitis	One or more focuses of pain esp. cervical and lumbosacral areas, pyrexia, depression	Any age but immature and elderly predisposed.
Bacterial meningitis	Severely depressed, pyrexia +/- other neurological deficits NB this is a very rare condition	Any age but neonates more predisposed

Disc extrusion is uncommon in dogs younger than two years of age. Survey radiographs may indicate possible sites of disc extrusion by identifying a narrowed intervertebral disc space, foramen or joint spaces, or by finding calcified disc material within the vertebral canal. For confirmation of the diagnosis, further imaging such as myelography or magnetic resonance imaging (MRI) is required. MRI is preferred because of the tendency for CKCSs to have syringomyelia and subsequently a small cisterna magnum and subarachnoid space, presenting an increased risk of intrathecal spinal needle placement. Lumbar, as well as cisternal, myelography is risky in this breed. Management of disc disease may be medical (analgesia

and exercise restriction for at least four weeks) or surgical. Surgical management is preferred for dogs with significant paresis or paralysis. For the optimum chance of return of function, dogs without deep pain perception should have decompressive surgery performed within 24 hours of loss of function. For a full review of the pathogenesis and management of disc disease, see Sharp and Wheeler (2004a,b).

Syringomyelia

Syringomyelia is a condition whereby fluid-containing cavities develop within the spinal cord, secondarily to the obstruction of cerebrospinal fluid (CSF) flow, especially through the foramen magnum. In the CKCS, this is typically due to Chiari-like malformation (occipital hypoplasia), a condition similar to Chiari type I malformation in humans (Rusbridge and others 2000). The consequence of an overly small occipital bone is reduced volume of the caudal fossa, the part of the skull that accommodates the cerebellum and brainstem. The CSF flow is obstructed by the cerebellum, which is often herniated through the foramen magnum, and by the caudal brainstem, which is often deviated dorsally (Fig 1).

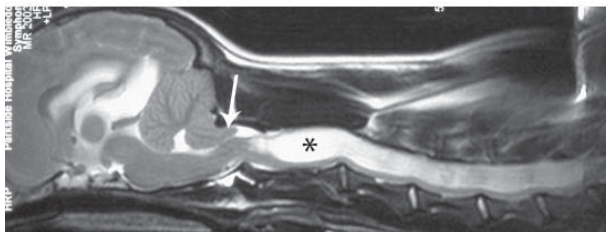

Figure 1 Midsagittal TW2 weighted image of the brain and cervical spinal cord. Syringomyelia (asterisk) secondary to Chiari-like malformation (occipital hypoplasia) in a 21 month female CKCS presenting with a 3 month history of yelping and a tendency to scratch at the right shoulder area. There is cerebellar herniation through the foramen magnum (arrow).

Syringomyelia will also occur in other conditions which obstruct CSF flow (Fig 2).

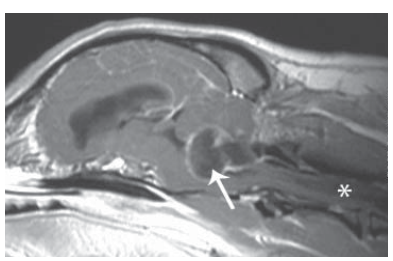

Figure 2 Midsagittal gadolinium enhanced TW1 weighted image of the brain and cervical spinal cord in a seven year female CKCS with syringomyelia (asterixis) secondary to a dermoid sinus (arrow). The dog presented with central vestibular signs that were slowly progressive over several months. The mass had been successfully debulked 2 years previously.

Clinical signs of Chiari-like malformation /syringomyelia (CM/SM) are usually are recognized between 6 months and 3 years of age. However dogs of any age may be presented, and dogs with more severe disease tend to be presented before 2 years of age. In addition to signs of spinal pain, affected dogs often scratch at one area of the shoulder, ear, neck or sternum. This is typically on one side only, while the dog is moving, and sometimes without making skin contact. The pain experienced by CKCSs with CM/SM (Table 1) is likely to be multifactorial, relating to obstruction of the CSF flow and spinal cord damage. Humans with syringomyelia report headaches, suboccipital or neck pain, back pain, trigeminal pain (such as facial pain) and radicular pain (pain which radiates into the lower extremity; in syringomyelia this often has a cape-like distribution). However, the most disabling pain is dysaesthesia, which is variously described as a burning pain, hyperaesthesia, pins and needles, and stretching or pressure of the skin (Todor and others 2000)

Dogs with syringomyelia may have other neurological deficits such as cervical scoliosis, thoracic limb weakness and pelvic limb ataxia (Rusbridge and others 2000). Facial nerve paralysis (Rusbridge and others 2000) and deafness (Skerritt and Skerritt 2001) have also been associated with the condition. However idiopathic facial palsy is common in the CKCS and so is hearing impairment (Munro and Cox 1997). Progression of the disease is very variable. Some dogs have the tendency to scratch with mild pain only and other neurological signs such as paresis never or very slowly develop. Others can be severely disabled by pain and neurological deficits within 12 months of the first signs developing. Mild syringomyelia may also be found as an incidental finding, with no recognised clinical signs, in the investigation of another neurological disease.

Survey radiographs may reveal a short caudal fossa and widened vertebral canal however the interpretation of this is subjective and the only definite way to diagnose syringomyelia and the associated skull malformation is by MRI.

Medical management can help, but in the author's experience typically does not resolve, the clinical signs. Pain in mild cases may be controlled by non steroidal anti-inflammatory drugs. (NSAIDs). Corticosteroids are very effective in reducing both pain and neurological deficits partly by reducing CSF pressure (Simpson 1989) and possibly because of a direct effect on pain mediators such as substance P. Dorsal horn substance P expression has been shown to be altered in humans with syringomyelia (Todor and others 2000) and corticosteroids have been shown to decrease substance P expression after neurological injury (Wong and Tan 2002). Although corticosteroids are effective in limiting the signs, most dogs require continuous therapy and subsequently develop the concomitant side effects of immunosuppression, weight gait and skin changes. If there is no alternative then the lowest possible dose that can control signs is used. Alternate day therapy is preferred. The author starts with 0.5mg/kg prednisolone / methylprednisolone daily.

Gabapentin (Neurontin; Pfizer) is successful in some dogs. This drug, originally patented as an anti-convulsant, is licenced as a neurogenic analgesic for humans. Gabapentin, and other anticonvulsants,

have a neuromodulatory effect on the hyperexcitable damaged nervous system. The author uses a dose of 10-20mg/kg two/three times daily. Gabapentin can also be given in combination with NSAIDs. Sedation may be seen, especially at higher doses, otherwise the side effects are minimal and on this basis the author prefers gabapentin over corticosteroids. The main disadvantage of gabapentin is that it is expensive and not licenced for dogs. Oral opioids are also an alternative for example pethidine tablets at 2-10mg/kg three to four times daily or methadone syrup at 0.1-0.5mg/kg three to four times daily.

Surgical management is indicated for dogs with significant pain or with worsening neurological signs. The most common procedure performed is cranial cervical (foramen magnum) decompression where the most of the supraoccipital bone and the cranial dorsal laminae of the atlas are removed (with or without a durotomy) (Churcher and Child 2000, Dewy 2004). Syringo-subarachnoid shunting has also been described (Skerritt and Hughes 1998). In the author's experience surgery is usually successful at significantly reducing the pain but some dogs may still show signs of discomfort /scratching. Also in the author's experience signs may recur or deteriorate in a proportion of dogs after several months/years. A similar situation occurs in the human field and many patients have repeated surgeries (Mazzola and Fried 2003). Vermeersch and others (2004) reported disappointing results in study on four CKCS surgically managed for syringomyelia with no clinical or MRI change three months after surgery. Dewey and others (2004) reported more favourable results following surgery in five dogs with three dogs resolved and two improved. However post-operative MRI was not obtained. The same group have been conducting a longer term study in a group of sixteen dogs; seven resolved, six improved, one died, one was euthanized and one had no improvement (Dewey 2005).

A question not yet resolved is whether Chiari-like malformation in CKCS without syringomyelia can also result in pain? Humans with this condition may have occipital-suboccipital headaches i.e. pain at the back of head (Stovner 1993). Some young CKCS with Chiari-like malformation have an unexplained tendency to scratch at the back of the head/ears. The main argument against this is that Chiari-like malformation with or without mild syringomyelia may be an incidental finding in CKCS undergoing MRI for another reason.

Dens abnormalities

Failure or abnormal growth of the dens occasionally occurs in the CKCS (Byneveltand others 2000) leading to compression of the upper cervical spinal cord (Fig 3). Diagnosis can usually be achieved with dynamic cervical radiography, although MRI and/or computed tomography might be useful for clarification and to rule out coexisting syringomyelia. Surgical management by atlantoaxial arthrodesis is the treatment of choice if there is atlantoaxial instability.

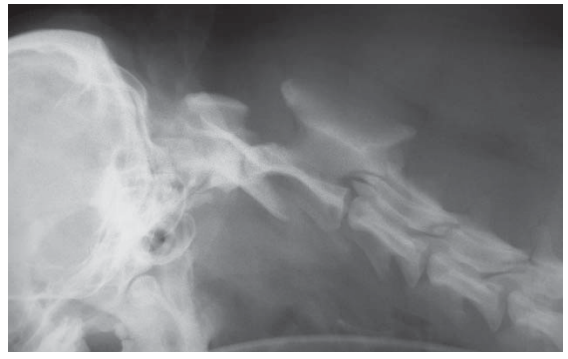

Figure 3 Lateral cervical radiograph with ventriflexion of the atlantoaxial joint in an 18 month old female CKCS that was presented with tetraparesis and had pain on ventriflexion of the neck. The dens is absent and there is atlantoaxial subluxation illustrated by dorsal widening between C1 and C2.

Granulomatous meningoencephalomyelitis

Granulomatous meningoencephalomyelitis (GME) is a severe CNS inflammatory disease characterized by large perivascular accumulations of mononuclear cells in the parenchyma and meninges of the brain and spinal cord (Braund and other 1978). The aetiology is unknown. It is most common in middle age dogs, although it can occur from age six months to ten years (Braund 1985). Female dogs are slightly more commonly affected than male dogs (Braund 1985). Clinical signs reflect the area of brain/spinal cord affected. The most common signs are spinal pain, depression, seizures, vestibular signs, paresis and postural deficits. Disseminated and focal forms are recognised and the latter may present with just involvement of the optic nerves presenting as sudden onset blindness (Braund 1985). Diagnosis is suggested by appropriate MRI and CSF changes and ruling out infectious causes of encephalitis (Fig 4) however confirmation can only be made by post mortem.

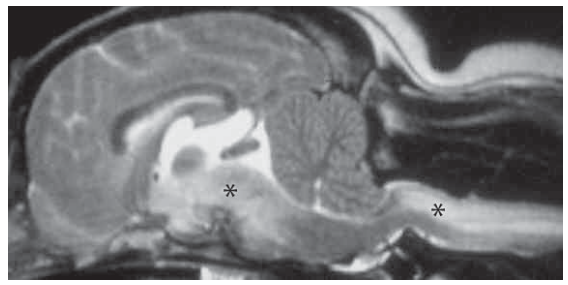

Figure 4 A midsagittal TW2 weighed image of the brain and cervical spinal cord in a 5 year old female CKCS presenting with cervical pain and depression. Note the high signal through the midbrain and spinal cord suggestive of inflammation (asterisk). CSF analysis revealed a mononuclear pleocytosis.

The author's most successful treatment regime is a combination of cyclophosphamide and prednisolone. The prednisolone is started at least 1mg/kg twice daily and reduced slowly over about 6 months. It is rare to be able to successfully withdraw the corticosteroids. The cyclophosphamide is continued for as long as possible; it is usually required to be discontinued after 4-6 months because of haemorrhagic cystitis. Haematology is monitored on a monthly basis. There is recent interest in using cyclosporin as an alternative to cyclophosphamide (Adamo and O'Brien 2004) and one study reported improved prognosis after radiation therapy, especially in those with focal lesions (Munana and Luttgen 1998).

Miscellaneous

Other less common causes of spinal pain and/or dysfunction include: other compressive myelopathies e.g. spinal tumours; inflammatory conditions e.g. discospondylitis; and conditions which increase intracranial pressure e.g. hydrocephalus and/or brain tumours. Many conditions causing spinal pain respond to corticosteroids however the general practitioner is urged to investigate as much as possible towards a final diagnosis before prescribing these drugs. GME is very unlikely to be successfully treated in the long term by anti-inflammatory doses of corticosteroids and diagnosis is very much more difficult in the face of these drugs. Some conditions, e.g. disc disease or atlantoaxial subluxation, may deteriorate if given steroids (or other analgesics) and allowed to exercise freely.

Conditions causing shoulder, sternum, head or ear scratching / foot chewing

Obviously the most common cause of skin irritation is primary skin disease and this should be ruled out first. Likewise, the CKCS has a predisposition to ear disease (Stern-Bertholtz and others 2003). If skin and ear disease have been eliminated and/or if the scratching is to one specific area then consider syringomyelia (see above and Table 2).

Table 2 Common conditions causing scratching / foot chewing in the CKCS

Condition	Characteristics of scratching	Age when signs start
Skin disease	Itchy in more than one site Evidence of skin disease e.g. erythaema No association with excitement / walking on leash Generally sitting/ standing when scratching	Any
Ear disease	Evidence of ear disease e.g. discharge Responds to treatment for ear disease No association with excitement / walking on leash Generally sitting/ standing when scratching	Any
Syringomyelia	Initially scratches at one site on neck / shoulder / ear Scratching more likely when excited or walking on a leash When scratching, minimal contact with skin Generally walking / turning when scratching Often cries while scratching	> 6m
Head / foot irritation syndrome	Act irritated by head, ears and feet Shakes or rubs head Kicks out pelvic limbs and nibbles feet Generally sitting/ standing when scratching May be associated with "fly-biting" behaviour	< 1y

The author is recognising a new syndrome of behavioural signs of discomfort in the CKCS for which an explanation has yet to be found. Signs include repeated episodes of head shaking or rubbing, ear scratching and chewing of pelvic limb paws. The CKCS may kick out the pelvic limbs as if intensively irritated. Signs may be seen as early as 12 weeks, unlike syringomyelia, which the authors have not seen in dogs less than 5 months of age. MRI of the skull typically reveals mild occipital hypoplasia but no syringomyelia. The hypoplasia is to the extent that could be considered acceptable for the breed and follow up MRI scans in a limited number of dogs do not show subsequent syrinx development. There is no evidence of ear disease or material within the tympanic bullae. MRI or radiography of the vertebral column is normal, as is limb muscle electrophysiology and nerve function studies, CSF analysis, haematology and serum biochemistry. There is no evidence of skin disease. The dogs have little or no response to NSAIDs, corticosteroids, anticonvulsants, gabapentin or the dopaminergic drug cabergoline. Milder versions of this behaviour may also be seen in association with "fly catching" (see below) however management for compulsive disorder using behavioural modification and appropriate neuropharmacological agents such as fluoxetine, clomipramine or selegiline has not proved effective. Some may respond to opioids such as buprenorphine injections or Fentanyl patches but otherwise effective management, like the aetiology, has not been determined.

Conditions causing seizures and seizure like events

Epilepsy

Idiopathic epilepsy is inherited in the CKCS and is seen in all colour varieties but is more frequent in

lines originating from whole coloured ancestors from the late 1960s especially where there were half brother sister matings (Rusbridge and Knowler 2004). Diagnosis is by ruling out other causes of seizures e.g. haematology and biochemistry to rule out reactive causes such as hepatic encephalopathy and MRI and CSF analysis to rule out structural and inflammatory disease e.g. GME (see above). The author's first line therapy is phenobarbitone or bromide monotherapy progressing to a combination of both drugs if the seizures are not adequately controlled. Some CKCS epilepsy cases are difficult to control and novel anticonvulsants such as Levetiracetam (Keppra; UCB Pharma) or Topiramate (Topamax; Janssen-Cilag) may be useful. For a more extensive review of the management of epilepsy see Podell (2004).

Hydrocephalous

In domestic animals, the most common cause of hydrocephalus is an obstruction of CSF ventricular drainage. It may be primary due to congenital malformation such as aqueductal stenosis or secondary e.g. a tumour (Summers et al 1995). In the CKCS primary hydrocephalus can also develop secondary to occipital bone hypoplasia and obstruction of ventricular drainage through the foramen magnum (Fig 5). The most common presenting signs are depression, seizures and central blindness. Immature dogs typically have a dome shaped head with a persistent fontanelle and ventrally deviated eyes. Treatment of hydrocephalus may be medical, typically with corticosteroids and diuretics (Simpson 1989) or surgical e.g. ventricular to peritoneal shunt placement or possibly by supraoccipital craniectomy.

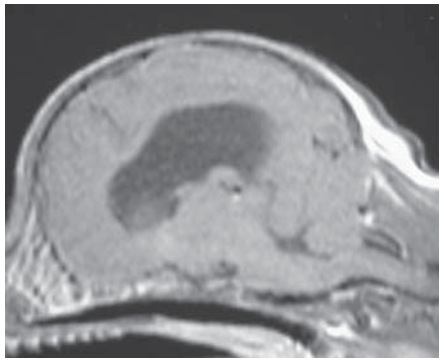

Figure 5 Midsagittal TW1 weighted 9 week female CKCS that was presented after a generalised tonic clonic seizure. There is marked dilation of the lateral ventricles and the skull shaped is more domed than normal. The mesencephalic aqueduct appears patent but there is severe caudal fossa overcrowding secondary to occipital hypoplasia.

Episodic Collapse (Hyperexplexia)

This is not a seizure but may be confused with one. The collapse is triggered by excitement and exercise and characterised by a brief period of bunny hopping with the head held down and the rear end raised so that the body is curled in a comma shape. This posturing rapidly progresses into collapse with increased limb extensor tone. The collapse lasts for approximately 2 minutes or less. Affected dogs may show signs from 3 months of age. This disease, originally described by Herrtage and Palmer in 1983, has been compared to hereditary hyperexplexia (startle disease) in humans (Garosi and others 2002) which in many cases is due to a mutation of the inhibitory glycine receptor (Tijssen and others 2002). Many dogs with the condition respond, at least initially, to clonazepam (Rivotril; Roche) at 0.5mg/kg three times daily (Garosi and others 2002). Some dogs seem to "grow out" of the problem. Clonazepam is thought to be effective because it enhances the GABA-gated chloride channel and presumably compensates for the defective glycine-gated chloride channel in hyperexplexia (Zhou and others 2002).

Fly-catching

This has previously been classified as a complex partial seizure presuming that the dog was having a hallucination (Delahunta, 1983). However, it is more likely that this is a compulsive disorder (Luescher 2002). Classically the dog acts as if watching then catching a fly. Some may also behave as if their ears or feet are irritated and some can also tail chase. In the author's experience, the episodes can last hours and are more common, at least initially, when the owners' focus is directed away from the dog e.g. when the family is watching television in the evening. In severe cases the dog is occupied in the behaviour almost full time. Compulsive disorders are compared to obsessive compulsive disorders in humans and are poorly understood; it is presumed that there is a neurochemical imbalance (Luescher 2002). Diagnosis is typically made on the basis of clinical history and elimination of other behavioural, medical and neurological disorders. Ideally the owner should make a video of the behaviour. If there is doubt as to whether it is epilepsy then a two - four week trial of phenobarbitone is recommended at 3mg/kg every 12 hours adjusting the dose to achieve a serum concentration of 25mg/l (120µmol/l). CKCS with fly catching typically make no response (DeLahunta, 1983). Referral to a veterinary behaviourist is recommended as there is often a learned component and treatment must involve behaviour modification in addition to drugs such as selective serotonin re-uptake inhibitors e.g. clomipramine at 2-3mg/kg twice daily or fluoxetine at 1-2mg/kg twice daily. Management of compulsive disorders has been reviewed by Luescher (2002). In principle the behavioural therapy is to train the dog with positive reinforcement (i.e. a reward of attention or small treat) to perform a desirable behaviour that is incompatible with the compulsive behaviour e.g. lying with head on floor between paws. As soon as the compulsive behaviour is seen then the dog is immediately distracted and instructed to perform the desirable behaviour. The reward can be progressively delayed so that the dog has to remain in the chosen position for increasingly longer times before the reward is given. If drugs are given then it can take 4 weeks before an effect is seen and they must be continued for at least 3 weeks after there has been the desired effect before attempting to withdraw over a minimum of 3 weeks. High protein diets i.e. high meat content tends to make compulsive

behaviours worse and conversion to a low protein diet can result in improvement of signs (Brown 1987) although in some dogs this may be only temporary.

Head nodding

Occasionally CKCS may present with the complaint of head nodding. Face twitching may also be seen and the body may be observed to bounce up and down when the dog is standing stationary. Occasionally the dog may stagger or appear to lose balance. Episodes tend to last a few seconds and may be very frequent. This movement disorder can have a variety of causes and underlying CNS pathology such as GME and syringomyelia should be ruled out and treated. It is more common in geriatric CKCS. The episodes stop during sleep and when walking. Investigation into the exact aetiology is ongoing.

Conditions causing abnormal head position
Vestibular disease

Vestibular syndrome is one of the most common neurological presentations. Clinical signs may include some or all of the following: head tilt; ataxia; circling; rolling; tendency to lean to side of head tilt; deviation eye ventrally (ipsilateral to head tilt) when the head is elevated above the horizontal plane. For prognostic purposes it is vital to distinguish between peripheral and central disease (Table 3). For a more extensive review on the diagnosis and treatment of vestibular disease see Muňana (2004).

Table 3 Differential diagnoses of vestibular disease in the CKCS

PERIPHERAL	CENTRAL
Vestibular signs	**Vestibular signs** Vertical nystagmus (take care not to confuse with rotatory) or that changes direction in different head positions suggests central disease
Proprioception normal	**Proprioceptive deficits** (ipsilateral)
Normal strength	**Paresis** (ipsilateral)
Mental status normal	**Altered mental status**
Cranial nerve deficits (CNVII and Horner's only	**Cranial nerve deficits** (esp. CN V, VII)
Common causes Idiopathic vestibular syndrome Otitis media-interna	**Common Causes** GME or Neoplasia Other space occupying lesion e.g. cyst Other inflammatory/infectious disease e.g. Neospora Infarction Trauma
Useful tests Serial neurological examination Auroscopic examination Radiographs or CT of bullae MRI Haematology biochemistry Thyroid function tests	**Useful tests** Serial neurological examination MRI CSF analysis Brain stem auditory evoked response

Infarction of the territory of the rostral cerebellar artery

CKCS seem to have an increased tendency for cerebrovascular disease (McConnell and others 2003) particularly with infarction of the rostral cerebellar artery. Affected dogs present with signs of acute onset rapidly progressive central vestibular syndrome (Fig 6).

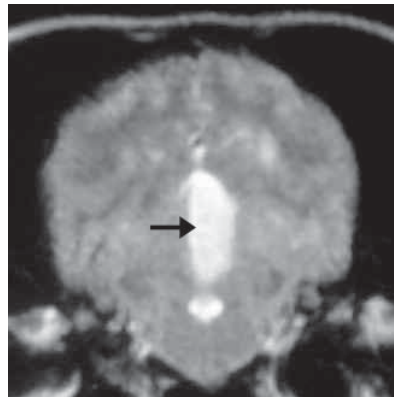

Figure 6 Transverse TW2 weighted image at the level of the rostral cerebellum. A 3 year old male CKCS that presented following acute onset intention tremor, depression and tetraparesis with a right sided head tilt, facial nerve paresis and lateral strabismus. MRI reveals a sharply delineated wedge shaped lesion of the left rostral cerebellar hemispheres typical of cerebellar infarction. Obstruction of the mesencephalic aqueduct by swelling resulted in secondary hydrocephalus contributing to raised intracranial pressure and cerebellar vermis herniation. The problem was compounded by mild occipital hypoplasia. Magnetic resonance angiography of the vertebral, carotid, brainstem and cerebral arteries and investigation for cardiac disease and bleeding disorders was unremarkable. This dog made a temporary improvement to intravenous methylprednisolone, furosemide and mannitol infusions. Ultimately an supraoccipital craniectomy was required to relieve the rising intracranial pressure and brain herniation following which the dog made a good recovery. He was maintained on 18.75mg aspirin daily.

Rostral cerebellar artery infarction in humans is associated with cardiogenic embolism and major artery occlusive disease e.g. carotid artery dissection (Yin and others 1994). The CKCS is predisposed to mitral valve disease (Haggstrom and others 1992); to increased platelet aggregation (Olsen and others); and arterial disease (Buchanan and others 1997) all of which offer some explanation for a tendency for cerebrovascular disease. In the U.K. any CKCS presented with signs of intracranial haemorrhage or infarction should be screened for *Angiostrongylus vasorum*. This parasite can result in bleeding and coagulation disorders and the CKCS appears to be predisposed to infestation (Chapman and others 2004).

Syringomyelia

In immature dogs the first presenting sign of syringomyelia may be scoliosis which could be confused with a head tilt of vestibular origin (Fig 7)

Figure 7 A 16 month old female CKCS with scoliosis that was presented for evaluation of a head tilt.

Future for the Breed

Occipital hypoplasia / syringomyelia is inherited in the CKCS. The inheritance is complex, possibly involving more than one gene (Rusbridge and Knowler 2003, 2004). The condition is very widespread throughout CKCS lines. A breeding program would result in further narrowing of the gene pool and the chance of increased frequency of other diseases. These disadvantages can be avoided with the availability of a DNA test for diagnosis, which would also permit identification of carriers or affected dogs without clinical signs. Guided by DNA testing, carriers can still be used in intelligent combinations so that the gene pool can be preserved. Consequently a DNA collection program is underway with the aim of genotyping, linkage analysis and positional gene cloning for occipital hypoplasia and also hereditary mitral valve disease and epilepsy. Episodic collapse (hyperexplexia) is a less frequent disorder; investigation of the inheritance and genetic defect is also underway (Penderis 2004).

Acknowledgement

The author is grateful to Drs. J Rothuizen and P.J.J. Mandigers for reading and commenting on the manuscript.

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Section 2

Pathophysiology of syringomyelia

Chapter 2.1

Syringohydromyelia in cavalier King Charles spaniels

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Journal American Animal Hospital Association
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Introduction

Syringohydromyelia is characterized by the development of fluid-filled cavities within the spinal cord. It is an acquired condition often classified into communicating and noncommunicating types.[1] Communicating syringohydromyelia results from disruption of cerebrospinal fluid (CSF) dynamics at the craniocervical junction and is often associated with developmental abnormalities in this area. The fluid is CSF-like in character. [1] Noncommunicating syringomyelia is characterized by cavities containing highly proteinaceous fluid and is found secondary to intramedullary neoplasia, vascular anomalies, arachnoiditis, and trauma.[1] The classical clinical signs of a syringohydromyelia are of a central cord syndrome (i.e., a grey matter lesion).

In veterinary medicine, there have been sporadic reports of syringohydromyelia often concurrent with developmental disorders of the craniocervical junction such as Chiari malformations [2,3] and Dandy-Walker syndrome.[2] It has also been described in association with spinal dysraphism [4] and with a vascular anomaly.[5] Syringohydromyelia with scoliosis secondary to suspected trauma has also been reported.[6] In this paper, syringohydromyelia secondary to deformity and overcrowding of the foramen magnum is described in seven Cavalier King Charles spaniels (CKCS).

Materials and Methods

Medical records of seven CKCS diagnosed with syringohydromyelia were reviewed. All dogs were evaluated by clinical and neurological examinations. The following additional diagnostic tests were performed: serum biochemistry and haematology (n=4), serum Neospora caninum and Toxoplasma gondii titres (n=2), CSF analysis (n=4), spinal radiographs and myelography (n=4), electromyography (n=4), peripheral nerve conduction and amplitude studies (n=3), and technetium-99m bone scintigraphy (n=1). Magnetic resonance imaging (MRI) was performed in all cases (case nos. 1, 2, 4, 5, 7;[a] case no. 3;[b] and case no. 6[c]). The dogs were positioned in sternal recumbency with the head and neck extended and the thoracic limbs drawn caudally. The images were collected using a circularly polarized extremity coil. T1- or T2-weighted sagittal images of the caudal fossa and cervical spine, together with T1- and T2-weighted transverse images of the brain and craniocervical junction, were obtained for each dog. Case no. 3 also had T2-weighted transverse images of the cervical spinal cord and proton density, and T1- and T2-weighted pre- and post-dimeglumine gadopentetate [d] contrast transverse images of the brain.

The extent of the clinical investigation depended on when the dogs were examined and the discretion of the primary clinician. Dogs that were presented first tended to have a more complete investigation. After the clinical syndrome of syringohydromyelia had become recognizable, fewer tests were required to obtain a diagnosis.

Results

Clinical Signs

The clinical signs are detailed in Table 1. Persistent scratching at one side of the shoulder/neck area was the initial reason for seeking veterinary advice. Scratching was most commonly seen by owners when walking their dog on a leash, especially if the collar was tight-fitting. Excitement, exertion, and barking could also elicit the response. In addition, owners commented that their pets resented any touching or grooming of the ear, limb, or neck of the “scratched” side. Occasionally affected dogs would cry as if in pain and often preferred to eat from a height. There were no skin lesions, and the dogs did not make skin contact when scratching. Prior to neurological assessment, all of the dogs had been investigated for possible dermatological or otological causes of their condition. No causes were found. In addition to

the scratching and neck/ear/limb hyperesthesia, variable neurological deficits were found, of which the most common was a lower motor neuron deficit of the thoracic limb ipsilateral to the "scratched" side (n=5). Proprioceptive deficits of this limb were also seen (n=2). Three dogs had ataxia and proprioceptive deficits of the pelvic limbs, and two had facial nerve paralysis. Case no. 6 had torticollis as a result of cervical scoliosis, with the head being twisted toward the "scratched" side. This dog was hyperesthetic in the sternal area. Case no. 3 had a history of generalized clonic seizures that occurred at a frequency of two per year.

Table 1 Clinical Signs of Affected Dogs

Case No	1	2	3	4	5	6	7
Age/Sex*	7 yrs/M	3 yrs/F	6 yrs/F	3 yrs/M	9 yrs/M	11 mos/M	8 yrs/M
Age onset clinical signs	6 mos	2 yrs	2 yrs†	18 mos	‡	8 mos	‡
Scratching shoulder region§	Yes (R)	Yes (L)	Yes (R)	Yes (L)	Yes (L)	Yes (R)	Yes (L, R)
Neck pain	No	Yes	No	Yes	Yes	Yes	Yes
Limb pain/sensitivity	Yes	Yes	Yes	Yes	Yes	No	No
Ear pain/sensitivity	Yes	Yes	Yes	Yes	No	No	No
Lumbar pain	No	Yes	No	No	No	No	No
LMN\ thoracic limb	Yes (R)	Yes (L)	Yes (R)	Yes (L)	Yes (L)	No	No
Thoracic limb CP¶ deficits	Yes (R)	Yes (L)	No	No	No	No	Yes (L)
Pelvic limb ataxia/ CP deficits	No	Yes (L)	Yes	No	No	No	Yes
LMN pelvic limb	No	Yes (L)	No	No	No	No	No
Facial nerve paralysis/ paresis	Yes (L, R)	No	No	No	Yes (L)	No	No
Scoliosis	No	No	No	No	No	Yes	No

* M=male; F=female

† Dog displayed signs since acquired by owners at two years

‡ Dog displayed signs for many years; owners unable to quantify further

§ R=right side only; L=left side only; L, R=bilateral

\ LMN=lower motor neuron neurological signs

¶ CP=conscious proprioception

Diagnostic Tests

Serum biochemistry and haematology tests were done in case nos. 1, 2, 3, and 6 and were unremarkable. Case nos. 1 and 2 were evaluated for possible *Toxoplasma gondii* and *Neospora caninum* infection and had negative titres. Cisternal CSF analysis in case nos. 1 and 6 suggested mild inflammatory change. Case no. 1 had a nucleated cell count of 8 cells/mm^3 (reference range, less than 6 cells/mm^3; lymphocytes, 78%; macrophages, 22%) with a protein level of 29 g/l (reference range, less than 30 g/l). Case no. 6 had a nucleated cell count of 11 cells/ mm3 (lymphocytes, 50%; neutrophils, 50%). The red blood cell count was 183 cells/mm3 (reference range, 0 cells/mm3), and the protein level was 34 g/l. In case no. 2 only a small amount of blood-contaminated CSF was obtained; results were consistent with iatrogenic haemorrhage. Cerebrospinal fluid analysis was normal for case no. 7. The results of electrophysiological investigation in four dogs are detailed in Table 2.

Table 2 Electrophysiological Findings

Case No.	Denervation Changes*†	Ulnar Motor Nerve Conduction Velocity and Amplitude ‡	Radial Sensory Nerve Conduction Velocity and Amplitude ‡§
1	R, L cervical paraspinal muscles	Normal	Normal
	R, L lumbar paraspinal muscles		
	R thoracic limb		
2	None	Normal	NO
6	R, L cervical paraspinal muscles	ND	ND
	R, L lumbar paraspinal muscles		
	L distal thoracic limb		
	R metacarpal interosseous		
	L pelvic limb		
7	R, L extensor carpi radialis and shoulder musculature	Normal	ND

* Presence of fibrillation potentials or positive sharp waves

† R=right side only; L=left side only; R, L=bilateral

‡ ND=not done

§ NO=attempted but could not be obtained

Four dogs had radiographs of the cervical spine. The images were normal for case nos. 1 and 2. Case no. 7 had a narrow fourth to fifth cervical (C4–C5) intervertebral disk space. Cervical radiographs for case no. 6 confirmed scoliosis with the concave side on the right [Figure 1].

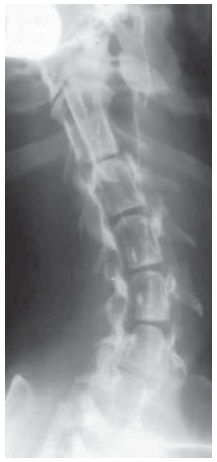


Figure 1 Ventrodorsal radiograph from an 11 month old male cavalier King Charles spaniel (case no 6) with cervical scoliosis

All four dogs also underwent cisternal myelography; the images of the cervical spinal cord were normal for case nos. 1, 2, and 7. In case no. 6, the spinal cord diameter appeared wider than normal. In case no. 2, little CSF was obtained at the cisternal site and there was failure of caudal contrast spread to the lumbar area. A lumbar puncture for intended lumbar myelography was performed. In this instance, the puncture resulted in a fast flow of CSF. This was thought suspicious of a syrinx, so a reduced volume of iohexol contrast media[e] was slowly introduced (50 mg/kg body weight rather than 90 mg/kg body weight). There was no resistance to injection, and the contrast medium delineated a syringohydromyelia extending from the second cervical (C2) vertebra to the cranial border of the fifth lumbar (L5) vertebra [Figure 2]. There were no complications following myelography. Bone scintigraphy in case no. 7 was normal.

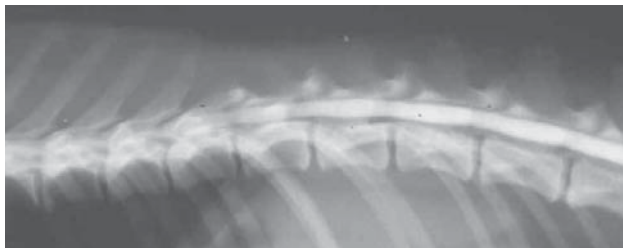


Figure 2 Lateral thoracolumbar radiograph of a Cavalier King Charles spaniel (case no. 2) with evidence of neck pain and neurological deficits of all four limbs. Iohexol contrast is outlining a syringohydromyelia cavity.

Magnetic Resonance Imaging (MRI)

A diagnosis of cervical spinal cord syringohydromyelia was made in each dog. Transverse images revealed lateralization of the syrinx consistent with the clinical signs [Figure 2].

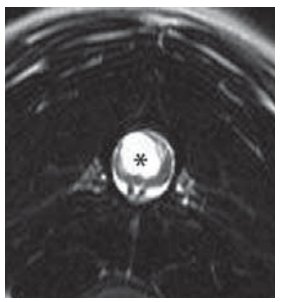


Figure 3 T2-weighted (TR 5090, TE 134) transverse magnetic resonance imaging (MRI) image at the level of the second cervical (C2) vertebra in a cavalier King Charles spaniel (case no. 3), showing a thin rim of spinal cord tissue surrounding a massively dilated syrinx (asterisk) which is lateralized to the right. The dog's main clinical signs were persistent scratching at the right shoulder and lower motor neuron deficits of the right thoracic limb.

The shape of the caudal fossa was disproportionately small resulting in difficulty accommodating the cerebellum and medulla resulting compression and obstruction at the foramen magnum [Figure 4].

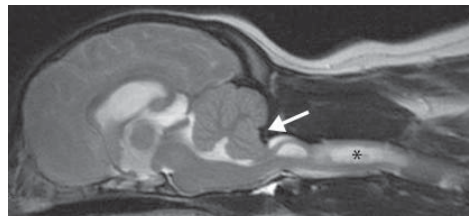


Figure 4 T2-weighted (TR 3800, TE 103) midsagittal MRI image of a cavalier King Charles spaniel (case no. 7), demonstrating cerebellar herniation with syringohydromyelia. The supraoccipital bone is indenting the cerebellum (small arrow). The syrinx (asterisk) is divided into several compartments by septations or haustra.

The abnormal caudal fossa did not accommodate the cerebellum, and there was caudal displacement of the cerebellum to the level of (case nos. 1, 2, 3, 6, and 7) or through (case nos. 4 and 5) the foramen magnum. This resulted in overcrowding within the foramen magnum and apparent compression of the brain stem at the cervicomedullary junction. In all dogs, the tentorium cerebelli osseum was more horizontal than normal, the caudal medulla had a kinked and elongated appearance, and the dorsoventral diameter of the craniocervical vertebral canal was small. The remainder of the skull and brain was normal. Subjectively, case nos. 3, 4, 6, and 7 had slightly larger ventricular systems than would be expected for their breed, suggesting an obstructive hydrocephalus. Ventricular enlargement was more pronounced for case nos. 1 [Figure 5] and 2.

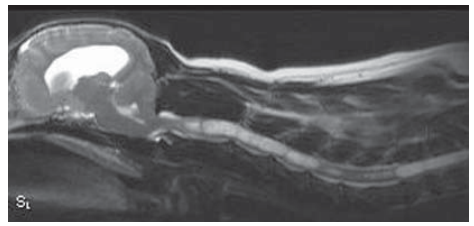


Figure 5 T2-weighted (TR 3400, TE 109) midsagittal MRI image of a cavalier King Charles spaniel (case no.1), demonstrating cerebellar herniation with syringohydromyelia and hydrocephalus. The dog did not have any clinical signs relating to the hydrocephalus.

However, there was no evidence of periventricular transependymal edema, indicating that the hydrocephalus, if truly present, was long-standing. In addition to these findings, MRI revealed a mild C2

to third cervical (C3) disk extrusion in case no. 5. This was suspected to be a contributing factor to neck pain in this dog. The normal MRI appearance of the caudal fossa and craniocervical junction is illustrated in Figure 6.

Figure 6A

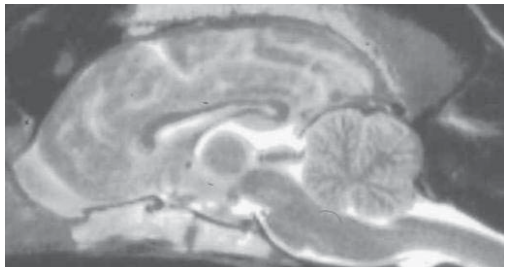
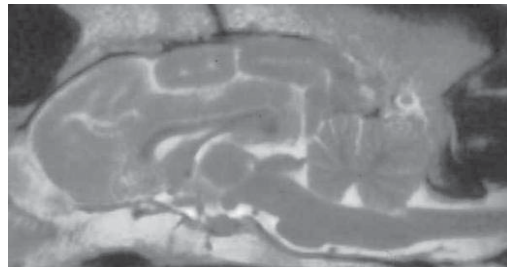


Figure 6B



Figures 6A, 6B midsagittal midline T2-weighted (TR 3500, TE 112) MRI image of the brain of a normal mesencephalic dog, a Staffordshire bull terrier (6A), and the brain of a dolichocephalic dog, a Dalmatian (6B). In comparison to the cavalier King Charles spaniel, the dorsoventral diameters of the foramen magnum and cranial cervical vertebral canal are larger. This is most evident by the amount of cerebrospinal fluid (hyperintense signal) that can be seen in the cisterna magna and around the brain stem and spinal cord. The mesencephalic dog has a small rostral indentation of occipital bone into the caudal fossa, but this is not as pronounced as what is seen in the cavalier King Charles spaniels in Figures 4 and 5.

Treatment and Progression

Surgical management was declined in all patients. The progress of case no. 1 was followed over three years. His discomfort and shoulder scratching did not resolve but were improved when medicated with prednisolone[f] (0.5 mg/kg body weight, per os [PO] on alternate days). Thoracic limb proprioception improved slightly after initiating prednisolone therapy, then it deteriorated to the status at initial presentation. Subsequently he has remained stable. He was also treated with artificial tears[g] (applied to the corneal surface of both eyes, tid) to prevent corneal exposure secondary to facial nerve paralysis. Attempts were made to improve pain control by medication with carbamazepine[h] (100 mg PO bid) and the serotonin uptake inhibitor, amitriptyline[i] (10 mg PO bid). Both these drugs are used as neuralgesics in humans. [7,8] Neither resulted in any clinical improvement; in fact, medication with amitriptyline resulted in a cutaneous drug reaction. Following long-term treatment with glucocorticoids, this dog has had recurrent episodes of pyoderma and has an obesity problem.

For case nos. 2 and 5, the discomfort and scratching were partly alleviated by carprofen.[j] Case no. 2 was initially medicated (2 mg/kg body weight, PO bid) during severe episodes of pain. This appeared to control her discomfort for one year. Subsequently, her neurological status deteriorated. She became more ataxic, there were more severe left-sided proprioceptive deficits, and the discomfort and scratching were worse. Continuous daily medication with carprofen (2 mg/kg body weight, PO, bid 3 months) did not alleviate the signs. The medication was altered to meloxicam [k] (0.1 mg/kg body weight, PO sid), and she appeared less distressed. Case no. 5 was medicated continuously with carprofen (1 mg/kg body weight, PO bid). His clinical signs have remained stable for one year. Case no. 3 (9.8 kg) was also medicated with carprofen (2 mg/kg body weight, PO bid); however, there was inadequate control of pain, and she was subsequently maintained on dexamethasone [l] (0.25 mg PO on alternate days for 2 months; then 0.25 mg PO every 3 days). Her clinical signs were much improved, and her owners reported that they were able to groom and pet her for the first time since she had been acquired. Clinical signs in case nos. 4 and 6 were improved by therapy with dexamethasone at a dose of 0.25 mg PO on alternate days and 0.5 mg PO sid, respectively. Case no. 6 had scoliosis, which also seemed to improve slightly over time. Both dogs were also initially treated with a three-week course of the carbonic anhydrase inhibitor acetazolamide [m] at 31.25 mg PO tid (case no. 4) and 50 mg PO bid (case no. 6). This drug decreases CSF production and was used in an attempt to retard the progression of the syringohydromyelia. After an initial improvement, the clinical status has been stable for both dogs, monitored for a period of 26 months (case no. 4) and four months (case no. 6). Case no. 7 was not treated, and the clinical status has remained stable. At the time of publication, all cases are alive.

Discussion

The clinical signs of cervical paraesthesia progressing to a segmental sensory loss and weakness, with long tract signs, are stereotypic for a cervical central canal syndrome and a gradually expanding syrinx. The abnormalities in these dogs were similar to Chiari type-I malformation in humans. However, in Chiari type-I malformation, the cerebellar tonsil herniation is greater and usually extends well below the level of the foramen magnum. The Chiari type-I occipital bone in affected humans is dysmorphic and the posterior fossa is small, but it does not have the abnormal shape that was typical for the dogs in this series.[1,9] However, in both Chiari type-I and the CKCS malformation, syringohydromyelia occurs secondary to overcrowding of the foramen magnum and obstruction of CSF flow. The first feature of syrinx development is a dilatation of the central canal, termed “hydromyelia.” Initially the cavity is lined by ependyma, but as expansion continues, this lining is split and fluid dissects (usually dorsomedially) into the grey matter, creating a syringohydromyelia [Figure 7].[10]

The term “syringomyelia” refers to a spinal cavity that is not lined by ependyma. The decussating fibres of the spinothalamic tracts, responsible for pain and temperature sensation, are the first to be affected by this syrinx expansion. Damage to these fibres and the interconnections within the dorsal grey column leads to pain and paraesthesia of the corresponding dermatome.[1,11] One hypothesis for the scratching is

that the dogs are attempting to brush off a perceived irritation. Abnormal skin perception is also suggested by the dogs' intolerance of touching and neck collars. Expansion of the syrinx ventrally damages ventral horn cells innervating limb and paraspinal musculature. Muscle atrophy, weakness, and decreased spinal reflexes will be observed clinically (i.e., lower motor neuron signs). If the paraspinal muscle atrophy is severe, the resulting muscular imbalance will result in scoliosis.[1,11] Electrophysiological studies in three of the dogs supported a diagnosis of cervical ventral horn cell damage. Denervation changes were found in the paraspinal and thoracic limb muscles, but motor nerve conduction velocities were normal. These findings suggest axonal loss.[12] The syrinx may extend throughout the length of the spinal cord, resulting in corresponding clinical signs. There was electromyographical evidence of lumbosacral ventral horn cell damage in case no. 6.

Figure 7A

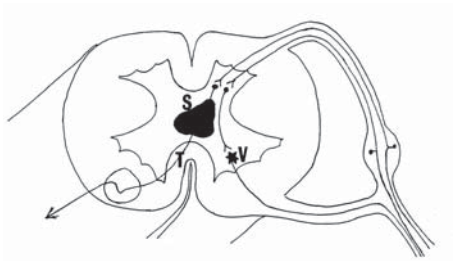


Figure 7B

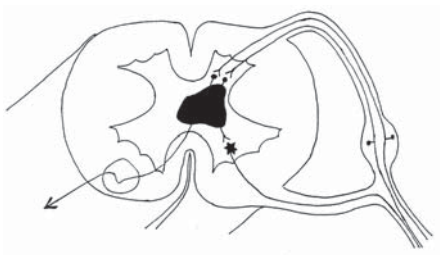
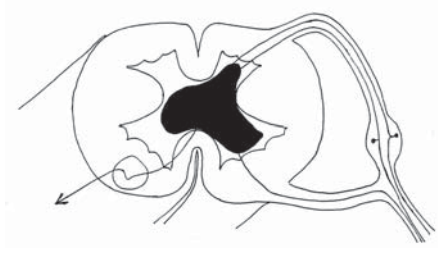


Figure 7C



Figures 7A - C (7A) Transverse section through the spinal cord of a dog with a progressively expanding syringohydromyelia. S=syringohydromyelic cavity; T=decussating spinothalamic tracts; V=ventral horn cell. (7B) The decussating spinothalamic tract and dorsal horn are damaged, resulting in paraesthesia of the corresponding dermatome. (7C)Continued expansion of the syrinx results in ventral horn cell lesions, leading to muscle atrophy and weakness. (*Adapted from Rengachary SS, Wilkins RH, eds. Principles of neurosurgery, 1994. Mosby-Year Book Europe, Ltd. Used by permission of Mosby International, Ltd.*)

Further distension of the syringohydromyelic cavity will lead to compression of the white matter tracts, resulting in pelvic limb ataxia and proprioceptive deficits[11] as seen in two of the dogs. The facial nerve paresis seen in case nos. 1 and 5 is difficult to relate to the underlying malformation. Cranial nerve deficits are common with human Chiari malformation, but they are almost exclusively bulbar (i.e., cranial nerves nine to 12). This is most likely due to traction on the cranial nerves or possibly compression of the caudal medulla within the foramen magnum or an ascending syringomyelia.[13] There was no MRI evidence of facial nerve compression or of ascending syrinx in any of the dogs. Traction of the nerve is possible, but in this instance one would expect other cranial nerves to be affected. Case no. 3 had seizures in addition to her other clinical signs. This was thought to be an unrelated problem; MRI of the forebrain did not suggest any underlying cause of the epilepsy. Humans with syringohydromyelia suffer an exacerbation of clinical signs when intrathoracic or intra-abdominal pressure increases; for example, coughing, sneezing, suddenly rising, or exertion.[13] This also appeared true with these dogs; owners reported increased scratching in their dogs during exertion, barking, or when excited. It is thought that rapid changes in intrathoracic or intra-abdominal pressure are an important factor in the pathogenesis of syringohydromyelia; however, the exact mechanism remains elusive. Several theories have been suggested.[13] The water-hammer effect of pulsatile CSF forced down the central canal from the fourth ventricle as a consequence of increased intrathoracic or abdominal pressure is one such theory.[14] However, a major weakness of this explanation is that it relies on there being a communication between the fourth ventricle and the central canal, which is present in only 10% of human patients. [15,16] The situation in dogs is not known. A second weakness of this theory is that if fluid could not escape through the lateral apertures, then "backing up" would be expected, resulting in hydrocephalus.[16] Hydrocephalus was only seen to a mild extent in the dogs of this study and is present in less than 10% of humans with a Chiari type-I malformation.[1] The suck effect is also a popular theory based on the observation that when intrathoracic or intra-abdominal pressure increases, the pressure in the lumbar sac rises more quickly than the head. Foramen magnum overcrowding may prevent rapid equilibrium of the pressure, resulting in CSF being sucked from the fourth ventricle to the central canal.[17] In addition, when lumbar sac pressure is increased, there is considerable rostral flow of CSF, which may also contribute.[13] This theory also relies on there being a patent connection between the fourth ventricle and the central canal. When syringohydromyelia develops, CSF will move less easily within the narrowed subarachnoid space than within the syrinx. Pressure differences can cause a surge of the fluid within the syrinx, resulting in further fissuring and damage to the spinal cord (i.e., slosh effect).[13] This is thought to be important for the continued development of a syrinx. The cervical vertebral canal stenosis seen in the dogs in this series may be an important contributory factor to this slosh effect. The only theory that does not rely on a fourth ventricle to central canal connection is one that initially seems least plausible. When subarachnoid CSF pressure is increased, fluid could be forced into the substance of the spinal cord. This suggests that the spinal cord is more permeable than it seems; however, since there are no tight junctions and the Virchow-Robin spaces are large, this theory is conceivable.[13,18] Syringohydromyelia may be a common problem within the CKCS breed. In addition to the cases in this

series, a further six dogs with consistent clinical signs have been examined by one of the authors (Rusbridge); however, MRI investigation was not possible. Following a letter reporting this condition,[19 59] anecdotal reports were received from veterinary surgeons and owners in the United Kingdom, Ireland, United States, Australia, Finland, and France describing CKCS with the typical scratching behaviour with or without other neurological signs. With a high incidence of affected dogs within one breed, the possibility of an inherited condition must be considered. Pedigree analysis of the dogs revealed a high frequency of certain names and lines. The same names and lines were commonplace in pedigrees of the anecdotally reported dogs. However, firm conclusions about the possible genetic nature cannot be made at this stage because the number of confirmed cases is small and many of the common names and lines were champion dogs and, therefore, popular for breeding. It has proved difficult to define the normal caudal fossa appearance in the CKCS. It is possible that it is "normal" for a CKCS to have a small caudal fossa, a narrow foramen magnum, and cranial cervical vertebral canal stenosis. The occipital bone abnormality and cerebellar herniation may be exaggerations of this conformational defect. The presence of a small cerebellar herniation in an already crowded foramen magnum may interfere with CSF dynamics, leading to syringohydromyelia. Further studies on CKCS skull morphology are currently in progress. Abnormal development of the occipital bone is the proposed pathogenesis of Chiari type-I malformation in humans.[9] Using computerized tomography (CT) and MRI, Nishikawa, et al., demonstrated a significantly smaller caudal fossa volume in humans with a Chiari type-I malformation (i.e., the hindbrain was literally too large for the skull, resulting in overcrowding).[9] They proposed that this be related to underdevelopment of the occipital somite. Other occipital bone anomalies in toy breeds are recognized.[20] It is possible that breeders of CKCS are unwittingly selecting for an undesirable skull shape much in the same way that in this breed the rostral skull is foreshortened, preventing adequate accommodation of the soft palate and other soft-tissue structures of the head, probably as a result of selection. Most of the dogs in this series were medically managed in a similar way to that described for hydrocephalus, [21] aiming to decrease the CSF volume. Either oral dexamethasone or prednisolone was used. The dogs were maintained on the lowest possible dose to control their clinical signs. Most dogs with neurological deficits made an initial slight improvement and subsequently remained stable or slowly deteriorated. The scratching and discomfort improved but did not resolve. Two dogs initially received the carbonic anhydrase inhibitor acetazolamide. Both glucocorticoids and acetazolamide decrease CSF production.[22] It is possible that glucocorticoids also had an anti-inflammatory effect. Cerebrospinal fluid analysis in two dogs suggested mild inflammation. Meningeal fibrosis and arachnoiditis have been described as associated with cerebellar herniation.[12] These adhesions may further impede CSF flow. Long-term medication with glucocorticoids is undesirable due to concurrent drug effects; case no. 1, which has been monitored for three years, has recurrent bouts of pyoderma and is obese. Attempts to improve pain control with the neuralgesics carbamazepine and amitriptyline were unsuccessful. Owners of case nos. 2, 3, and 5 elected not to medicate with glucocorticoids, because they were concerned regarding the long-term side effects. In these dogs, carprofen was useful in reducing the discomfort; however, it appeared less effective than glucocorticoids. Case no. 2 deteriorated, and medication was altered to meloxicam, which was more effective in this dog. Treatment for case no. 3 was altered to dexamethasone. In humans with a Chiari type-I malformation, early surgical intervention to re-establish CSF flow is recommended for deteriorating patients.[22] The preferred method is to recreate a cisterna magna via a suboccipital craniotomy and first cervical (C1) vertebra laminectomy with dural opening.[1] Dural grafting and cerebellar tonsil resections are performed if necessary.[1] An alternative method is to place a shunt between the syrinx and the subarachnoid space.[23] In theory, similar surgical methods could be used in the dogs in this series. Surgery is performed with a view to preventing further deterioration; existing neurological deficits are often permanent, and pain control can be an ongoing challenge.[1] Surgical management was declined by owners of dogs in this series, because the dogs seemed to cope with their disability, the prognosis for improvement was guarded, and the surgery itself held risks.

Conclusion

Syringohydromyelia results in clinical signs of central cervical spinal cord disease. It should be differentiated from other causes of cervical disease. The CKCS breed is predisposed, and the suggested pathogenesis is abnormal development of the occipital bone leading to a small caudal fossa, cerebellar herniation, and overcrowding of the foramen magnum. Clinical signs can be partially alleviated with glucocorticoid therapy.

A Philips Gyroscan T5-II, 0.5 Tesla, maximum 10 mT/m gradients; Hammersmith, UK
B Siemens Impact Expert, 1 Tesla, 20 mT/m gradients; Bracknell, UK
C 0.5 Tesla Superconducting magnet; SMIS Ltd., Guilford, UK
D Magnevist (469 mg/ml); Schering Health Care Ltd., Burgess Hill, UK
E Omnipaque (240 mg/ml); Nycomed (UK) Ltd., Birmingham, UK
F Prednicare (5 mg); Animalcare Limited, York, UK
G Viscotears Liquid Gel; Ciba Vision Ophthalmics, Southampton, UK
H Tegretol (100 mg); Geigy Pharmaceuticals, Watford, UK
I Tryptizol (10 mg); Thomas Morson Pharmaceuticals, Hoddesdon, UK
J Zenecarp (20 mg); C-Vet Veterinary Products, Leyland, UK
K Metacam oral suspension; Boehringer Ingelheim Limited, Bracknell, UK
L Dexamethasone tablets BP (2 mg); Organon Laboratories, Ltd., Cambridge,UK
M Diamox (250 mg); Lederle Laboratories, Gosport, UK

Acknowledgments

The authors are grateful for the expertise of Amanda Carroll and Sue McAllen of the Radiology Department, Parkside Hospital, Wimbledon, and to the radiographers at Bedford Hospital. The authors would also like to thank the Cavalier King Charles Spaniel Club for contributing toward the cost of one of the MRI scans and to Mrs. J. Ireland and Mrs. S. Birt for their tireless patience and dedication.

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Chapter 2.2

Syringomyelia: Current concepts in pathogenesis, diagnosis and treatment

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Journal of Veterinary Internal Medicine
2006; 20, 469-479.

Introduction

Syringomyelia is a condition in which fluid-filled cavities develop in the spinal cord (Fig 1).
Previously, it was considered a rare condition in veterinary medicine but it is now a relatively common neurological diagnosis. This change is in part due to increased availability of magnetic resonance imaging (MRI) and also due to increased prevalence in certain breeds, most notably the cavalier King Charles spaniel (CKCS)[1].

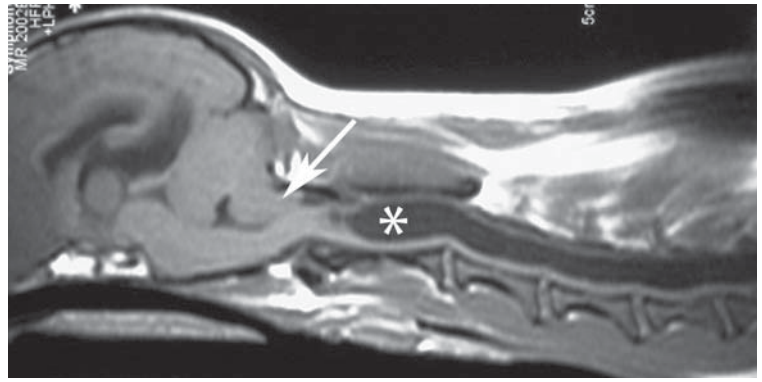

Figure 1 Midsagittal T1-weighted image of the brain and cervical spinal cord of an affected dog. Syringomyelia (asterixis) secondary to occipital hypoplasia in a 21-month female CKCS presented with a 3-month history of yelping and a tendency to scratch at the right shoulder area. Cerebellar herniation through the foramen magnum is present (arrow).

Syringomyelia can be caused by various primary problems, including abnormalities of the caudal fossa (the Chiari malformations), tethered spinal cord, trauma, arachnoiditis, and tumour.[1,2] Here, we review the clinical and pathogenic characteristics of syringomyelia for the purpose of updating veterinarians on current views of pathogenesis, diagnosis and treatment.

History of the classification of syringomyelia and Chiari malformation

Cavitation within the spinal cord was first described by Stephanus in the 16th century.[3] Olivier d'Angers first used the term syringomyelia in 1824 and at that time the cavity was believed to be a dilated central canal that communicated with the fourth ventricle.[4] It was later proposed that dilatation of the central canal be termed hydromyelia and that a distinction be made between this dilatation and syringomyelia on the basis that the former structure was lined by ependyma and the latter by glial cells.[5] It subsequently has been shown that this distinction is somewhat arbitrary in that hydromyelia may extend into the spinal cord substance to form syringohydromyelia partially lined by ependyma[6] and cavities may rupture into the central canal. [7] The term syringomyelia now is generally acceptable for all clinical conditions characterized by spinal cord cavitation containing fluid identical with or closely resembling cerebrospinal fluid (CSF).[7] This classification does not include (protein-containing) cavities associated with tumours.[7]
Syringomyelia traditionally was classified into communicating and non-communicating types in which communicating implies disruption of CSF dynamics at the cranial cervical junction and non-communicating implies a primary spinal cord condition.[8] These terms are confusing however because the communication referred to a connection between the syringomyelic cavity and the fourth ventricle, which actually is present in fewer than 10% of affected human patients. This categorization now tends to be disregarded.[9]

In 1891, Hans von Chiari, a pathologist in Prague, described 4 types of abnormality based on autopsy of infants with hydrocephalus who died shortly after birth. [10,11] The type 1 malformation was described as "elongation of the cerebellar tonsils and the medial part of the inferior cerebellar lobes into cone-like projections, which accompany the medulla into the spinal canal".[12] Arnold's name subsequently was added by two of his loyal students on the basis of the description of a single case consistent with a Chiari type II malformation (i.e., in association with spina bifida). For many years, the spectrum of disorders of cerebello-medullary descent was referred as Arnold-Chiari syndrome.[12] In recent years however the trend has been to simplify the name to Chiari malformation. This name is now convenient shorthand for a wide range of abnormalities not necessarily consistent with Hans von Chiari's original description type I malformation, but all characterized by decreased posterior fossa volume with caudal descent of the cerebellar tonsils, and often the brainstem.[12, 13] It is debatable whether the term Chiari malformation should be applied to the dog. The analogous condition, characterized by decreased volume of the caudal fossa and caudal displacement of the caudal cerebellar vermis into or through the foramen magnum is very similar to the human condition.[14] The condition in the dog however is inconsistent with the historical description, not in the least because dogs do not have cerebellar tonsils. It may be more correct to use an anatomical description (e.g., occipital hypoplasia with syringomyelia[1] or caudal occipital malformation syndrome[15]). Arnold Chiari malformation is an inappropriate descriptive term unless the pathology also includes myelomeningocele in addition to a cerebello-medullary malformation[2].

Pathophysiology of Chiari-associated syringomyelia

The syringomyelia that accompanies caudal fossa abnormalities is thought to be a consequence of abnormal CSF dynamics. In the normal mammal, CSF moves caudally and rostrally between the head and vertebral column. This rapid efflux and influx is due to expansion and contraction of the intracranial arteries during the cardiac cycle.[16] If the subarachnoid space is obstructed (e.g., by cerebellum at the foramen magnum), syringomyelia can develop. In 1950, Gardner proposed the *water-hammer theory* and suggested that when systolic CSF flow through the foramen magnum and outflow from the fourth ventricle were obstructed, ventricular CSF was forced into the central canal with each arterial pulse. This dilated the central canal and eventually resulted in syringomyelia.[17] Although an elegant theory (and one that predated the advent of MRI), it is not supported by clinical evidence because the majority of affected human patients do not have a patent connection between the central canal and the fourth ventricle.[18] Dogs and other small mammals are more likely to have a patent connection (Milhorat, personal communication), but evidence that a syrinx develops from CSF forced into the central canal is lacking (Fig 2).

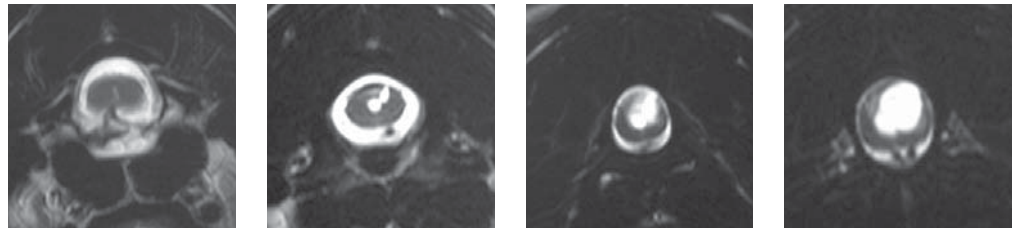

Figure 2 Serial transverse T2-weighted images of the spinal cord (left to right) from the cranial cervical junction to the caudal border of C2 in a 16-month-old male CKCS presented for pain. In the left image (A) a normal central canal is visible as a small white dot in the centre of the spinal cord. In the next image (B) the central canal is dilated but still separate from the developing syrinx within the dorsolateral quadrant of the spinal cord. In the next 2 images (C, D), the 2 cavities are conjoined with what appears to be remnants of the ependymal lining of the central canal traversing the space.

In 1976, Williams described the *suck effect theory*[19] and proposed that when the foramen magnum is obstructed and intraabdominal or intrathoracic pressure is increased (e.g., by coughing), that a pressure difference develops between the head and vertebral column. This pressure difference could result in fluid being sucked from the ventricles into the central canal. This theory however also relies on a connection between the fourth ventricle and central canal, and implies lower pressure in the syrinx when in fact research has shown that pressure in a syrinx is higher than that outside of the spinal cord.[20]

Because it seems unlikely that syrinx fluid comes from the ventricles, it was proposed that spinal CSF is forced into spinal cord parenchyma through the perivascular spaces.[21] Radiographic contrast and horseradish peroxidase studies have shown that CSF can flow into the spinal cord along the outside of veins and arteries.[22] However if syrinx pressure is higher than CSF pressure, this theory also seems implausible and also does not explain why syrinx fluid has significantly lower protein content than CSF.[20]

One of the current popular theories is the *piston theory*,[23, 24] proposed by Oldfield et al, which suggests that the displaced cerebellar tonsils act like a piston and with each systole are forced caudally creating a pressure wave within the entrapped subarachnoid space and syrinx. Movement of fluid and pulsations of the wall of the syrinx cavity can be observed in ultrasound studies performed intraoperatively in human patients, and the pulsations decrease after durotomy.[23] This movement is associated with the cardiac cycle not with respirations. This theory is a reasonable explanation for syrinx progression and is similar to a previously proposed mechanism, the *slosh effect*, which suggests that surging of fluid within the syrinx results in additional fissures and damage to the spinal cord.[25] There are two main arguments against the *piston effect* being the sole mechanism for syrinx formation. Firstly, it also relies on CSF being forced into the spinal cord from the subarachnoid space. Secondly, if the soft spinal cord was exposed to such a force from outside it would seem more likely to be crushed than expand with a syrinx.[26]

New and challenging concepts of syringomyelia

Based on experimental work in laboratory rodents, Greitz and others introduced the *intramedullary pulse pressure theory*[26, 27, 28] which is one of the first general theories to provide an explanation for the pathophysiology of syringomyelia regardless of etiology (e.g., Chiari malformation, post-traumatic syringomyelia, arachnoiditis, syringomyelia secondary to tumours in the caudal fossa or vertebral canal). The main principles of this theory are that 1) syringomyelia is caused by repeated mechanical distension of the spinal cord and 2) the ensuing cavitation arises from extracellular fluid originating from the high-pressure system in the microcirculation of the spinal cord and not CSF from the low-pressure system in the subarachnoid space (Fig 3).

The driving force of syringomyelia is the systolic CSF pulse pressure (i.e. the pressure wave of CSF displaced from the head during arterial pulsations). When the subarachnoid space is obstructed, there is a significant decrease in pressure transmission to distal CSF spaces (Fig. 3, 4a). Consequently, there is increased transmission and reflection of the systolic CSF pulse pressure into spinal cord tissue in close proximity to the obstruction (Fig 4a).

The *intramedullary pulse pressure theory* suggests that this increased pressure in the spinal cord and the decreased pressure in the nearby subarachnoid space distends the spinal cord just below the blockage. In addition, part of the systolic CSF pulse pressure is reflected into the spinal cord at the obstruction also distending the compliant spinal cord just above the blockage[29] (Fig 4b).

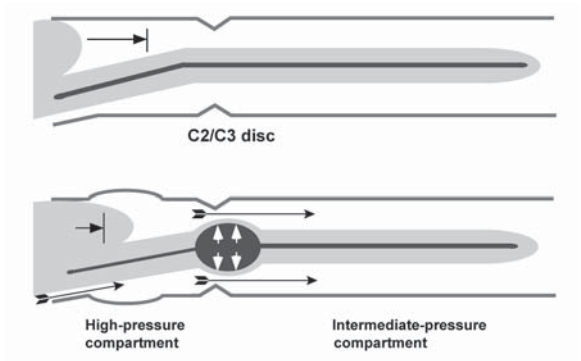

Figure 3 Syringomyelia secondary to Chiari malformation In Chiari malformation, the increased cerebellar motion in the vertebral canal increases the systolic CSF pulse pressure distal to the obstruction at the foramen magnum and a shock-like spinal pressure wave is created. The systolic CSF flow jet ventral in the foramen magnum decreases the hydrostatic CSF pressure, but this pressure difference is rapidly equalized in the cervical high-pressure compartment. At more caudally located physiological impingement of the subarachnoid space, such as C2/C3 intervertebral disc level, the Venturi effect or the suction effect of the systolic CSF flow-jet is unrestricted. Therefore, syringomyelia typically develops at and caudal to the C1 spinal segment.

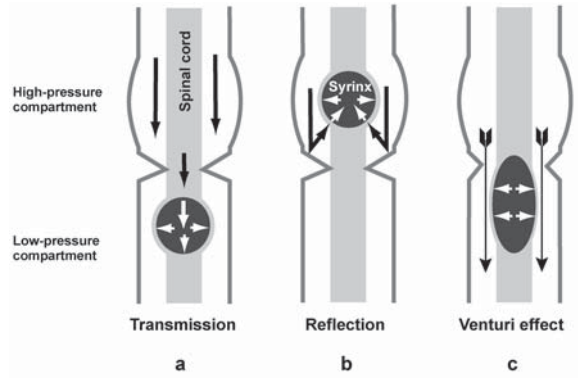

Figure 4 Posttraumatic syringomyelia. Subarachnoid adhesions cause a fixed type of obstruction that decreases the transmission of systolic CSF pulse pressure (i.e. the pressure wave of CSF displaced during systole) distal to the obstruction. a) Systolic CSF pulse pressure (represented by the black arrows) is transmitted through the spinal cord at the obstruction. The increase in spinal cord pressure and decrease in subarachnoid pressure results in distention of the spinal cord just below the obstruction (represented by white arrows). b) Part of the systolic CSF pulse pressure simultaneously is reflected into the spinal cord at the obstruction resulting in an increase in spinal cord pressure and consequently distention of the spinal cord just above the obstruction. c) At partial subarachnoid obstructions, the CSF flow jet (represented by arrows with tails) decreases the hydrostatic pressure in the CSF (Venturi effect) which in turn distends the spinal cord. Syringomyelia develops by collection of extracellular fluid in the distended spinal cord.

This repeated mechanical distention of the cord results in dilatation of the central canal and accumulation of extracellular fluid which eventually coalesces into cavities. Contrary to prevailing theories hypothesizing filling of the syrinx by CSF, this theory is in accord with the second law of thermodynamics indicating that both filling and distension of the syrinx occur along and not against pressure gradients. Thus, filling occurs down the pressure gradient from the spinal cord microcirculation to the syrinx and distension occurs down the pressure gradient from the syrinx to the subarachnoid space. Consequently, development of syringomyelia is independent of the presence of a pathway between subarachnoid space and syrinx. The hypothesis that syringomyelia is due to accumulation of extracellular fluid rather than CSF also provides an explanation for the observation that potentially reversible oedema develops in the spinal cord before syrinx development in some patients.[27,30]

In situations in which partial obstruction of the subarachnoid space occur (e.g., in Chiari malformation), the Venturi effect contributes to decreased subarachnoid pressure (Fig 3, 4c). The Venturi effect (also known as the Bernoulli theorem) states that total mechanical energy of flowing fluid remains constant implying that increased fluid velocity in a narrowed flow channel decreases hydrostatic pressure in the fluid. This type of mechanism lifts the wings of aircraft. When the subarachnoid space is obstructed

(e.g. dorsally within the foramen magnum by displaced cerebellum), CSF displaced by each systole is forced through the narrower opening resulting in high velocity jets of CSF ventrally in the foramen magnum[31] (Fig 5a, b). In accordance with the Venturi effect, this high velocity jet paradoxically decreases the hydrostatic pressure in the subarachnoid space as compared to that in the cord and causes a "suction effect" (i.e. centrifugally directed transmedullary pressure gradients that distend the spinal cord at and immediately below the obstruction). Again, repeated spinal cord distension results in extracellular fluid accumulation and eventually syringomyelia. The Venturi effect also explains why syringomyelia can develop at a distance from the obstruction of systolic CSF flow at the foramen magnum (i.e. in any part of the spinal cord including the medullary conus). The reason for this extended Venturi effect in Chiari malformations is that the piston-like downward motion of the displaced caudal cerebellum increases systolic pressure transmission to the spinal subarachnoid space. In this way, a shock-like CSF pressure wave is created that affects all parts of the vertebral canal.

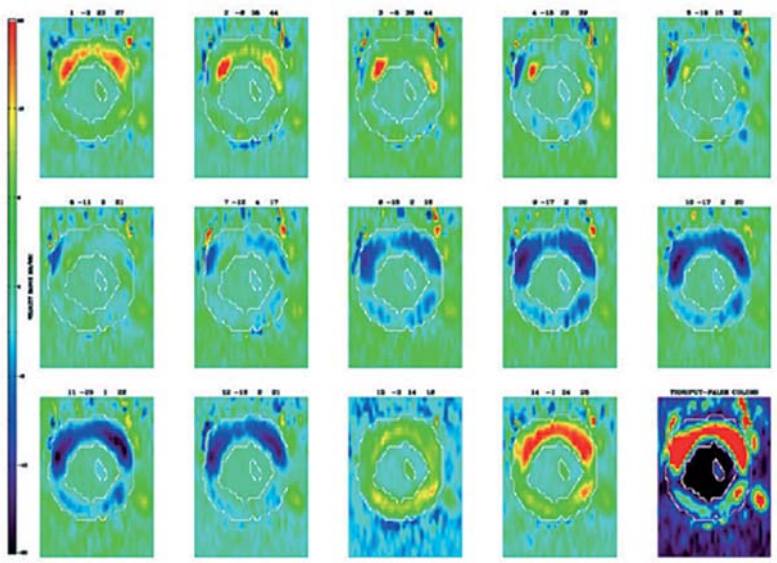

Figure 5a Colour plots of velocities representing the foramen magnum through 14 time points of the cardiac cycle (the last plot is a through-put). Rostral flow velocities are displayed in green, yellow and red with green being the slowest and red the fastest; caudal flow is displayed with light blue, deep blue, violet/black, with light blue being slowest and violet/black faster. In this child with a Chiari I malformation abnormal jets of abnormally high velocities occur in the anterior quadrants of the foramen magnum (note the red colour for velocities nearing 10cm/second in the plots displaying rostral velocities, and the black colour in the plots displaying caudal velocities).

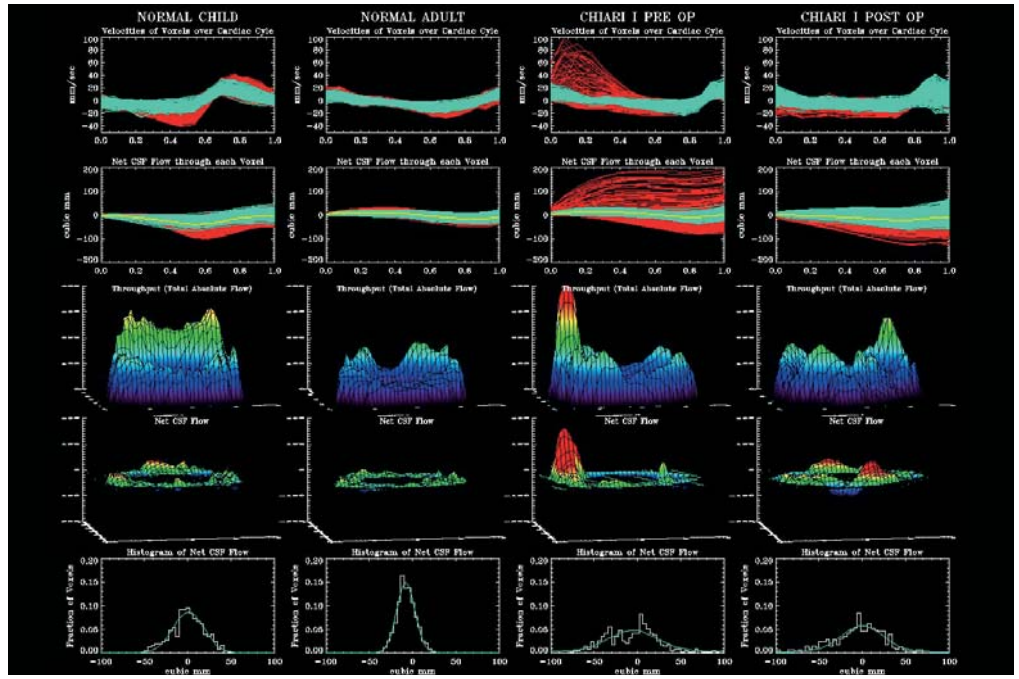

Figure 5b Surface plot images of a normal child, normal adult and child with Chiari I malformation pre- and post-operatively (left to right). In the upper row, each curve represents the velocity in one voxel though the cardiac cycle. The red traces represent the anterior half of the subarachnoid space, and are significantly increased in the preoperative Chiari I child. The green traces represent the posterior half of the subarachnoid space, which tend to be near normal in the Chiari I child. In the second row, cumulative flow volume in each voxel over time (a constant fraction of the cardiac cycle) is displayed in each voxel; anterior voxels are represented in red and posterior voxels are green. Although there are significant abnormalities in selected voxels, the mean CSF cumulative flow in all voxels (yellow trace) is zero. In the third row, the magnitude and spatial distribution of net CSF flow (cumulative CSF flow volume over the entire cardiac cycle) is represented as a surface plot. (Negative net flow volumes are obscured by the plane of the surface). In the normal patients most of the voxels display very little net flow. In the preoperative Chiari I child, a large number of voxels have non-zero net flow at the end of the cardiac cycle. Postoperatively, the net flow in each voxel approaches that of normal. In the fourth row, the figures represent through-put (sum of the absolute value of the velocities in each voxel at different time points in the cardiac cycle). The preoperative Chiari I child had high velocity jets exhibiting a large net rostral flow. This decreased significantly after surgery. The bottom row shows the distribution of the net cumulative flow. Normal subjects show a narrow Gaussian-like distribution, implying that the amount of non-zero cumulative flow volume is determined by random factors. The pre-operative Chiari I child has two distinct distributions: one for the jet and one for the remainder of the non-jet subarachnoid space. The overall distribution is significantly wider than that of the normal subjects. Postoperatively the histogram has a Gaussian-like distribution similar to the normal adult.

The most common location of syringomyelia is in the cranial or middle cervical spinal cord, often with a syrinx-free segment in the most cranial part of the cervical spinal cord (Fig 1). The first cervical spinal cord segment is usually protected from spinal cord cavitation and the suction effect by the increased counter-pressure caused by the moving herniated part of the cerebellum. The cross-sectional area of the vertebral canal varies slightly in dogs with small encroachments at the intervertebral levels. Due to increased CSF velocity at the intervertebral disc level, the Venturi effect is increased and may explain why the syrinx often develops over the first intervertebral disc space in dogs (i.e. within the C2-C4 spinal cord segments) and at the thoracic inlet where there is a narrowing in the diameter and change in angulation of the vertebral canal (Fig 3, 4c, 6). If a slightly bulging disc is present in the lower cervical region in humans, cavitation usually starts immediately below that level.[2] The segmental character with minor intervertebral encroachments of the subarachnoid space contributes to progression of the syrinx.

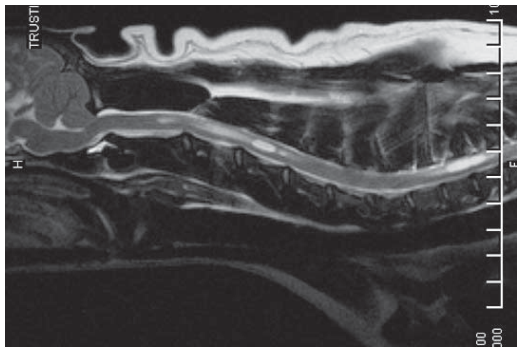

Figure 6 Midsagittal T2-weighted image of the caudal fossa, cervical and cranial thoracic spinal cord of a 20-month-old female CKCS. MRI was being performed as a screening for suitability for use in a breeding program and at the time of the imaging the dog had no clinical signs related to syringomyelia. Syringomyelia is present from C2 to C5 and from T1 toT3. There is noticeable narrowing of the ventral subarachnoid space at the C2/C3 and C7/T1 disc levels implying an increased Venturi effect in these regions. The change in angulation of the vertebral canal at these levels may also contribute to this effect.

Once formed, the syrinx further decreases the cross-sectional area of the subarachnoid space, which in combination with the increased CSF velocity and Venturi effect may cause self-progression of the syrinx. Progression also occurs in accord with the *slosh* and *piston effect* by systolic compression of the upper part and dilatation of the lower part of the syrinx.

Any subarachnoid obstruction decreases craniospinal compliance. Compliance is the "giving property" of a system and craniospinal compliance is decreased by 50% in Chiari malformations.[24] The decreased compliance significantly increases the driving force of syringomyelia (i.e. the CSF pulse pressure). There is an even greater increase in intracranial and spinal systolic pulse amplitude during and immediately after Valsalva manoeuvres such as straining or coughing.[24, 32] The exaggerated systolic pulse pressure explains why patients with Chiari malformations often experience rapid worsening of clinical signs during or immediately after such activities.

In 2004, Levine proposed a *vascular theory*.[20] When the foramen magnum is obstructed, there is a tendency for transiently higher CSF pressure above the obstruction than below it. Consequently, blood vessels tend to dilate below the obstruction and collapse above it. The spatially uneven change in vessel calibre produces mechanical stress on the spinal cord, particularly caudal to the obstruction. The mechanical stress, coupled with venous and capillary dilatation, partially disrupts the blood–spinal cord barrier, allowing ultrafiltration of crystalloids and accumulation of a protein-poor fluid. This theory is basically a variant of the *intramedullary pulse pressure theory* and like that theory offers an explanation for why syrinx pressure is higher than CSF pressure; why extensive gliosis, edema, and vascular wall thickening regularly occur; and, why the composition of syrinx fluid is not identical to that of CSF[20].

At the present time, the exact mechanism of syrinx development and progression still remains unclear. The main debates appear to be: 1) Does the syrinx form because of increased pressure in the subarachnoid space or because of increased pressure within the spinal cord? 2) What is the source of the fluid within the syrinx – CSF or extracellular? As first shown experimentally by Greitz and others[27], most researchers now are concluding that syringomyelia represents a collection of extracellular fluid but the exact mechanism of its accumulation still is under debate[33].

Clinical signs of syringomyelia

By far the most important clinical sign of syringomyelia is pain.[14, 34, 35] Pain is most commonly localized to the cervical region but may be intermittent and difficult to localise. Owners may report that their dog is worse at night, when first getting up, during hot or cold temperature extremes, when excited, or related to posture (e.g. preferring to sleep with its head elevated). Affected dogs may be overly sensitive to touch on one side of the head, neck, shoulder or sternum. In addition, affected dogs often scratch at one area of the shoulder, ear, neck or sternum. Scratching typically occurs on one side only, while the dog is moving and sometimes without making skin contact.[14]

The pain experienced by animals with syringomyelia is likely to be multifactorial and related to obstruction of CSF flow and spinal cord damage. Humans with syringomyelia report headache, suboccipital or neck pain, back pain, trigeminal pain (i.e. facial pain) and radicular pain (e.g. pain that radiates into the lower extremity; pain that has a cape like distribution over the shoulders in syringomyelia).The most disabling pain however is dysesthesia which variously is described as burning pain, hyperaesthesia, "pins and needles" and stretching or pressure of the skin.[35] Dysesthetic pain may be sympathetically mediated and sympatholytic treatment affords relief. [35]

Signs of pain are not well correlated with the size of the syrinx, i.e. human or animal patients with bigger or longer syrinxes are not necessarily in more pain than those with smaller syrinxes.[34, 36] Damage to the dorsal horn is a key feature in the chronic pain of syringomyelia (Fig 2).[35] Human patients with deviated syrinx, especially if deviated into the dorsal horn, were unlikely to have their pain improve even after successful surgery.[34] The duration of pain also was a significant feature (i.e. those who had experienced their symptoms longer were less likely to recover).[34] The dorsal horn of the spinal cord is the most important relay centre for transmission of sensory information to the brain and is subject to a great deal of plasticity, both pharmacological and physiological, in persistent pain states. [37] Expression of substance P in the dorsal horn is altered in syringomyelia and much research now is focused on the changes in neurotransmitters and neuromodulators after injury or development of a syrinx.[38] Clarifying the mechanism of pain will allow development of new avenues of pain management.[38]

Some dogs, more commonly younger patients, develop scoliosis with syringomyelia.[14] It was originally thought that scoliosis was due to unilateral ventral horn cell damage, unequal paraspinal muscle atrophy and muscular imbalance. It appears more likely however that syringomyelia extending into the dorsal grey column over a number of spinal cord segments on one side results in an imbalance of afferent information from the cervical neuromuscular spindles. This unilateral loss of proprioceptive information leads to scoliosis with the neck curving away from the lesion.[39] Humans with Chiari malformation and scoliosis do not necessarily have syringomyelia and the mechanism of scoliosis is not well understood.[40]

Dogs with syringomyelia may have 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).[14] Facial nerve paralysis[14] and deafness[41] have also been associated with the condition in the CKCS. Idiopathic facial paralysis is common in the CKCS as is hearing impairment.[42] Hearing loss and vestibular signs have been documented in human patients with Chiari malformation but these complication typically occur for those with bulbar extension of the syrinx. [43] To the authors' knowledge, none of the documented canine cases [14,41]of syringomyelia with facial paralysis or deafness had bulbar extension of the syrinx and an association has yet to be established. CKCS with syringomyelia and ventricular dilatation secondary to caudal fossa crowding also may be presented with seizures but idiopathic epilepsy also is common in this breed [1] and this association also may be circumstantial.

The first clinical signs of syringomyelia secondary to caudal fossa overcrowding in CKCS typically are recognized between 6 months and 3 years of age. However, dogs of any age may be presented, and dogs with more severe lesions tend to be presented before 2 years of age. [1] Progression of the condition is very variable. Some dogs only have a tendency to scratch with mild pain and other neurological signs such as paresis develop slowly or not at all. Other affected dogs can be severely disabled by pain and neurological deficits within 6 months of the first signs observed. Syringomyelia also may be found as an incidental finding, with no recognized clinical signs, in the investigation of another neurologic disease.[36]

Diagnosis of syringomyelia

MRI is essential for diagnosis of syringomyelia (Fig 1). Syrinx fluid has the T1 and T2 relaxation characteristics of CSF and multiplanar imaging allows assessment of the width, dorsal horn involvement, and longitudinal extent of the cavity. 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.[2, 20] Syringomyelia however is merely the effect of an obstruction within the subarachnoid space, and the goal of imaging is to determine the cause of the syringomyelia. In the instance of Chiari-like malformation, the occipital bone is presumed to be small resulting in a reduced caudal fossa volume, the caudal cerebellar vermis and medulla extend into or through the foramen magnum, and there may be ventricular dilatation[14].

The advent of phase contrast MRI which can demonstrate CSF flow (i.e. cine MRI) has greatly improved diagnostic capability in humans. For example, the diagnosis of clinically significant Chiari malformation previously was made on the basis of the size of tonsillar herniation, with greater than 3 to 5mm being significant. [44] However Milhorat et al showed that the size of the herniation was not related to clinical signs and that the most important factor was decreased cerebellomedullary cistern volume, smaller posterior fossa and decreased CSF flow around the tonsils as identified by cine MRI. [44] Another study yielded similar results and also determined that postoperative cine MRI findings correlated with success (i.e. patients with restored CSF flow had improvement in symptoms).[45] Cine MRI is most useful in cases of borderline Chiari malformation, in demonstrating other CSF obstruction; or when the question of whether decompression is needed is not readily answered using traditional MRI.[31] Studies now are focusing on the complex flow patterns at the foramen magnum in human patients with Chiari malformation. Techniques that assume homogenous CSF flow may be too simplistic and measurements of bulk flow or CSF velocity cannot distinguish symptomatic from healthy individuals. [31] Iskandar et al found that children with Chiari I malformation had a marked heterogeneity of flow at the foramen magnum which resolved after successful surgery.[31] The flow abnormalities documented included bi-directional flow with high velocity jets of CSF displaced by each systole forced through a narrower opening, typically anterior in the foramen magnum (Fig 5).[31]

Cine MRI requires additional software and ECG monitoring which is available to veterinarians, and hopefully in the future we will discover whether this diagnostic modality is useful for small animals. A preliminary study in a group of 30 dogs[46] has indicated that non-invasive cine MRI can be performed and that CSF flow is abnormal in dogs with caudal fossa abnormalities.[46]

Treatment of syringomyelia

In humans, a small and asymptomatic syrinx often will not require treatment[2] and the same probably is true for small animals. Thus an argument can be made for monitoring such patients with serial MRI scans. For canine patients, surgical management is indicated when analgesics do not control discomfort or when

neurological deficits are present. Medical management may be chosen for patients with only mild pain, when finances do not allow surgical management, or when surgical management has failed to resolve the signs.

Medical

Long-term studies of medical management of syringomyelia are not yet available. Figure 7 illustrates the treatment algorithm currently used by one of the authors (CR). The drugs used can be divided into 3 types: analgesics, drugs that reduce CSF production, and corticosteroids. Pain in mild cases may be controlled by non steroidal anti-inflammatory drugs (NSAIDs).[14] In more severe cases anticonvulsants (which have a neuromodulatory effect on the hyperexcitable damaged nervous system) may be useful (e.g. gabapentin[a]).[47] Oral opioids (e.g. pethidine[b] or methadone[c]) also are an alternative.

Proton pump inhibitors such as omeprazole[d] can inhibit CSF formation and therefore may be useful in decreasing CSF pulse pressure,[48, 49] but clinical data on their use and effectiveness currently are lacking. They may not be suitable for long-term management and a maximum of 8 weeks of therapy has been recommended because chronic gastric acid suppression results in hypergastrinemia and increased risk of carcinoids in laboratory animals.[50] Carbonic anhydrase inhibitors such as acetazolamide[e] also decrease CSF flow[51,52, 53] and also may be helpful in treating syringomyelia[14] but adverse effects of abdominal pain, lethargy and weakness may limit long-term use (Clare Rusbridge, unpublished findings). Furosemide[f] also decreases intracranial pressure[54, 55] and therefore could be useful in the treatment of syringomyelia. Furosemide's effect however may be due to diuresis and reduction in blood volume and one study found no effect on CSF pressure in nephrectomized dogs.[56]

Corticosteroids are very effective in decreasing both pain and neurologic deficits[14] although the exact mechanism is not known. Corticosteroids may decrease CSF pressure[57] but laboratory evidence of this effect is lacking.[58] Corticosteorids possibly have a direct effect on pain mediators such as substance P.[59] Although corticosteroids may be effective in limiting signs and progression, most dogs require continuous therapy and subsequently develop adverse effects such as immunosuppression, weight gait and skin changes.[14]

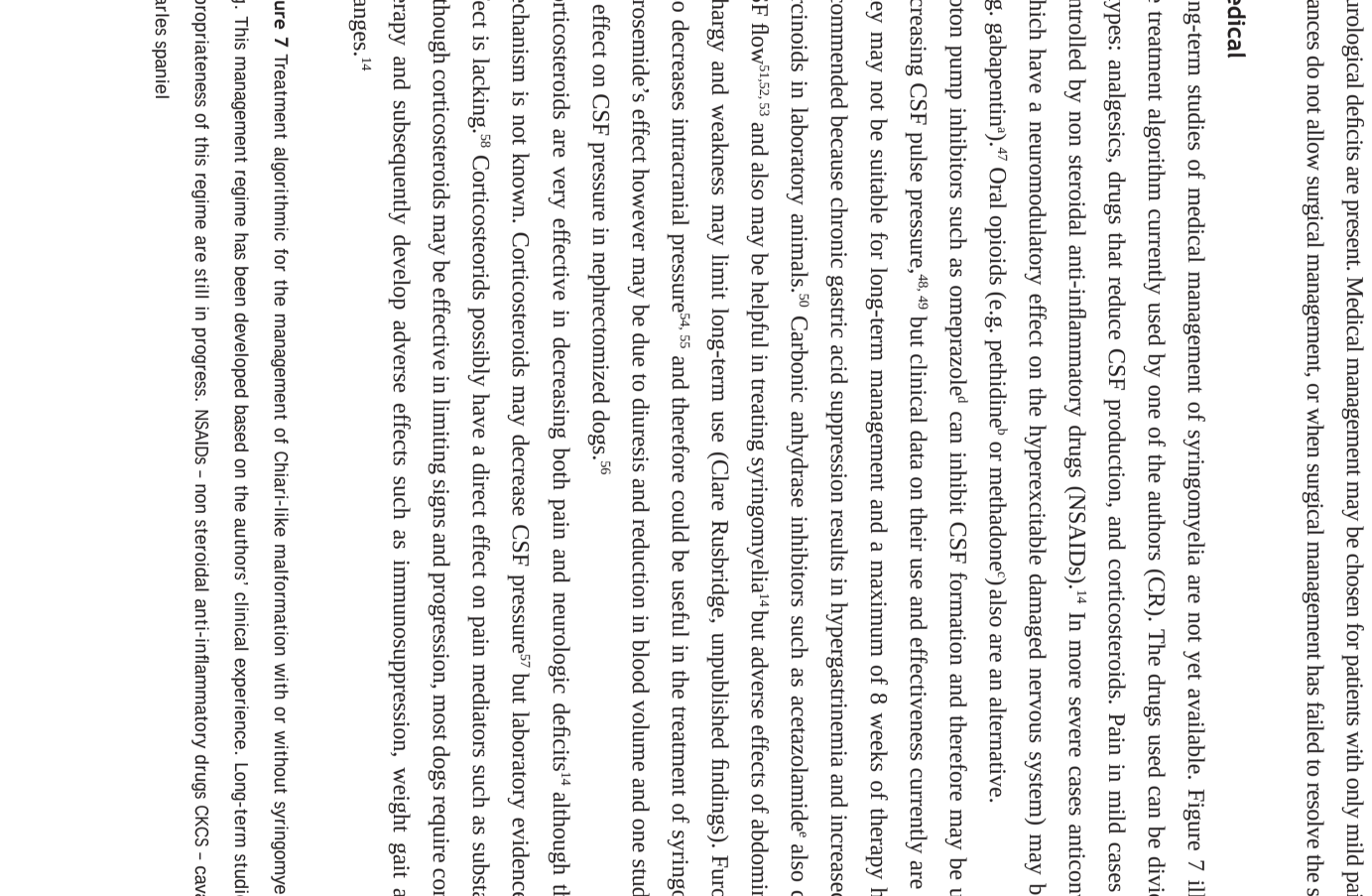

Figure 7 Treatment algorithmic for the management of Chiari-like malformation with or without syringomyelia in the dog. This management regime has been developed based on the authors' clinical experience. Long-term studies on the appropriateness of this regime are still in progress. NSAIDs – non steroidal anti-inflammatory drugs CKCS – cavalier King Charles spaniel

Surgical

Surgical management is indicated for dogs with refractory pain or with worsening neurologic signs. The aim of surgery is to restore CSF dynamics and if this effect can be achieved (e.g. by removing or debulking a tumour) then the syrinx can resolve.[60] The most common procedure for caudal fossa overcrowding is cranial cervical (also referred to as foramen magnum or suboccipital) decompression in which the supraoccipital bone and sometimes the cranial dorsal laminae of the atlas are removed (with or without a durotomy) to decompress the foramen magnum.[15, 61, 62, 63] Success reported in the small number of dogs in these studies varied from no improvement [62] to resolution of clinical signs.[15 63] The largest case series of 16 dogs found that 81.25% of affected dogs had improvement or resolution of clinical signs after surgery, but 25% had a recurrence within the follow-up period. This report also indicated that successful postoperative outcome was more likely if surgery was performed early in the course of the disease.[63] There have been no reports of resolution of syringomyelia after cranial cervical decompression in the dog, but this impression may be in part due to lack of postoperative MRI scans due to financial reasons. Syringo-subarachnoid shunting also has been described. [64]

The general principle for surgical management of humans with syringomyelia is that treatment should be directed at the etiology of the syrinx. [2] Cranial cervical decompression is generally the first procedure of choice for symptomatic humans with Chiari malformation, and it is widely acknowledged that direct draining of the syrinx is not associated with a good long-term outcome because stents or shunts become obstructed and can result in tethering [2]. Shunting to the subarachnoid space or to the pleural cavity is only indicated when the syrinx persists or is progressive after suboccipital decompression.[2, 65] There is great variation in the type of cranial cervical decompression performed. One key argument focuses on whether or not to open the dura. Most surgeons favour routine dural opening at surgery and closure with a pericranial or synthetic patch graft.[2,65] The arguments against dural opening are that this procedure increases the complication rate. Advocates however argue that up to 55% of patients have extensive scarring and other obstructions to CSF flow that can only be identified and removed by durotomy. [66, 67] Some recommend intraoperative ultrasound to tailor surgery to the individual and ensure that optimal CSF flow through the foramen magnum is achieved. [68]

Another crucial issue in surgery for Chiari malformation is the number of patients requiring two or more surgeries. Most large case series in human medicine report a failure rate of at least 10%. [68,69] Researchers have been unable to identify a single reason for surgical failure. [65, 66]. Also of concern is the number of patients with persistent pain post-operatively. Approximately 41% of humans with symptoms of dysesthesia who undergo decompressive surgery for syringomyelia have persistence or intensification of pain post-operatively. Conventional medications such as NSAIDS, opioids and gabapentin provide minimal or no relief and, based on response to sympathetic blockade, pain is thought to be sympathetically mediated. Most human patients gradually improve over several months but in many persistent unpleasant sensations persist.[70] As previously mentioned, damage to dorsal horn and duration of signs are thought to be significant [35,39] and, in a study of persistent post-operative dysesthetic pain, 84% of patients experienced extension of the syrinx into the dorsolateral quadrant of the spinal cord on the same side and level of the pain.[70] In conclusion, our understanding of syringomyelia that results from caudal fossa abnormalities, specifically its pathogenesis and exact relationship to the clinical syndrome still is incomplete. The new theories based on physical principles seem promising and may shed new light on the pathophysiology of syringomyelia. This disorder is an area of active research and it is hoped that the recent description of a naturally-occurring animal model of the condition in the CKCS will encourage the veterinary profession to contribute to the understanding of this debilitating condition.

Foot notes

a. Neurontin 100mg capsules, Pfizer Pharmaceuticals, Ltd. Vega Baja, PR 00694
b. Pethidine hydrochloride 50mg Martindale Pharmaceuticals, Romford, Essex, RM3 8UG
c. Methadone Hydrochloride tablets usp 5 mg, 10 mg, Physeptone, Martindale Pharmaceuticals, Romford, Essex, RM3 8UG
d. Losec capsules 10, 20, and 40 mg; AstraZeneca, Hurdsfield Industrial Estate, Macclesfield, Cheshire, SK10 2NA
e. Diamox 250mg tablets, Lederle Laboratories, Gosport, UK
f. Frusemide tablets 20 and 40mg; Millpledge Pharmaceuticals, Whinleys Estate, Church Lane, Clarborough, Retford, Notts, DN22 9NA
g. Rimadyl Palatable Tablets 20 and 50mg; Pfizer Limited, Ramsgate Road, Sandwich, Kent CT13 9NJ
h. Medrone tablets 2 and 4mg; Pfizer Limited, Ramsgate Road, Sandwich, Kent CT13 9NJ

Acknowledgements

The authors are grateful to Dr Mark Quigley of the Department of Astronomy, University of Wisconsin for his help and expertise in the preparation of Figures 5a and b. The authors also thank Dr Jan Rothuizen for his critical appraisal of the manuscript.

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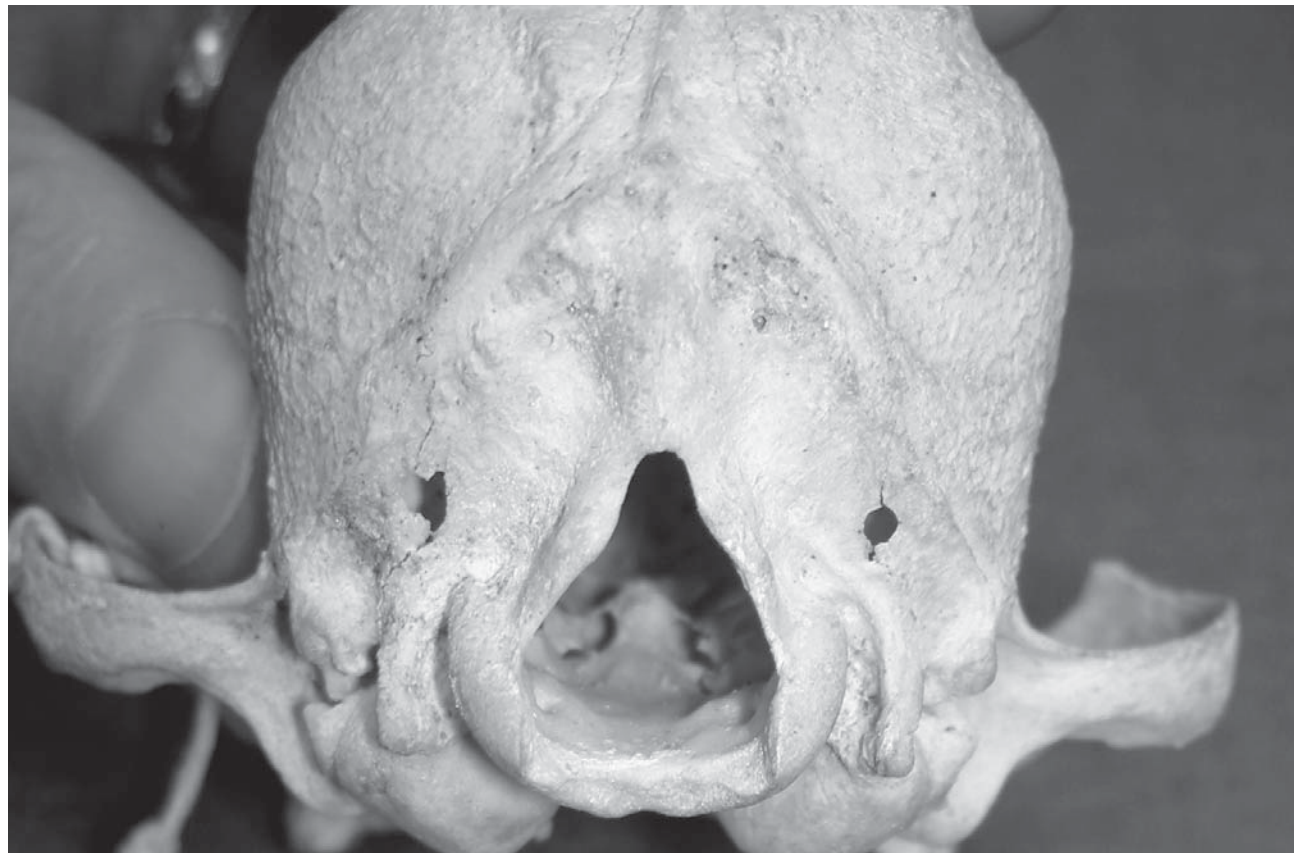

Section 3

Comparison of occipital hypoplasia
(Chiari-like malformation) and occipital dysplasia

Chapter 3.1

Co-existence of occipital dysplasia and occipital hypoplasia/syringomyelia in the cavalier King Charles spaniel

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Journal of Small Animal Practice
2006; 47, 603-606

Introduction

The foramen magnum is a ring of bone formed from 4 occipital bone centres; the supraoccipital bone dorsally, the basilar part ventrally and the exoccipitals which bear the occipital condyles laterally (Evans 1993). In addition to providing an exit for the spinal cord, the foramen magnum allows cerebrospinal fluid (CSF) to shunt rostrally and caudally between the head and spine. This rapid efflux and influx compensates for brain expansion and contraction during the cardiac cycle (Oldfield and others 2001). Obstruction to CSF movement can result in development of syringomyelia, a condition whereby fluid containing cavities develop within the spinal cord. The most common cause of syringomyelia in veterinary medicine is occipital bone hypoplasia (Chiari-like malformation) (Rusbridge and others 2000) which is inherited in the cavalier King Charles spaniel (CKCS) and may be seen in other toy breeds (Rusbridge and Knowler 2003, 2004). It is hypothesised that the basi and possibly supraoccipital bone are shortened reducing the volume of the caudal fossa. The cerebellar vermis is often pushed through the foramen magnum and the

medulla is deviated dorsally. Syringomyelia may vary in severity, but for many affected animals is a debilitating neurological disease with clinical signs such as dysesthesia, cervical/occipital pain, paresis, ataxia and scoliosis. One of the most common signs is a tendency to scratch at the shoulder or neck area. The scratching is unlike that seen with ear and skin disease. Generally the dog moves and scratches at the same time; makes minimal or no skin contact; often cries whilst scratches; and initially does it only to one area within the dermatome corresponding to the area of damaged spinal cord.

Other abnormalities of the development of the canine occipital bone are recognised, in particular, occipital dysplasia where there is incomplete ossification of the supraoccipital bone resulting in a widening of the foreman magnum (Parker and Park 1974, Watson and others 1989). This defect varies from a small dorsal notch resulting in a keyhole shaped foramen magnum to a wide midline defect. Watson and others (1989) examined the shape of the foramen magnum in 36 dogs (33 Beagles) and found a considerable variation in the shape of the foramen magnum even within the same breed; the more brachiocephalic the skull the more likely there was occipital dysplasia. In all cases the bony defect was covered by a tough connective tissue membrane which extended as far as the nuchal tubercles so, despite the bony defect, the functional shape of the foramen magnum opening was oval and brain prolapse was prevented. Watson and others (1989) also demonstrated that the presence or absence of the dorsal notch of the foramen magnum is primarily due to variations in the degree of ossification of the ventromedial part of the supraocciptial bone and the authors concluded that it should be regarded as a variation not an anomaly as it did not appear to be associated with any impairment of function. In contrast, Parker and Park (1974) did find neurological deficits in some of the dogs (miniature and toy poodles, Yorkshire terriers, Lhasa apsos, Chihuahuas, Beagle, Pomeranian, Shih Tzu and Maltese) they studied, however it was not established whether these were related to occiptial dysplasia. Some of the dogs had concurrent hydrocephalus. Syringomyelia was not reported as a finding in any of the cases that received a post mortem and in no cases was there any apparent permeant protrusion of the cerebellum into the spinal canal. However not all the dogs had a full post mortem and examination of the spinal cord for syringomyelia. In particular three dogs with a large dorsal notch and a long standing history of ataxia did not have post mortem examination.

In this report two dogs with concurrent occipital dysplasia and hypoplasia with secondary syringomyelia are described. The dogs were related to each other and to other dogs with occipital hypoplasia and secondary syringomyelia but without occipital dysplasia.

Case history

Dog V

A 10 year old male CKCS was presented for examination as the owner was concerned about the possibility of occipital hypoplasia/syringomyelia. This popular stud dog had been identified in a previous study (Rusbridge and Knowler 2003) as being an important ancestor in an extended family of CKCS

with syringomyelia secondary to occipital bone hypoplasia and he was the sire and grandsire of several magnetic resonance imaging (MRI) confirmed cases. The only reported irregularity was he had a mild tendency to scratch at his right mid cervical area. This had been noticed since he was approximately18 months old. There were no other neurological deficits at this time. Ten months after the initial examination the owner reported that he was becoming more sensitive around his right ear and over the following three months he developed tetraparesis more severe on the right with more severe pain. He deteriorated to the stage that the owner elected for him to be euthanatised. Gross post mortem findings are illustrated in Figure 1 a and b.

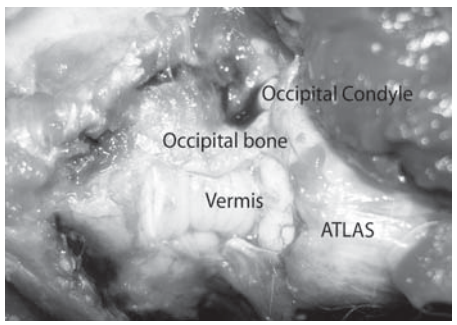

Figure 1a Gross anatomy of the occipital and cranial cervical area in dog V. The neck is flexed. The defect in the occipital bone was originally covered by a tough connective tissue membrane. When the head was in a normal position the cerebellar vermis extended through the foramen magnum.

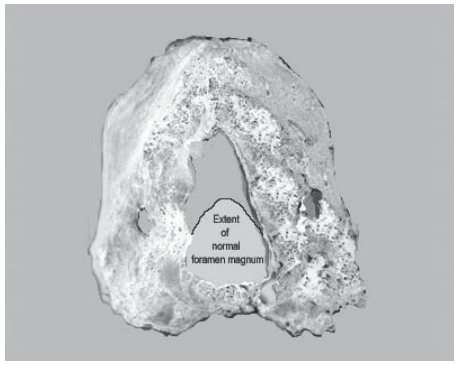

Figure 1b The occipital bone from dog V illustrating the extensive dorsal widening of the foramen magnum

There is a large defect in the supraoccipital bone which was originally covered with a tough membrane that was confluent with the atlantooccipital membrane. In a normal neck position the cerebellum extended into the foramen magnum. There were no other gross lesions that could provide an explanation for the neurological signs and histopathological examination confirmed syringomyelia (Figure 1c).

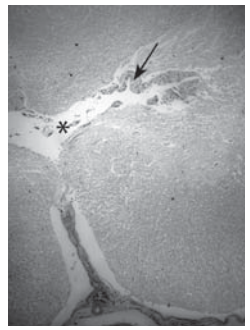

Figure 1c Cross section of the cervical spinal cord from Dog V. There is an irregularly shaped cavitation of the cord (asterixis) centred upon the spinal canal and extending as fissures into adjacent grey and white matter. Focally the cavitation extends to the dorsal and ventral subdural space. The cavities are bordered by frayed parenchyma. There is a little neovascularization, accompanied by a few macrophages, in the wall of the central areas of the cavities (arrow). (Trichome x 40)

A simplified familial relationship between Dog V and other dogs with occipital hypoplasia/syringomyelia is illustrated in Figure 2. For the majority of dogs it is not known whether or not there is concurrent occipital dysplasia as this cannot be readily appreciated on MRI. However there were two descendants where the occipital bone was inspected intraoperatively. Dog T (grandson) and dog O (great grandson) had onset of the signs of syringomyelia at 14 and 28 months respectively. Both had severe signs of pain and neither could be exercised as a consequence. Both were confirmed by MRI and subsequently had a suboccipital craniectomy with atlas cranial laminectomy and durotomy to relieve the obstruction at the foramen magnum. In both dogs there was no dorsal notch to the foramen magnum, i.e. no occiptial dysplasia.

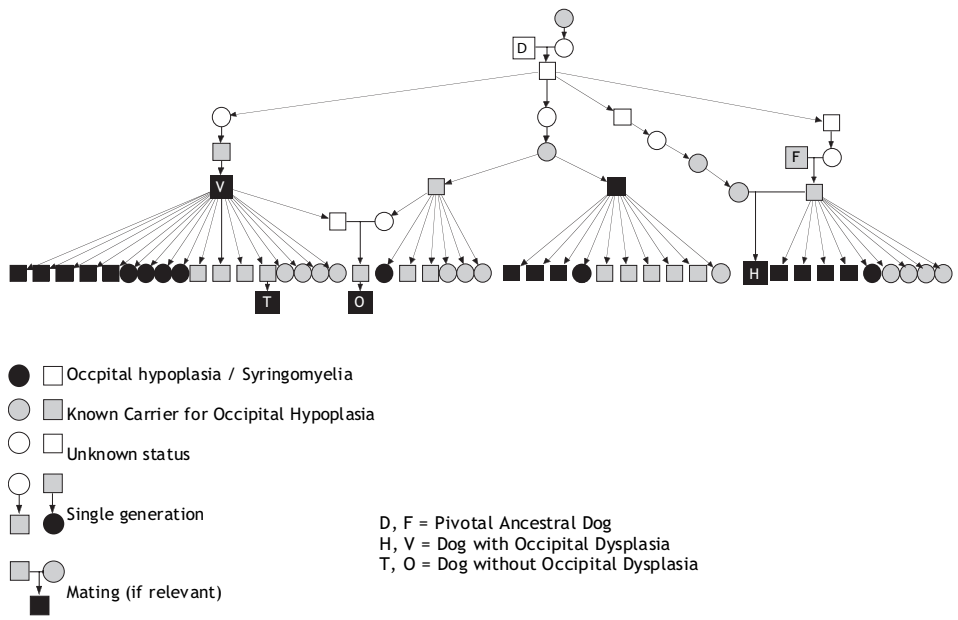

Figure 2 Simplified diagram of one familial relationship between dogs V, H, T and O. The pivotal ancestral dogs had been identified in previous studies (Rusbridge and Knowler 2003, 2004).

Dog H

Dog H was an 8 year old male CKCS with a five year history of brief episodes of unexplained pain. These episodes had become more frequent over the last six months. There was an approximate nine month history of a tendency to scratch at the shoulders (both sides) with a six month history of pelvic limb ataxia and a three week history of thoracic limb weakness. A scoliosis had also been noticed. There had been a partial but not sustained response to 4mg methylprednisolone daily (Medrone; Pfizer) and 200mg gabapentin (Neurontin; Pfizer) twice daily. Neurological examination revealed a bilateral thoracic limb weakness more severe on the right. There was carpal hyperextension of this limb with atrophy of the shoulder muscles and a tendency to stumble. Proprioceptive responses were delayed in the pelvic limbs. A tendency to scratch at the right shoulder was noted. MRI of the brain and vertebral column revealed a small caudal fossa, overcrowding of the foramen magnum and syringomyelia from the level of C1 to L3/L4 (Figure 3).

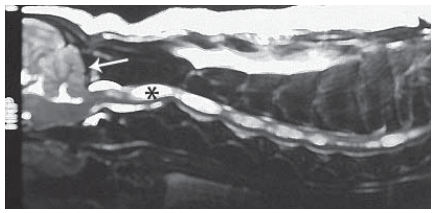

Figure 3 Midsagittal TW2 weighted image of the caudal brain and cervical spinal cord form Dog H. The arrow indicates the occipital bone; the occipital dysplasia cannot be appreciated. The asterixis illustrates the syringomyelia.

The width of the syrinx was variable, and at its maximum at the level of C2, was two thirds of the diameter of the spinal cord. Cervical scoliosis was confirmed. Other than the hypoplasia no other irregularity of the occipital bone was identified. The caudal fossa had been imaged in both sagittal and axial orientations. Due to the rapidly progressive clinical signs and inadequate response to corticosteroids and gabapentin the owner elected for surgical management. A standard approach to the caudal fossa was made. When the supraoccipital bone was exposed it was apparent that it was dysplastic. There was an arch shaped dorsal widening of the foramen magnum. The bony defect was filled by a thick membrane. Above the bony defect there was a band of normal bone (3mm wide) above which was another hole 5mm x 3mm. The bony defect was widened and the thick connective tissue membrane over the defect and the thickened atlantooccipital membrane were removed. The surgery was then continued with a cranial C1 laminectomy which was extended to ~5mm below the tip of the vermis (about 1/3 length of the atlas arch). Finally a durotomy was made from just below the tip of the vermis to the level of the foramen magnum. This allowed further decompression of the cerebellum and allowed the surgeon to ensure that the vermis had been adequately exposed and to facilitate removal of arachnoid adhesions (there were none). The resulting triangular defect was patched with biocompatible collagen matrix (Vet BioSISt ™ ; Cook/ Global Veterinary Products). Closure was routine. Three weeks after surgery the owner reported a marked improvement in demeanour, exercise tolerance, strength and coordination. The scratching behaviour had reduced. The familial relationship of dog H to dog V is illustrated in Figure 2.

Discussion

The occipital bone forms from fusion of the mesenchyme of at least 3 occipital somites (Marin-Padilla 1991). The mesenchyme forms cartilage which in turn undergoes the process of endochondral ossification to form bone. In addition there is membranous tissue caudal to the cartilaginous supraoccipital bone plate which undergoes intramembranous ossification and ultimately fuses to the cartilaginous part. (Matsumura and others 1994). It is proposed that occipital dysplasia occurs when the ventromedial portion of the developing supraoccipital bone fails to ossify (Watson and others 1989). In contrast it is proposed that occipital hypoplasia occurs because of an early paraxial mesodermal insufficiency (Marin-Padilla 1991). Occiptial dysplasia appears not to cause a functional problem because the overall shape and size of the caudal fossa are unchanged. In contrast occiptial hypoplasia results in a reduced volume caudal fossa which in turn can lead to the development of syringomyelia. Occipital dysplasia is common in dogs with a rounded skull shape (Watson and others 1989) and occipital hypoplasia is common in the CKCS therefore it is not surprising that the two conditions should occur in the same dog. What is unusual about dogs V and H is that the progression of the signs of syringomyelia was initially very slow and neither dog displayed severe signs until middle to old age. The majority of dogs with syringomyelia secondary to occipital hypoplasia present with severe compromise before 7 years of age (Rusbridge and other 1997). It is possible that the membrane covering the supraoccipital defect allows for a dynamic expansion and less severe obstruction of CSF movement through the foramen magnum. As a consequence it is possible that syringomyelia could develop more slowly resulting in later onset signs. In other words, dogs with occipital hypoplasia and dysplasia potentially may have a milder phenotype than with occiptial hypoplasia alone.
If this is the case then there are implications for breeding. If the dog is a breeding male, then the mild or subclinical signs may not be recognised by the owner especially when the dog is young. If the dog becomes a popular stud dog then the potential for occipital hypoplasia but not necessary occipital dysplasia may be disseminated widely in the breed. Dog V sired over 50 litters and has hundreds of descendants across the world. Many breeders arrange for their potential breeding stock to have a brain and/or upper cervical MRI with the aim of selecting those without occipital hypoplasia/syringomyelia for at least one half of a mating. If the onset of syringomyelia has been delayed by occipital dysplasia then a dog may be erroneously thought to have a milder phenotype and used for breeding purposes. This is especially important if the screening is done before the age of 18 months. Occipital dysplasia is difficult to identify

on MRI however the foramen magnum can be radiographed in a manner described by Parker and Park (1994) with the dog in dorsal recumbency and with the nose flexed at 25-40º and the x-ray bean centred on the frontal sinus. CT is also likely to be useful. However before recommendations are made for screening it should be established what is acceptable and unacceptable – i.e. what degree of caudal fossa volume reduction leads to syringomyelia.

Conclusion

Occipital dysplasia may be seen in conjunction with occipital hypoplasia possibly resulting in less obstruction of the foramen magnum and later/slower onset of syringomyelia. However, the affected dogs may still pass on a tendency for a more severe phenotype to their descendants. The presence of occipital dysplasia in conjunction with occipital hypoplasia should be taken into account in any future studies on imaging, CSF flow or genotyping and further work is needed to establish whether occipital dysplasia does affect the pathogenesis of syringomyelia.

Acknowledgements

The authors are grateful to Alexander deLahunta for reading and commenting on this text and to Dr Andrew Torrance of TDDS Laboratories and Dr Malcolm Silkstone of Abbey Veterinary Services for preparing and interpreting the histology of Dog V.

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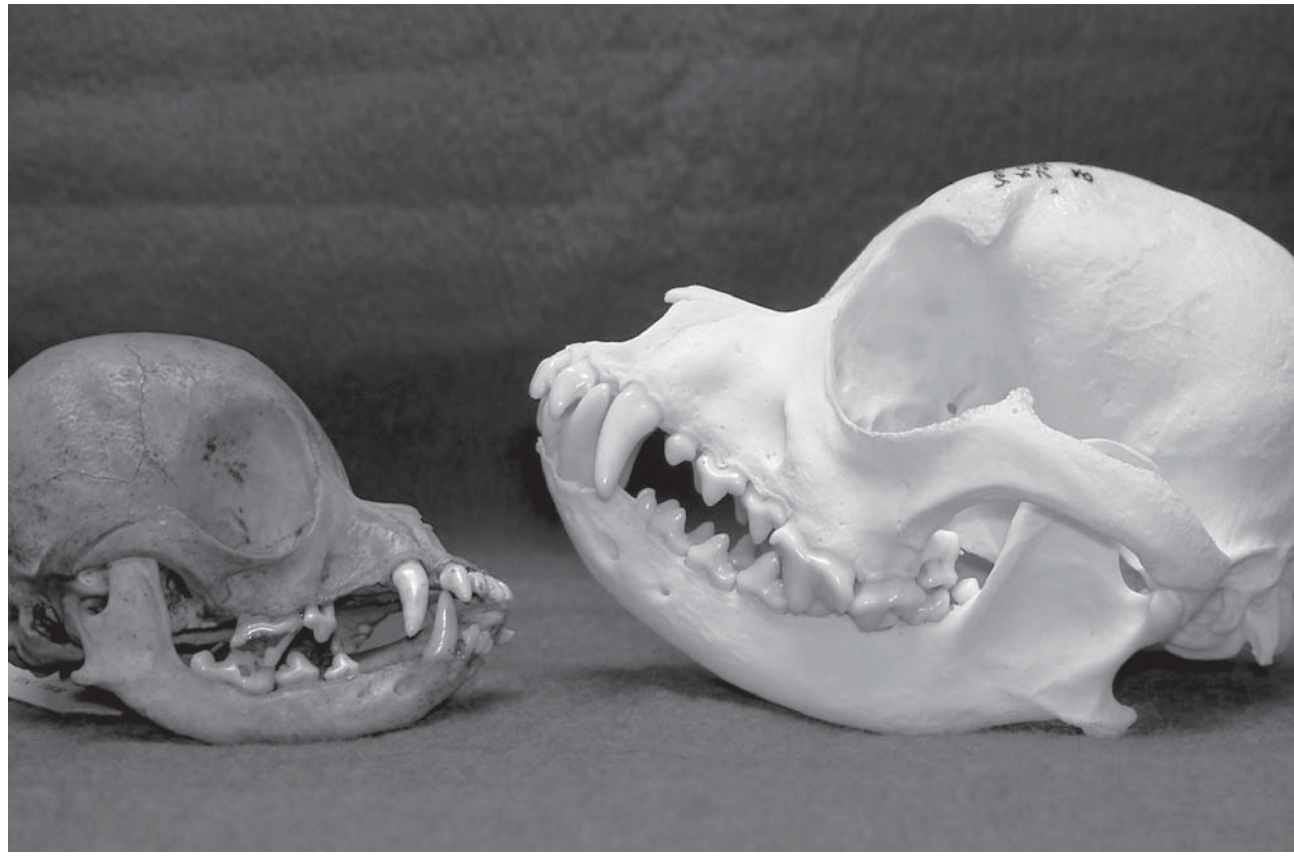

Section 4

Chiari-like malformation
in the cavalier King Charles spaniel

Chapter 4.1

Association between cervical and intracranial dimensions and syringomyelia in the cavalier King Charles spaniel

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Introduction

Since its first recognition in the 1990s (Rusbridge and others 2000), Chiari-like malformation (CM) of the skull, syringomyelia (SM) and their associated clinical signs have become well-known entities in the cavalier King Charles spaniel (CKCS). CM refers to the apparent mismatch in volume of the caudal brain structures to the caudal skull, which is associated with herniation of the most caudal aspects of the cerebellum through the foramen magnum (Rusbridge and others 2000). SM refers to the accumulation of fluid within the parenchyma of the spinal cord. CM is thought to cause SM through changes in the dynamics of CSF flow through the foramen magnum and in the cranial part of the cervical spinal cord (Pinna and others 2000, Iskander and others 2004, Rusbridge and others 2006) and occurrence of both disorders simultaneously is abbreviated to CM/SM in this paper.

Clinical signs typically associated with canine syringomyelia include apparent spontaneous neck or head discomfort, scoliosis and frequent scratching at the skin on the lateral aspect of the neck/ shoulder/ ear, often accompanied by signs suggesting pain, for example vocalisation (Rusbridge 1997). Comparable signs occur in affected human patients, who can report signs of headache, and neuropathic pain, such as paraesthesias and unusual sensitivity to light touch (Greenlee and others 1999, Nogajski and others 2006).

Chiari type 1 malformation in man (CMI) can remain undiscovered until adulthood although detection rates have increased with greater MRI scan availability (Masson and Colombani 2005). Whilst it appears that CM is related to underdevelopment of the posterior cranial fossa, SM is diagnosed in only 32-74% of patients with CMI, suggesting that there may be other predisposing factors in the pathogenesis (Masson and Colombani 2005). Likewise CM/SM is hypothesised to be a multifactorial disease in CKCS (Cerda-Gonzalez and others 2006) and various explanations for the occurrence of SM in the presence of skeletal abnormalities have been mooted. For example CSF flow dynamics have been studied and descriptors such as *Venturi effect* have been used to explain why a high velocity CSF jet passing through a partially obstructed foramen magnum and/or narrowed vertebral canal might cause SM (Iskander and others 2004, Rusbridge and others 2006). Whilst it is logical to conclude that skull morphology is a causal factor in development of SM in dogs, previous attempts to link specific measurements of the volume of the skull or cerebellum with the incidence of SM, or clinical signs suggestive of SM, in CKCS dogs, have met with little success (Lu and others 2003, Cerda-Gonzalez and others 2006). In this article we further describe the relationship between various anatomical measurements and the incidence of SM.

Material and methods

The population consisted of 85 CKCS that included all CKCS (25 dogs) that presented to Stone Lion Veterinary Centre (SLVC) Neurology service in a 2 year period (June 2003 to June 2005) and had a brain and/or cervical MRI scan for any reason. In addition there were also 60 breeder- owned CKCS that had a brain and cervical MRI scan either for diagnostic reasons or for screening prior to breeding. Siemens Magnetom Symphony 1.5T MRI units were used in each case. The DICOM ™ MRI images for each dog were blinded by replacing identifying information with a numerical code by a co-worker who had no role in the assessment or interpretation of the images. The anonymous images were then uploaded into a DICOM ™ viewer (Merge eFilm, Spegelt 34, 5674 CD Nuenen, Netherlands, www.merge-efilm.com). The diagnosis of SM, confirmed by detection of a fluid signal within the spinal cord parenchyma, was made independently by each of 3 of the authors from T2- weighted sagittal and transverse images of the cervical spinal cord.

Two intracranial measurements were used to represent caudal fossa area. The length of the caudal fossa was measured as the length of the basioccipital bone from its most caudal landmark to the junction between the rostral brainstem and the subarachnoid space (Figure 1; line a) as an estimate of the length

of base of the caudal fossa. In preliminary trials, this measurement was determined by the authors to be the most repeatable and consistent measurement of the floor of the caudal fossa. The height of the caudal fossa was taken as a line running perpendicular to the length of the caudal fossa, from the highest point in the caudal fossa to the skull base (Figure 1; line b). The caudal fossa area was represented by calculating the caudal fossa length multiplied by half the caudal fossa height. The product of these two measurements was termed the area of the caudal fossa triangle.

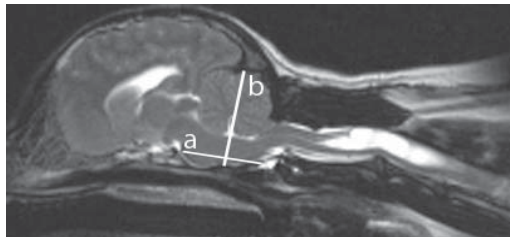

Figure 1 Midsaggittal T2 weighted MRI of the brain and upper cervical spinal cord from case 52, a 4.1 year old female neutered CKCS with syringomyelia
Line a. represents length of the caudal fossa
Line b. represents height of caudal fossa

Four measurements of the vertebral canal height were recorded (Figure 2). The greatest dorsoventral distance across the spinal canal at C1/2 (line c) C2 (line d) C2/C3 (line e) and C3 (line f.)

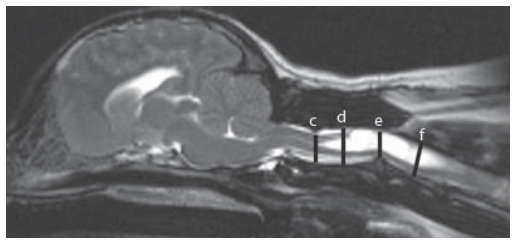

Figure 2 Midsaggittal T2 weighted MRI of the brain and upper cervical spinal cord from case 52
Line c. represents the greatest dorsoventral distance across the spinal canal at C1/C2,
Line d. the distance across C2,
Line e. the distance across C2/C3
Line f. the distance across C3

The angle across the C2/C3 junction was measured as the external angle at the intersection of lines showing the angle of the C2 and C3 vertebrae (Figure 3, line g and line h).

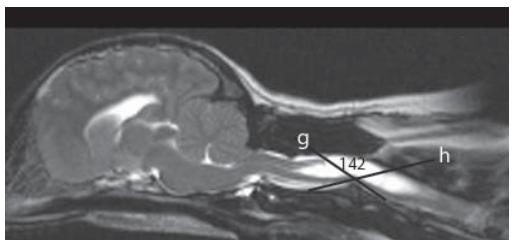

Figure3 Midsaggittal T2 weighted MRI of the brain and upper cervical spinal cord from case 52
The angle of the C2/C3 junction (in this case 142º) is indicated by external angle formed at intersection of line **g**. and line **h**.

For the study population, the mean of those measurements made by the examiners was used for further analysis. For the decision regarding appearance of syrinx (this applied only when syrinx was less or equal to 0.1mm dilatation of the central canal [3 dogs]) a consensus call was applied. Once the data analysis was complete, records were unblinded and corresponding information on age at the time of the MRI scan, gender, and clinical signs, including historical pain, could be added.

Statistical analysis was conducted using the statistical programmes SAS v9.1.3 (SAS Institute Inc., Cary, NC, USA.) and NCSS (NCSS v.2004, Hintze, J. (2001). NCSS and PASS. Number Cruncher Statistical Systems. Kaysville, Utah). Normality of variables was first evaluated and then parametric or non-parametric tests were used as appropriate, to test for differences in the two populations. Tests used were Mann-Whitney U, Chi-square, Equal-Variance T-Test and Aspin-Welch Unequal Variance Test. Significance was set to $p<0.05$.

Results

Results are shown at Table 1 (Univariate Statistics) and Table 2 (Association test results for presence of syrinx).

Table 1 Univariate statistics for study population of 78 CKCS

Parameter	Number of Dogs	Mean	%	Standard Deviation	Standard Error	Minimum	Maximum	Range
Sex (% males)	78		39.7					
Age at time of scan (years)	78	3.0		2.05	0.23	0.6	9.3	8.7
Syrinx present	78		75.6					
Caudal fossa height (cm)	47	3.14		0.16	0.02	2.80	3.50	0.70
Caudal fossa length (cm)	47	2.54		0.14	0.02	2.27	2.80	0.53
Area caudal fossa triangle (cm^2)	47	4.00		0.33	0.05	3.36	4.73	1.36
Caudal fossa ratio	47	0.81		0.05	0.01	0.71	0.93	0.22
Widest point C2 (cm)	77	1.01		0.08	0.01	0.83	1.20	0.37
Width canal C2/C3 (cm)	77	0.73		0.06	0.01	0.60	0.87	0.27
Widest point C3 (cm)	77	0.84		0.07	0.01	0.73	1.03	0.30
C2/C3 angle (°)	77	147.11		6.15	0.70	133.67	166.33	32.67
Narrowest point C1/C2 to dens (cm)	74	0.98		0.09	0.01	0.63	1.20	0.57

Table 2 Association test results for presence of syrinx

Parameter	SM	Number of dogs	Mean	%	Standard Deviation	Standard Error	p-value	Test
Sex (% males)	N	19		36.8			0.7663	Chi-square
	Y	59		40.7				
Age at time of scan (years)	N	19	1.6		1.09	0.25	**0.0001**	Mann-Whitney U
	Y	59	3.4		2.10	0.27		
Narrowest point C1/C2 to dens (cm)	N	18	1.01		0.10	0.02	0.1299	Equal-Variance T-Test
	Y	56	0.97		0.09	0.01		
Widest point C2 (cm)	N	19	1.01		0.05	0.01	0.7693	Aspin-Welch Unequal-Variance Test
	Y	58	1.01		0.09	0.01		
Width canal C2/C3 (cm)	N	19	0.70		0.06	0.01	**0.0116**	Equal-Variance T-Test
	Y	58	0.74		0.06	0.01		
Widest point C3 (cm)	N	19	0.81		0.04	0.01	**0.0099**	Aspin-Welch Unequal-Variance Test
	Y	58	0.85		0.07	0.01		
C2/C3 angle (°)	N	19	146.16		5.89	1.35	0.4412	Equal-Variance T-Test
	Y	58	147.42		6.25	0.82		
Caudal fossa height (cm)	N	6	3.02		0.14	0.06	**0.0395**	Equal-Variance T-Test
	Y	41	3.16		0.16	0.02		
Caudal fossa length (cm)	N	6	2.53		0.12	0.05	0.8713	Equal-Variance T-Test
	Y	41	2.54		0.14	0.02		
Area caudal fossa triangle (cm^2)	N	6	3.82		0.18	0.07	0.1584	Equal-Variance T-Test
	Y	41	4.03		0.34	0.05		
Caudal fossa ratio	N	6	0.84		0.07	0.03	0.1115	Equal-Variance T-Test
	Y	41	0.81		0.05	0.01		

Significant values are in bold. Y – syringomyelia present N – syringomyelia absent

7 dogs were excluded because of missing or corrupted MRI data, which left 78 dogs for the analysis. Of those, 59 dogs had SM. This resulted in a study of 78 dogs consisting of 59 SM and 19 non-SM dogs. The average age at the time of the MRI scan was 3 ± 2.05 years (SD - standard deviation) and 40% of dogs were male. We found a significant difference in the age at the time of scan between dogs with SM versus those without (p=0.0001). Overall, older dogs were more likely to have SM. There was no difference between males and females for the presence of SM.

The area of the caudal fossa triangle had a mean of 4 ± 0.33cm^2 (SD). This parameter was not associated with presence of syrinx (p=0.158). The length of the caudal fossa was not associated with SM (p=0.8713) however the caudal fossa height was (p=0.0395). However the difference in values (0.14cm) was minimal, especially given that the smallest measurement we could appreciate was 0.1cm. Dogs with SM had a mean height of 3.16 ± 0.16cm compared to dogs without SM that had a mean of 3.02 ± 0.14cm. The narrowest point at C1/C2 had a mean of 0.98 ± 0.09cm (SD) and there was no significant association with the presence of SM, (p=0.130). The widest point at C2 had a mean of 1.01 ±0.08cm (SD) and was not associated with presence of SM (p=0.769).

The height of the cervical canal at the C2/C3 junction had a mean of 0.73 ± 0.06cm (SD). Dogs with SM had a mean width of 0.74 ±0.06cm (SD) versus 0.70 ± 0.06cm (SD) for dogs without SM. Although this difference was statistically significant (p=0.012) the actual value (0.04cm) is not measurable within a clinical setting. Likewise there was a significant association between the height at C3 and the presence of SM (p=0.010). Dogs with SM had a mean height of cervical canal of 0.85 ±0.07cm (SD) versus 0.81(±0.04) cm in dogs without SM. The association remained significant after adjustment for age (p=0.015) however again the difference (0.04cm) was not measurable within a clinical setting. The angle at C2/C3 did not show a significant correlation to the appearance of syrinx (p=0.4412).

Discussion

This study found that the caudal fossa height and the height of the vertebral canal at C2/C3 and C3 were significantly larger in dogs with SM. However for all of these parameters the mean difference between the two groups was so small that they are not or only barely measurable with standard techniques and it is debatable whether they could be truly associated with SM. Further study is needed before drawing any conclusions. This is especially true for the measurements of vertebral canal height at C2/C3 and C3 as a chronic expanding syrinx may cause vertebral canal widening by bone resorption and therefore the apparent difference could be a consequence rather than a cause of SM.

The area of the caudal fossa triangle was not correlated to SM. This may be either because there is no relationship between overcrowding of the caudal skull and SM, or that the dimensions measured in this study did not accurately represent caudal fossa volume. Although conclusions cannot be drawn because of these limitations, this study does support the general view that the pathogenesis of SM involves more than foramen magnum overcrowding. Cerda-Gonzalez and others (2006) also found no difference in caudal fossa volume in CKCS with and without SM. This finding also has implications for MRI screening of potential breeding stock. Most importantly it is not possible to predict whether or not a young dog with CM is at risk of developing SM.

The *intramedullary pulse pressure theory* (Rusbridge and others 2006) suggests SM occurs because of

repeated mechanical distension of the spinal cord due to abnormal pressure differences between the spinal cord and the subarachnoid space. It was hypothesised that an important contribution were the changes in CSF flow and/or turbulence that occur as the vertebral canal narrows particularly in the C1 to C3 area (*Venturi effect*). However this study found no association between vertebral canal narrowing and development of SM. There was also no association between the angulation at C2/C3 and development of SM. The older dogs in the study had a greater incidence of SM than the younger ones. The reason for this association is not clear. It is likely that SM develops with time and/or that clinical signs in presence of SM take longer to appear in some dogs than in others. A similar situation occurs in CMI in humans where symptoms of SM often take time to develop (Masson and Colombani 2005). An alternate argument is that the apparent relationship of SM and age is skewed by sampling techniques; for example it is not known whether those dogs that presented for MRI as part of a diagnostic work-up were more likely to represent the population's older cohort. Correspondingly, animals undergoing MRI, but as part of a screening programme, may represent the younger cohort, which may have tended to be asymptomatic. It is not obvious therefore whether anatomical parameters should have been adjusted for age prior to assessing the significance of their association with SM. Nor is it clear whether allowance should have been made in this study for parameters such as the size, or weight of individuals, which may have helped to amplify the differences between the SM and non-SM groups. Further studies are required to analyse matched groups of CKCS at various ages to determine the effects of age and body size on occurrence of SM.

Conclusion

This study did not find a significant correlation between a small caudal fossa and development of SM. There was also no correlation between narrowing of the cranial cervical canal and development of SM. The study did find a significant association with widening of the vertebral canal at C2/C3 and C3 however we recommend caution in drawing a conclusion from these results because the actual difference was smaller than our ability to measure using standard techniques. Considerable further reasearch into this disorder is required for example a study in age and weight matched young CKCS with and without SM is planned. Finally, in order to establish if reduced caudal fossa area is a widespread problem within the CKCS breed, comparative studies of caudal fossa size between various breeds are required.

Acknowledgements

The principal author (HC) conducted this study as a participant in the Cambridge Infectious Diseases Consortium Clinical Research Outreach program. The authors would like to acknowledge the help of the Diaconessenhuis Meppel CKCS syringomyelia screening program and to Paul Mandigers and Utretch University for his continuing support of our CKCS studies. We are also indebted to Parkside Hospital, Wimbledon and radiographers Bob Bates and Eileen Morgan.

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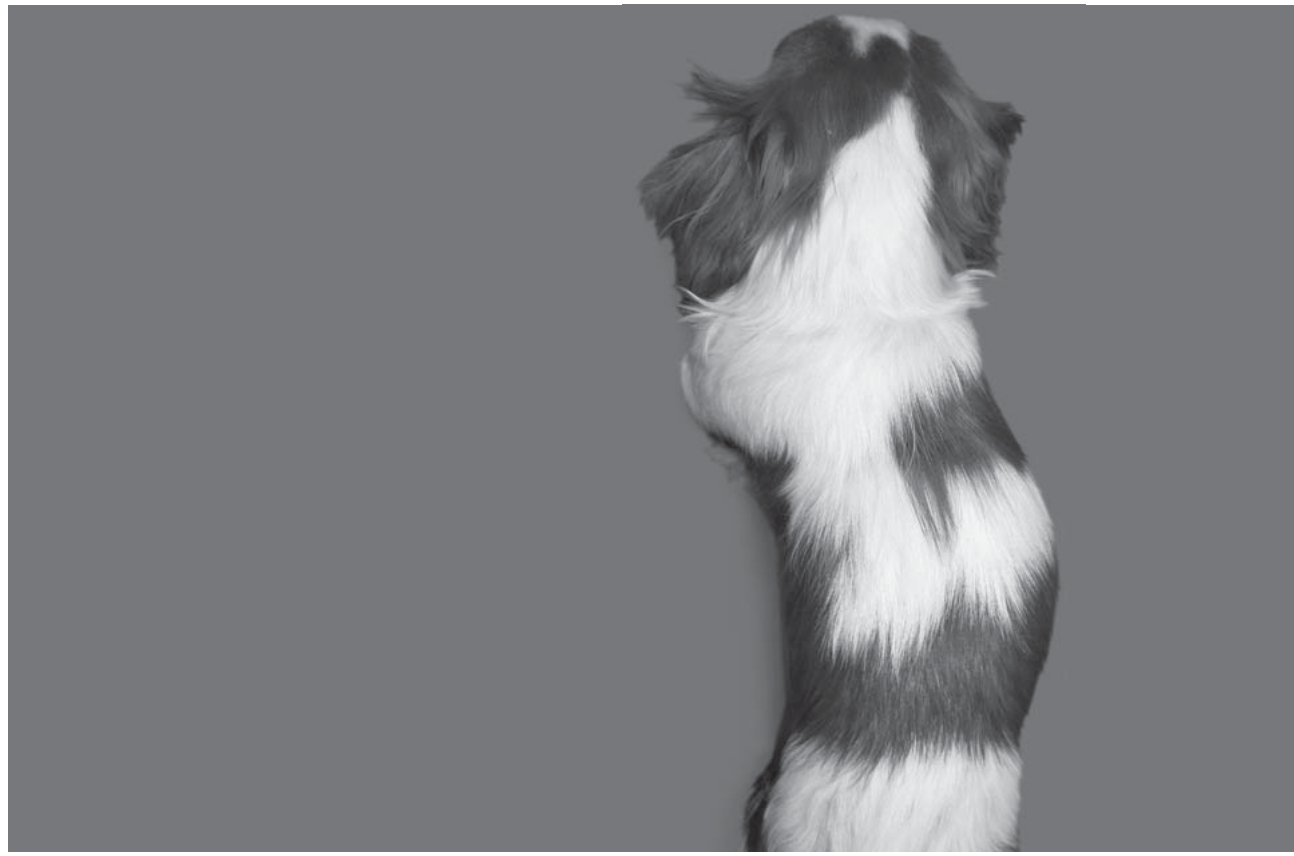

Section 5

Pain and scoliosis in Chiari-like malformation and syringomyelia

Chapter 5.1

Syringomyelia in cavalier King Charles spaniels: the relationship between syrinx dimensions and pain

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Accepted - Journal of Small Animal Practice

Introduction

Canine Chiari-like malformation (CM) is a condition characterised by a mismatch between the caudal fossa volume and its contents - the cerebellum and brainstem (Rusbridge and others 2000), meaning that the neural structures become caudally displaced, obstructing the foramen magnum and the pressure wave of cerebrospinal fluid (CSF) emanating from the head during arterial pulsations. An important consequence of CM and obstruction of CSF flow is syringomyelia (SM) (Fig 1).

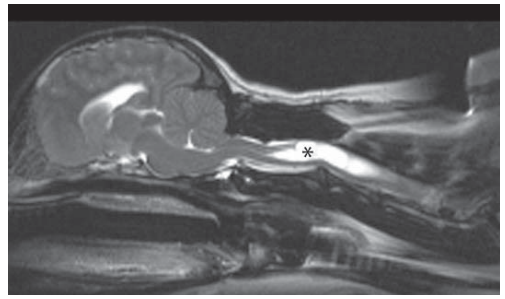

Figure 1 Midsaggittal T2 weighted MRI of the brain and upper cervical spinal cord from case 52, a 4.1 year old female neutered CKCS that had signs of pain from 1.7 years old. Clinical signs included yelping whilst scratching at the right shoulder area. This was more likely when she was excited. Note that whilst this syrinx is wide it is not especially long.

The pathogenesis of syrinx development is much debated (reviewed by Rusbridge and others 2006) but they most likely contain extracellular fluid that accumulates within the central canal and/or spinal cord substance as a consequence of abnormal pressure differentials between the spinal cord and subarachnoid space. The cavalier King Charles spaniel (CKCS) is predisposed to CM and SM (Rusbridge and Knowler 2003, 2004).

Both CM and SM are associated with pain. In humans, Chiari malformation has been diagnosed in patients presenting with a variety of symptoms including headache, pain in the trigeminal territory, back pain, temporomandibular joint disorder, complex regional pain disorders and fibromyalgia (Thimineur and others 2002). In dogs, signs of discomfort such as ear and facial rubbing/scratching can be observed in dogs that have CM alone. In such cases it is postulated that the pain is due to CSF obstruction and abnormalities of medullary sensory processing (Thimineur and others 2002).

SM in humans can cause chronic, disabling pain, which is thought to arise because of damage to the dorsal horn of the spinal cord grey matter (Todor and others 2000). The dorsal horn is a key centre for processing of sensory information for transmission to the brain and, importantly, is 'plastic' – meaning that the neural connections and communications can be reorganised, sometimes resulting in persistent pain states (Stanfa and Dickenson 2004). In affected dogs, pain most commonly is localized to the neck and is more apparent during sudden posture change. The skin over one side of the head, neck, shoulder or sternum may be overly sensitive to touch and dogs frequently scratch at that area- often without making skin contact – a clinical sign referred to as "phantom" scratching (Rusbridge and others 2000). It is suspected that these behavioural signs reflect aspects of 'neuropathic pain', in which pain arises because of abnormal somatosensory processing in the peripheral or central nervous system. This takes two main forms: i) allodynia, in which a normally non-painful stimulus evokes pain in the affected individual, and ii) dysaesthesia, in which stimuli evoke inappropriate sensation which is often painful. In SM it is suspected that neuropathic pain syndromes are caused by damage to one or both spinal cord dorsal horns (reviewed by Rusbridge and Jeffery, 2006).

In the current study we examined the hypothesis that SM-associated pain in dogs is associated with asymmetrical damage to the dorsal part of the spinal cord (*i.e.* either right or left side is preferentially damaged).

Material and methods

Quantitative data was derived from magnetic resonance imaging (MRI) scans of 85 CKCS (60% female). The population consisted of all CKCS (25 dogs) that presented to Stone Lion Veterinary Centre (SLVC) Neurology service in a 2 year period (June 2003 to June 2005) and had a brain and/or cervical MRI scan (Siemens Magnetom Symphony 1.5T) for any reason. There were also 60 breeder- owned CKCS that had a brain and cervical MRI scan (Siemens Magnetom Symphony 1.5T) either for diagnostic reasons or for screening prior to breeding. For each animal, T2-weighted (T2W) sagittal and transverse scans were examined; transverse scans were obtained at a plane 90^0 to the longitudinal axis of the spinal cord.

Before obtaining the MRI, the presence or absence of signs of likely SM-associated pain was recorded. This was determined by examination by one of the authors (CR) or owner reporting of typical history: yelping, scratching behaviour, apparent discomfort or avoidance of being touched over the ear, neck, shoulder or sternum, or abnormal head posture (for example consistently sleeping with the head raised). Owner assessment of pain was conducted using a tick box form that has been described previously (Rusbridge and others 2005). One of the authors (CR) subsequently examined 16 of 60 breeder owned dogs and confirmed that form filling was accurate for these dogs.

From the initial cohort of 85 dogs, five dogs were excluded because of diagnosis of concomitant other painful disease and six dogs were excluded because of missing or corrupted MRI data. This left 74 dogs for the analysis. The DICOM ™ MRI images for each dog were blinded by replacing identifying information with a numerical code by a co-worker (MH) who had no role in the assessment or interpretation of the images. The anonymous images were then uploaded into a DICOM ™ viewer (Merge eFilm, Spegelt 34, 5674 CD Nuenen, Netherlands, www.merge-efilm.com). The images of the cervical spinal cord were examined by three of the authors (CR, HC, NDJ) independently for the presence of a syrinx. If present, the maximum width of syrinx in one dorsal horn was measured on a transverse scan and right /left asymmetry recorded (Fig 2). If there was left / right asymmetry the length of this asymmetric region was determined by measuring the distance on the scout view between the first and last slice that had right/left asymmetry (Fig 3).

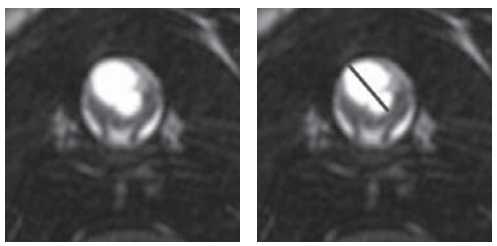

Figure 2 T2 weighted transverse image through the syrinx depicted in figure 1a) demonstrating the asymmetrical involvement of the right dorsal horn. If the spinal cord is transected in a dorsal plane into ventral and dorsal halves, then the spinal cord around the ventral syrinx is equal left to right. By contrast in the dorsal half of the spinal cord there is more damage to the right side of the spinal cord b) A syrinx width measurement was obtained by measuring the widest diameter of the syrinx (black line). This dog had a maximum width of 0.8cm.

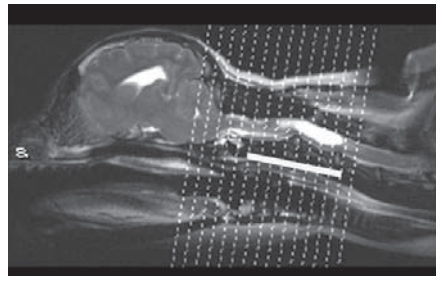

Figure 3 Scout view for the transverse images for case 52. The length of the asymmetrical dorsal grey column involvement was obtained by recording the image numbers through which there was a continuous asymmetrical syrinx then measuring the distance between the first and the last image on the scout view (white line).

For analysis, the mean of the three reviewers' measurements was determined for parametric data and a consensus decision reached for categorical decisions (*e.g.* presence of syrinx). Once the measurements were complete, the images were unblinded. Dogs were categorized into those with pain and those without pain. Data on age at the time of the MRI scan, sex, clinical signs, syrinx size and symmetry and length were compared between the two groups. Statistical analysis was conducted with the statistical program NCSS 2004 (Number Cruncher Statistical Systems. Kaysville, Utah, USA). Normality of variables was first evaluated and parametric or non-parametric tests used as appropriate.

Significance was set to $p<0.05$. Scatter plots were generated with GraphPad Prism v4.03

Results

Of the 74 dogs that were examined, 55 had SM, with a mean maximum syrinx diameter of 0.41cm and mean length of 3.93 cm. Only 35% of the syrinx dogs had historical or clinical evidence of pain and 27% showed abnormal scratching, implying that not all syrinxes were associated with these clinical signs. The sex or age of the dog did not appear to correlate with clinical signs of pain (Table 1). However, when comparing dogs with and without pain, we found a strong association with maximum syrinx width ($p<0.0001$; ANOVA) (Table 1 and Fig 4); dogs showing pain had a mean maximum width of syrinx of 0.58cm compared with a mean of 0.32cm in dogs without pain.

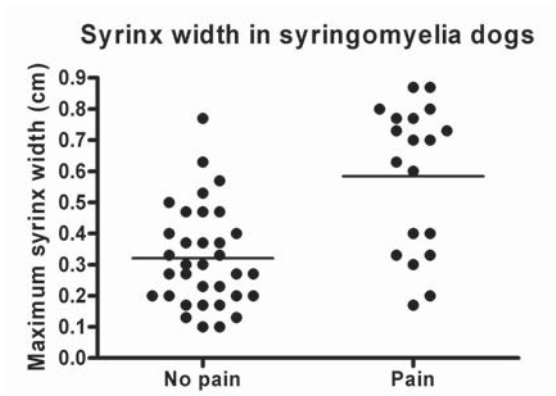

Figure 4 Scatter plot illustrating the relationship between maximum width of the syrinx and presence of absence of pain in dogs with syringomyelia. The horizontal line indicates the mean value

Table 1 Comparative statistics of CKCS with syringomyelia with and without pain

		N	Mean or %	Std dev	p-value	Test
Sex (% males)	Pain	19	8/19 (42.1%)	0	0.7727	Two-tailed Fisher exact
	No pain	36	13/36 (36.1%)	0		
Age at time of scan (years)	Pain	19	3.73	2.34	0.3452	One-way ANOVA
	No pain	36	3.17	1.94		
Max width syrinx	Pain	19	0.58	0.24	**<0.0001**	One-way ANOVA
	No pain	34*	0.32	0.16		
Syrinx asymmetry	Pain	19	16/19 (84.2%)		**0.0171**	Two-tailed Fisher exact
	No pain	33*	16/33 (48.5%)			
Asymmetry into dorsal horn	Pain	19	15/19 (78.9%)		**0.0419**	Two-tailed Fisher exact
	No pain	33*	16/33 (48.5%)			
Length of dorsal horn asymmetry	Pain	15	5.15	2.32	**0.0039**	Mann Whitney
	No pain	16	2.8	1.09		

* There were 19 dogs "with pain" and 36 "without pain" however for some MRI parameters the appropriate MRI images were not available so these dogs are not included in the final analysis. Bold figures indicate significant p-values.

Left/right asymmetry was only found within the dorsal half of the spinal cord, into which all syrinxes extended. Dogs that exhibited pain were more likely to have an asymmetrical syrinx (in the dorsal half of the spinal cord). 15/19 (79%) dogs with pain, and 16/33 (49%) dogs without pain had asymmetric syrinxes in the dorsal half of the cord (p=0.0419). For those with an asymmetrical syrinx, the mean length in the dorsal half of the cord was 5.15cm in the painful group compared to 2.8cm for the non–painful group (p=0.0039; Mann Whitney). However, asymmetry and maximum syrinx width were strongly correlated (Fig 4; Fig 5), meaning that the causal relationship between asymmetry and pain could not be established without more detailed analysis.

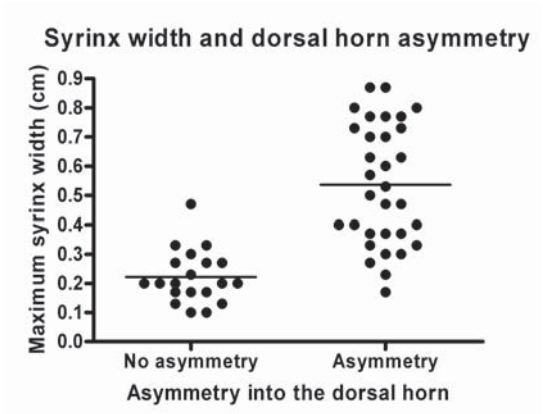

Figure 5 Scatter plot illustrating the relationship between maximum width of the syrinx and dorsal horn asymmetry. The horizontal line indicates the mean value.

To test the hypothesis that syrinx asymmetry into the dorsal half of the spinal cord was associated with pain independently of maximum syrinx width, we conducted logistic regression with adjustment for maximum syrinx width. The association between dorsal horn asymmetry and pain was not statistically significant when controlling for maximum syrinx width (p=0.7911), but that of the syrinx width remained significant after controlling for dorsal horn asymmetry (p=0.0022), meaning that width appeared to be the more significant feature associated with pain. Out of the 31 dogs with asymmetric syrinxes (in the dorsal half of the cord), syrinx length was correlated with pain (p=0.0039); the mean asymmetric syrinx length was 5.2cm and 2.8cm for dogs with and without pain respectively. The association was insignificant (p= 0.0579) after correcting for maximum syrinx width in logistic regression. Therefore, overall, the strongest predictor of pain in dogs with SM was syrinx width (p= 0.00034; one-way logistic regression).

Five out of 47 syrinx dogs (11%) had scoliosis and all five were in the painful group (p=0.0101, Fisher exact test). Dogs that had scoliosis, previously diagnosed on clinical examination, all had an asymmetrical syrinx that involved the dorsal half of the cord (mean maximum width 0.8cm and mean length of 5.1cm). Statistical analysis showed that scoliosis was associated with syrinx width (p=0.0222) but not with length (p= 0.1270).

Since syrinx dimensions had such a strong relationship with pain in this cohort of dogs we calculated a specific size that might be used in future as an indication of the likelihood of a syrinx being the cause of pain in an individual CKCS. In this study, dogs in pain had a mean maximum syrinx diameter of 0.58 (standard deviation ± 0.24) cm, and those without pain had a maximum syrinx width of 0.32 (standard deviation ± 0.16) cm. 95% of dogs with a syrinx at least 0.64cm wide had associated clinical signs. Finding a syrinx of this size or more in a CKCS with consistent clinical signs would thus provide reliable evidence that the syrinx could be incriminated as the cause.

Discussion

In this study we show that pain is most likely to be observed in association with large, long and asymmetric syrinxes. Of these, maximum syrinx width was the strongest predictor of pain. These results offer a new perspective on a previous study in which the length of the syrinx was found not to correlate with clinical signs (Lu and others, 2003). However those authors examined the overall length of the syrinx without considering the cross sectional location of the damage. In contrast, we found that pain was associated with long syrinxes in the dorsal half of the cord. It is possible that the asymmetry is important in the pathogenesis of central neuropathic pain.

The finding that larger, and specifically, wider, syrinxes are more likely to be associated with pain is not unexpected, since a greater degree of fluid accumulation within the cord is more likely to disrupt normal cord function, through compression or tissue destruction. Our findings also broadly support the

hypothesis that disruption of the function of the dorsal part of the cord is associated with pain in these patients, since syrinx asymmetry (always found in the dorsal cord) was associated with pain, although asymmetric syrinxes were always wide as well, meaning that the two features are difficult to separate in terms of significance. Although the resolution of the scans was insufficiently detailed to permit diagnosis of the precise site in the dorsal half of the cord that was involved we feel it is reasonable to assume that impairment of dorsal horn function is the cause of pain in these animals. The mechanisms by which this can occur are discussed in a forthcoming companion article (Rusbridge and Jeffery, 2006).

This study also found a relationship between cervical scoliosis and syrinx width (Fig 6). Scoliosis as a consequence of SM was originally thought to be due to unilateral ventral horn cell damage, unequal paraspinal muscle atrophy and muscular imbalance (Rusbridge and others 2000). We did not find a correlation between ventral asymmetry and scoliosis in this study. An alternative explanation was suggested by Van Biervliet and others (2004) who, after observing scoliosis secondary to cervical myelitis, proposed that damage of the dorsal grey column over a number of spinal cord segments on one side results in an imbalance of afferent information from the cervical neuromuscular spindles. This unilateral loss of proprioceptive information leads to scoliosis.

Figure 6 Case 27, a 9 month old female CKCS that was presented with scoliosis and pain. The scoliosis developed over a 3 week period. This dog had 6.3 cm of left cervical dorsal grey column involvement and maximum syrinx diameter of 0.7cm. The syrinx also extended into the thoracic region.

A potential source of error in this study is that pain is a subjective parameter and as such some dogs may have been wrongly categorized. However, owners and breeders generally will recognise signs consistent with pain in their animals, especially those associated with SM, since they are often pronounced and persistent. Limitations in owner observation can of course influence the presentation of animals for a multitude of problems (*e.g.* lameness) but these limitations do not invalidate a study that is designed to relate historical signs of pain to a specific pathological feature. In fact, it could be argued that historical evidence of pain is a more useful parameter to relate to imaging findings than a clinical examination, since this relates directly to owners' perceptions about their animal.

Another limitation of this study is that the population may be biased with a tendency towards clinical signs of pain for the dogs presenting to the SLVC and against clinical signs of pain in the dogs screened for breeding purposes. In an attempt to overcome the bias toward pain for the SLVC dogs, all CKCS having a MRI scan in a 2 year period at the SLVC were included and the images were blinded. A final limitation of this study is that only the cervical spinal cord was assessed; although SM secondary to CM typically starts in the upper cervical regions and at the thoracic inlet (Rusbridge and others 2006) it is possible that there could have been more extensive dorsal grey column damage caudal to the area under study.

In conclusion, the likelihood of pain associated with SM is determined by size and length of asymmetry of the syrinx. Maximum syrinx width is the strongest predictor of pain. The putative implication of dorsal horn damage in the pathogenesis of pain has implications for pain management, since it may be more appropriate to use drugs that have a site of action at the level of the dorsal horn. It also may have an implication for prognosis as damage to the dorsal horn can be associated with persistent neuropathic pain.

Acknowledgements

The principal author (CR) conducted this study as a participant in the Cambridge Infectious Diseases Consortium Clinical Research Outreach program.

The authors would like to acknowledge the hard work and dedication of everyone involved with the Diaconessenhuis Meppel CKCS syringomyelia screening program in particular Dana Schuller-Kuyper, Pirkko Blijham-Keckman, Penny Knowler, Paul Mandigers, the Dierenartsenpraktijk Hoogeveen veterinary practice, Colin Vos, W.J. Boeve, Caroline Kos, Emily Legebeke, Jeanet van Elven, Karin van der Sluis, Lydia Bosma, Hellen de Vent, Tanja de Ruiter and Anja de Boer. We are also grateful to Paul Mandigers and Utretch University and finally we would like to thank Parkside Hospital, Wimbledon and radiographers Bob Bates and Eileen Morgan.

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Chapter 5.2

Pathophysiology and treatment of neuropathic pain associated with syringomyelia

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Accepted - The Veterinary Journal

Introduction

When the head aches, all the members partake of the pain. *Miguel de Cervantes Saavedra (1547–1616) Don Quixote. Part II. Chap. II.* So great was the extremity of his pain and anguish that he did not only sigh but roar. 1 *Mathew Henry (1662–1714) Commentaries. Job iii.*

Neuropathic pain, resulting from disordered neural processing within the nervous system, (Table 1) is poorly recognised in animals and consequently is difficult to manage. In this article we discuss the mechanisms involved in the development of central neuropathic pain with particular emphasis on the pain associated with Chiari-like malformation and syringomyelia (CM/SM). Chiari malformation is a condition characterised by mismatch between the caudal fossa volume and its contents - the cerebellum and caudal brainstem – and commonly results in syringomyelia, (fluid-filled cavitation of the spinal cord) because of obstruction of cerebrospinal fluid movement though the foramen magnum (Fig 1) (Rusbridge, 2000).

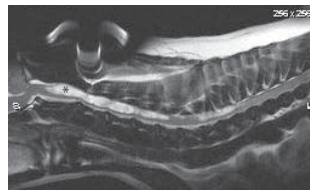

Figure 1 Mid-sagittal T2 weighted MRI of upper cervical spinal cord from a 2.6 year old female CKCS that had signs of pain from 1.9 years old. Clinical signs included yelping whilst scratching at the right shoulder area. This was more likely when she was excited. There is a syringomyelia (asterisk) secondary to canine Chiari-like malformation.

Table 1 Pain, an explanation of common terms

Pain	Characteristics
Nociceptive pain	Information about tissue trauma transmitted by normal nerves to the central nervous system.
Neuropathic pain	A clinical syndrome of pain due to abnormal somatosensory processing in the peripheral or central nervous system. The spectrum may include spontaneous pain, paresthesia, dysthesia, allodynia, or hyperpathia
Neuralgia	Pain in distribution of nerve or nerves
Hyperpathia	Increased pain from stimuli which are normally painful
Allodynia	Pain from a stimulus that is not normally painful. Examples *Touch* – pain from touch of clothing *Thermal* – pain from draft of warm or cold air on the skin. *Location allodynia (ephapse)* - pain in area distinct from location of stimulus *Dynamic mechanical allodynia* – pain from a lightweight moving mechanical stimulus (e.g. soft brush moved back and forth) *Kinesthetic (motion) allodynia*– pain from motion (usually called *kinesthetic dysesthesia* because the feeling evoked by such movement is dysesthetic burning)
Hyperalgesia	Used by some instead of allodynia. Means “pain in the area stimulated” and can include nociceptive as well as neuropathic pain.
Paresthesia.	A spontaneous or evoked abnormal sensation (not unpleasant)
Dysesthesia	A spontaneous or evoked unpleasant abnormal sensation. It is usually associated with burning, but is difficult to describe because the patient has never felt this sensation before developing neuropathic pain. The message perceived by the brain is one of “tissue destruction” with burning the most prominent component (Berg, 2001)

CM/SM is particularly common in the cavalier King Charles spaniel (CKCS) (Rusbridge et al, 2000). Pain is a predominant feature of the disease and is reported in ~ 80% affected humans and ~ 35% affected

dogs (Todor et al, 2000, Rusbridge et al., 2006b), although there is controversy as to how CM/SM results in pain. A recent study in dogs found that pain was positively correlated with syrinx width - *i.e.* dogs with a wider syrinx were more likely to experience discomfort and dogs with a narrow syrinx may be asymptomatic, especially if the syrinx was symmetrical and not deviated into the dorsal horn (Rusbridge et al, 2006b). This suggested that damage to the spinal cord dorsal horn (Fig 2) may be the significant factor in the development of syringomyelia-associated pain.

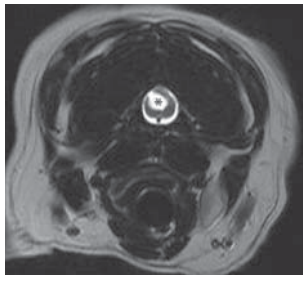

Figure 2 T2 weighted transverse image through a syrinx (asterisk) demonstrating the asymmetrical involvement of the right spinal cord dorsal horn

The type of behaviour exhibited by affected dogs is suggestive of neuropathic pain, since it has the characteristics of allodynia, *i.e.* pain arising in response to a non-noxious stimulus, or dysaesthesia - *i.e.* a spontaneous or evoked unpleasant abnormal sensation, described by some humans as a painful burning itchiness or an intense feeling of insects crawling on the skin (Woolf, 2004). For example they appear to dislike touch to certain areas of skin and may be unable to tolerate grooming or a neck collar. Dogs with a wide syrinx may also scratch, typically on one side only, while the dog is walking and often without making skin contact (Rusbridge et al, 2000), such behaviour is often referred to as an “air guitar” or “phantom” scratching. This sign is highly suggestive, of dysaesthesia, which human sufferers report is the most disabling type of pain associated with syringomyelia (Todor et al, 2000).

Chiari malformation alone has been suggested to cause pain in some affected humans (Milhorat et al, 1999), such as headache, pain in the trigeminal territory, back pain, temporomandibular joint disorder, complex regional pain disorders and fibromyalgia (Thimineur et al, 2002). It is proposed that Chiari malformation and direct compression of the medulla oblongata can result in a disorder of sensory processing resulting in a pain syndrome, often affecting the face (Thimineur et al, 2002; Taylor and Larkins, 2002). The rostral ventral medulla plays a critical role in the modulation of pain and projects directly to the trigeminal nuclei and spinal cord dorsal horn. Although some patients appear to improve after surgical decompression at the foramen magnum, there is still controversy as to whether Chiari malformation with minimal/no cerebellar herniation (so called Chiari 0) is painful. (Taylor and Larkins, 2002; Meadows et al, 2000; Milhorat et al, 1999). Dogs with Chiari-like malformation without syringomyelia can also exhibit signs of discomfort, for example ear and facial rubbing/scratching (Fig 3).

Figure 3 a, b A 2 year old female cavalier King Charles spaniel that was presented with persistent head rubbing that was most noticeable in the morning, when first getting up. The clinical signs were somewhat relieved by oral frusemide therapy and the dog subsequently was managed with a cranial cervical decompression.

As in people it may be difficult to be certain that the discomfort is related to the Chiari-like malformation because magnetic resonance imaging has shown that many CKCS have the malformation without apparent clinical signs. Finally some of the signs of CM/SM suggest posture-related pain (Fig 4) which could be explained by effects on CSF flow (Rusbridge 2006c).

Figure 4 A 3 year old female cavalier King Charles spaniel with Chiari-like malformation and severe syringomyelia. The owner took this image to illustrate her concern that her dog was sensitive about head position and in particular had begun to sleep with her head elevated. When on the owner’s sofa, the dog would arrange cushions to allow her head to be positioned with the same degree of elevation.

Since currently available treatment for syringomyelia-associated pain is rather inadequate for both human and canine patients (Rusbridge et al, 2006c; Baron, 2000; Todor et al, 2000) it is to be hoped that greater understanding of the underlying mechanisms might lead to more effective treatment. In this article we review pain pathways involving the dorsal horn, relate this to injuries caused by syringomyelia and suggest medical management that may be appropriate.

The spinal cord dorsal horn and pain perception

Physiological pain and central sensitisation

The dorsal horn has a pivotal role in pain perception; it receives sensory information from the periphery (pain, temperature and touch) and is subject to considerable local and descending modulation. Incoming sensory information undergoes substantial processing within the various laminae of the dorsal horn (nociception primarily within laminae I, II and V), and is then relayed via ascending pathways to the brain (Rexed, 1952). Nociceptive information (mechanical, thermal and chemical) is transmitted by small non-myelinated C fibres which terminate predominantly in laminae I (marginal) and II (substantia gelatinosa) with some fibres penetrating to deeper layers (Todd, 2002, Rexed, 1952).

Within the dorsal horn, C fibres release excitatory neurotransmitters, in particular substance P and glutamate, and produce slow excitatory postsynaptic potentials that may last for up to 20 seconds. There is phenomenon of temporal summation which is often referred to as "wind up", and the 'gain' of this neuronal response (i.e. the robustness with which the impulse is subsequently propagated) is influenced by normally inactive N-methyl-D-aspatate (NMDA) type glutamate receptors (Woolf and Salter, 2000). In a non-depolarised cell NMDA receptors are blocked by magnesium, but the coincidence of cell depolarisation and presynaptic glutamate release will remove this blockade allowing activation of the NMDA receptors thereby allowing calcium entry into the cell. Therefore, if C fibres are activated more than transiently the elevated intracellular calcium level will activate many intracellular signalling cascades, including the production of nitric oxide, culminating in release of more substance P. The result is that pain "winds up" (i.e. is amplified on its way to the brain) with a consequent elevated perception of pain (Woolf and Salter, 2000). "Wind up" is an immediate central sensitisation that occurs in seconds, but if the noxious stimuli are sufficiently persistent they generate activity-dependent changes in transcription. This takes hours to be induced but outlasts the initiating stimulus for prolonged periods providing the basis for very long-lasting changes in function. Posttranslational changes in the dorsal horn make these affected neurons more sensitive to other impulses (Costigan and Woolf, 2000).

There are further mechanisms that regulate the excitability of the pain pathways. For instance, gamma-aminobutyric acid (GABA) is the main inhibitory control over the wind up system, preventing release of substance-P and maintaining homeostasis between excitatory and inhibitory central nervous system activity (Woolf, 2004). The autonomic system also influences pain perception: C fibres containing substance P and glutamate terminate around or partly on preganglionic sympathetic neurons in the intermediolateral nucleus of the spinal cord as well as on dorsal horn neurons (Zou, 2002, Ohtori et al, 2002, Baron, 2000) and substance P and glutamate receptors within preganglionic sympathetic neurons are up-regulated during nociception (Ohtori et al, 2002).

Central neuropathic pain

Pain can be divided into three categories: physiological, inflammatory and neuropathic (Woolf and Salter 2000). Physiological pain - such as the pain in response to a needle prick - serves to protect an animal from injury. Inflammatory pain is caused as a consequence of tissue damage. Neuropathic pain is a clinical syndrome of pain due to abnormal somatosensory processing in the peripheral or central nervous system and may include spontaneous pain, paresthesia, dysthesia, allodynia, or hyperpathia (Table 1). Neuropathic pain serves no beneficial purpose to the animal and can be regarded as a disease in itself. The pathophysiology of neuropathic pain is complex and incompletely understood (reviewed by Woolf and Salter 2000 and Costigan and Woolf 2000). However, there are 3 pivotal phenomena intrinsic to the development of neuropathic pain 1) *central sensitisation* i.e. the process of "wind up" and the resulting transcriptional changes in dorsal horn neurons leading to altered synaptic neurotransmitter levels and number of receptors (Woolf and Salter 2000). 2) *central disinhibition* i.e. an imbalance between the excitatory and inhibitory side of the nervous system. (Costigan and Woolf 2000, Yaksh, 1989) 3) *Phenotypic change* of mechanoreceptive Aβ-fibers (light touching) to produce substance P so that input from them is perceived as pain (Neumann et al, 1996).

Syringomyelia and central neuropathic pain

It has previously been suggested that the primary mechanism of syringomyelia-associated pain is damage to the decussating fibres of the spinothalamic tract, the ascending pathways, or both (Rusbridge et al, 2000; Nurmikko, 2000; Beric et al, 1988) but there is little evidence to support this view. Ducreux et al (2006) demonstrated that lesions of the spinothalamic pathways alone are not sufficient for development of central pain in syringomyelia patients. In a study examining pain-related somatosensory evoked potentials following CO2 laser stimulation (pain SEPs) in 8 humans with syringomyelia, Kakigi et al (1991) showed that the function of the ascending fibres through the dorsal columns is intact in most patients, whereas dorsal horn function is impaired. Studies in humans have suggested that dorsal horn damage may be implicit in the development of syringomyelic pain (Todor et al, 2000), although the exact mechanism is unclear. A similar situation is likely in the dog in which wide syrinxes that involve the spinal cord dorsal horn are more likely to result in behavioural signs of pain and allodynia/dysesthesia (Rusbridge et al, 2006b). Injury to the spinal cord produces a cascade of interactive reactions that can be broadly divided into three mechanisms, anatomical changes, neurochemical (excitotoxic) changes and inflammatory changes (Finnerup and Jensen, 2004).

Anatomical changes in syringomyelia

Syringomyelia typically starts centrally and dissects to the outer spinal cord. As mentioned above, the output of the dorsal horn depends on the considerable interaction and processing of nociception which

occurs between the various laminae of the dorsal horn (Todd and Spike, 1993). Therefore it is plausible that the damage that syringomyelia causes to the deeper layers whilst preserving the superficial layers might cause imbalance between the various processing pathways, through death or dysfunction of specific cell types. For instance, if the deeper layers contain or are influenced by GABA and glycine inhibition, as suggested by Cronin et al (2004), then selective damage could result in central disinhibition. There is support for this point of view, since, in laboratory rodent models, neuronal loss in the dorsal horn, whilst sparing the superficial laminae, results in spontaneous (excessive grooming) and evoked (mechanical and thermal) allodynia behaviour (Yezierski et al, 1998). Spinal cord injury can also result in reorganization of neural pathways, such as invasion of laminae III and IV by calcitonin gene-related peptide containing primary afferents normally only found in laminae I and II (Christensen and Hulsebosch, 1997).

Neurochemical changes in syringomyelia

Anatomical changes inevitably lead to a changed expression of neurotransmitters (or other chemicals), changed expression of receptors, or both. In a study examining the distribution of substance P, 9 of 10 human subjects with syringomyelia had a substantial increase in substance P immunoreactivity in laminae I, II, III and V caudal to the syrinx. There was a marked reduction or absence of substance P immunoreactivity in segments of the spinal cord occupied by the syrinx and central cavities produced bilateral abnormalities, whereas asymmetrical cavities produced changes that were ipsilateral to the lesion. No alterations in substance P immunoreactivity were found in the spinal cord of an asymptomatic patient with a small central syrinx. The authors concluded that syringomyelia was associated with abnormalities in spinal cord levels of substance P, which would likely alter modulation and perception of pain (Todor et al, 2000; Milhorat et al, 1996). The same authors theorised that syringomyelia may result in changes in concentrations of other neurotransmitters (or neuromodulators), such as GABA, resulting in “disinhibition” of pain pathways. Inhibitory neurons containing GABA have a high susceptibility to hypoxia (Zhang et al, 1994) so may be more selectively damaged.

Inflammatory changes in syringomyelia

Neuroinflammation and neuroimmune activation following spinal cord injury are suggested to play a role in persistent pain (DeLeo and Yezierski, 2001), perhaps mediated through glial cell production of cytokines and altered expression of nociceptive peptides (DeLeo and Yezierski, 2001). For example, preliminary data suggested that one cytokine, interleukin-1, leads to an increase in substance P (Adler, 2003).

Possible treatment options

Surgery

The most directly relevant means of treating Chiari malformation or syringomyelia is to correct the underlying anatomical or functional abnormality. In humans, surgical intervention is recommended for progressive syringomyelia (Medows et al, 2006). However, even after an apparently successful procedure resulting in collapse of the syrinx, the patient may still experience significant pain especially if the spinal cord dorsal horn was compromised (Nakamura et al, 2004; Milhorat et al, 1996). In dogs, surgery appears less successful than in humans because, although there may be a clinical improvement, the syringomyelia is generally persistent (Rusbridge,2006a; Dewey et al, 2005; Vermeersch et al, 2004; Skerritt and Hughes, 1998). Until a reliable surgical option is defined, medical management of the clinical signs is likely to be the mainstay of veterinary therapy. Here we describe some of the pharmacological options.

Drugs

Chiari-like malformation

If other potential causes of discomfort than could be attributed to Chiari-like malformation have been be ruled out it may be worthwhile prescribing drugs that reduce the CSF pulse pressure, such as furosemide (Frusecare; Animal Care). These drugs would not be expected to affect the clinical course in ear, skin or oral disease which could conceivably cause similar clinical signs. A positive response therefore supports a supposition that the discomfort is secondary to Chiari-like malformation and cranial cervical decompression surgery could be considered. As Chiari malformation alone may result in disordered medullary dorsal horn processing (Thimineur et al, 2002)) neurogenic analgesics such as those described below could also be considered.

Syringomyelia

Due to the complex pathophysiology of neuropathic pain, the most successful approach is often judicious polypharmacology, rather than to address the entire problem with one class of medication (O’Hagan, 2006; Wiese et al, 2005). Unfortunately many of the possible medications are not licenced in the dog and their pharmacokinetics and/or adverse effects are not known. No large studies have been done on the medical management of syringomyelia which is often a matter of treatment trials in individual dogs based on anecdotal evidence. There is a need for a multicenter study to rationalise the approach.

Nonsteroidal anti-inflammatory drugs (NSAIDS)

Recent evidence has suggested that cyclooxygenase-2 (COX-2) may contribute to the development and management of neuropathic pain (Takahashi et al, 2005), although these findings are contested (Broom 2004). Anecdotally COX inhibitors such as meloxicam (Metacam, Boehringer Ingelheim Limited)

and carprofen (Rimadyl, Pfizer Limited) appear to help some dogs with syringomyelia. Drugs such as deracoxib (Deramaxx; Novartis Animal Health) and fibrocoxib (Previcox, Merial), which are highly specific for the inhibition of cyclooxygenase 2 pathway (coxibs), may be more appropriate for treating syringomyelia pain. Coxibs are lipophilic and achieve significant cerebrospinal fluid concentrations and may cause analgesia via a central action (Bergh and Budsberg, 2005; Dembo et al, 2005).

Anti-convulsant drugs

Several anti-convulsants have an anti-allodynic effect (Attal et al 1998) and are reported by human patients to be particularly effective for neuropathic pain that is burning and lancinating in nature (Costigan and Woolf 2000). Gabapentin (Neurontin, Pfizer Limited) is a drug that was originally developed as an anti-convulsant but clinically has been more useful for treatment of neurogenic pain in people (Coderre et al, 2005). It is thought to prevent the release of glutamate in the dorsal horn via interaction with the alpha2delta subunit of voltage-gated calcium channels (Gilron and Flatters, 2006). Anecdotally gabapentin can offer some relief to dogs with syringomyelia.

Pregabalin (Lyrica, Pfizer) is emerging as an effective drug for neuropathic pain in humans. It is a structural, but not functional, analogue of GABA which is also thought to exert its pharmacodynamic effect by modulating voltage-gated calcium channels resulting in a reduction of glutamate and substance P release (Hamandi and Sander, 2006). The pharmacokinetics and potential toxicity in dogs are currently unknown. In people the typical side effects are dizziness, somnolence and weight gain but acute psychosis and epileptiform EEG changes have also been reported (Olaizola et al, 2006). Anecdotally pregabalin can be useful for treatment of syringomyelia associated pain in dogs however the cost is prohibitive for many clients.

Corticosteroids

Corticosteroids are believed to provide long-term pain relief because of their ability to inhibit the production of phospholipase-A-2 (Nolan, 2000) and to inhibit the expression of multiple inflammatory genes coding for cytokines, enzymes, receptors and adhesion molecules (Barnes, 1998). Corticosteroids are also reported to have an effect in sympathetically mediated pain (Gellman 2000) and decrease substance P expression (Wong and Tan, 2002). Anecdotally, oral drugs such as methylprednisolone (Medrone; Pfizer Limited) and prednisolone (Prednicare, Animalcare Limited) provide relief in some dogs with syringomyelia.

Opioids

Neuropathic pain tends to be only partially responsive to opioid therapy (Woolf and Mannion, 1999) and NMDA receptor activation is a major contributor to opioid tolerance (Mao et al, 1995) Most people with neuropathic pain require repetitive dose escalation and eventually become unresponsive (Moulin et al, 2005). Methadone may be especially useful in the management of intractable neuropathic pain since it appears to have NMDA antagonist activity. In dogs with CM/SM, opioids are most useful in the perioperative period e.g. a fentanyl transdermal patch (Duragesic, Janssen Pharmaceutica). Some dogs obtain relief of pain from oral opioids but the effective dose and agent can vary greatly between individuals and there is the problem of dispensing a controlled drug (Brearley and Brearley, 2000). For this reason opioids are not commonly used for long term pain relief in animals.

Possible new avenues of pain relief

The ideal drug for treating neuropathic pain in the dog would be oral, effective, specific, have suitable pharmacokinetics allowing daily to thrice daily administration and a wide safety margin. For most of the compounds listed below the pharmacokinetics are unknown and others have already been established as unsuitable. Unfortunately many of newer compounds are not specific to the desired site of action and consequently may have other, typically neurological or cardiovascular, effects. Therefore many have been developed to be delivered neuraxially (i.e. intrathecal or epidural administration) via an ambulatory infusion pump, which has obvious practical and ethical considerations in the dog.

NMDA receptor antagonists

Treatment of chronic neuropathic pain is difficult because central sensitisation has already occurred. As this is mediated through the NMDA receptor an ideal medication would include an NMDA receptor antagonist. Ketamine non-competitively antagonizes NMDA receptors (Nolan, 2000) and is also suggested to impair excitability in superficial dorsal horn neurones by blocking sodium and voltage-gated potassium currents (Schnoebal et al, 2005). Although it has proven benefit in the treatment of neuropathic pain (Cohen and DeJesus, 2004), systemic administration results in unacceptable side effects such as behavioural disturbances and neurotoxicity (Vranken et al, 2005). The use of a topical mixture of 1% ketamine/2% amitriptyline over 6-12 months avoided these side-effects whilst improving analgesia for neuropathic pain syndromes in people (Lynch et al, 2005).

Dextromethorphan is a noncompetitive NMDA antagonist which has analgesic and anticonvulsant properties but it has a short half-life, rapid clearance, and poor bioavailability in the dog so is unlikely to be useful (Kukanich et al, 2004). It is likely that other agents will emerge from current laboratory research on NMDA receptor blockade.

Calcium channel blockers

Activation of voltage-dependent calcium channels is critical for neurotransmitter release and neuronal excitability, and antagonists, such as gabapentin and pregabalin, can be antinociceptive (Matthews and Dickenson, 2001). This has led to development of new analgesics, most notably the conotoxin peptides produced by marine predatory cone snails (genus *Conus*). Each component of Conus peptides selectively

targets a specific subtype of ion channels, neurotransmitter receptors or transporters. These diversified toxins are generally categorized into several families based on their characteristic arrangements of cysteine residues and pharmacological actions (Wang and Chi, 2004). One cationic peptide ziconotide, is derived from the venom of *Conus magus* and is marketed under the trade name of Prialt (Elan Pharmaceuticals). It is the first N-type calcium channel blocker approved for clinical use and represents the first new proven mechanism of action for chronic pain intervention in many years (Snutch, 2005). However intrathecal administration is necessary, because of its systemic toxicity, limiting the usefulness in the dog.

Sodium channel blockers

Clinical and experimental data indicate that changes in the expression of voltage-gated sodium channels in the dorsal horn play a key role in the pathogenesis of neuropathic pain and that drugs that antagonise these channels are potentially therapeutic (Amir et al, 2006; Hains et al, 2003). Unfortunately, the available sodium-channel blockers are not selective and also act on neural and cardiovascular sodium channels, therefore adverse effects can limit their use (Woolf and Mannion, 1999). Sodium-channel blockers used in human medicine include local anaesthetics, such as lidocaine and mexiletine (Kalso, 2005). The therapeutic dose of lidocaine for pain control is far below that which blocks nerves impulse propagation or affects cardiovascular function, but its applicability is limited because it cannot be administered orally. The oral formulation mexiletine is reported to be well tolerated in the dog when treating arrhythmias (Meurs et al, 2002), but this does not mean that is safe if the dog has normal heart muscle function and experience in people suggests that an effective pain control dose is difficult to achieve because of adverse effects (Kalso, 2005).

Tricyclic antidepressants, e.g. amitriptyline (Wang et al, 2004), and some anti-convulsants, e.g. phenytoin, carbamazepine and oxcarbazepine, antagonise sodium channels and are often first-line therapy for neuropathic pain in humans (Lalwani et al, 2005; Wood el al, 2004). Amitriptyline is likely to have suitable pharmacokinetics as it has been used successfully in the dog for behavioural problems (Virga et al, 2001) but it is not yet established whether amitriptyline will be effective for neuropathic pain in the dog. Potential adverse effects include ventricular arrhythmias, but these usually only occur at much higher dose rates (Ansel et al, 1993). The anti-convulsants phenytoin, carbamazepine and oxcarbazepine are unlikely to be successful because of inappropriate pharmacokinetics (Overduin et al, 1989; Schicht et al, 1996; Frey et al, 1980) Development of novel and specific sodium channel blockers is a very lively area of research (Woolf and Mannion, 1999).

Serotonin (5-hydroxytryptamine)

Serotonin (5-HT) is involved in the transmission of nociception in the central nervous system (Colpaert et al, 2002) and inhibits nociceptive responses, wind-up, and after-discharges in spinal neurons through an action on 5-HT1A receptors (You et al, 2005). The selective, high-efficacy 5-HT(1A) receptor agonist, (3-chloro-4-fluoro-phenyl)-[4-fluoro-4-[[(5-methyl-pyridin-2-ylmethyl)-amino]-methyl]piperidin-1-yl]-methanone (F 13640) has been reported to produce long-term analgesia in rodent models of chronic nociceptive and peripheral neuropathic pain (Colpaert et al, 2002) and it also has a curative-like action on allodynia in rats with spinal cord injury (Colpaert et al, 2004). It appears to induce two neuroadaptive phenomena: firstly, activation of 5-HT1A receptors which cooperate with nociceptive stimulation, but paradoxically cause analgesia, and secondly, inverse tolerance, so that the resulting analgesic effect increases rather than diminishes (Colpaert et al, 2002). Many anti-depressants affect serotonin concentration in the CNS but, surprisingly, selective serotonin reuptake inhibitors such as fluoxetine are ineffective in neuropathic pain models. By contrast, antidepressants acting on the noradrenergic (for example milnacipran and duloxetine) or both the noradrenergic and serotonergic systems (for example amitriptyline) are effective (Mochizucki, 2004). The analgesic action of anti-depressants is more likely to be a reflection of sodium channel blockade, since fluoxetine, for example, produces a substantially slower blockade than amitriptyline (Pancrazio et al, 1998).

Sympathetically maintained pain

There is evidence that dysaesthetic pain of syringomyelia is sympathetically maintained because sympatholytic treatment can afford relief when traditional pain relief such as opioids and anti-epileptic drugs are ineffective (Todor et al, 2000). Sympathetically mediated pain is notoriously difficult to treat, although in humans regional sympathetic blocks can give temporary relief and ganglionectomy provides a more permanent potential solution (Todor et al, 2000; Gellman, 2000). Some studies suggest that acupuncture significantly affects the autonomic nervous system (Andersson, 1995) and there is evidence that it is useful adjunctive treatment for sympathetically mediated pain in people (Gellman, 2000). Anecdotally it is reported to be beneficial for some cases of canine syringomyelia. The alpha-2 agonist clonidine is thought to produce analgesia at the spinal level through stimulation of cholinergic interneurons in the spinal cord (Li and Eisenach, 2001). However it is administered neuraxially for neuropathic pain (Martin et al, 2006, Hassenbusch et al, 2002) and results of some clinical trials in people have been disappointing (Ackerman, 2003)

Transplant studies

Transplant of cultured cells that release pain-relieving chemicals such as GABA offer a new direction in the treatment of chronic pain. Preliminary studies have shown that injecting such cells in the subarachnoid space in an excitotoxic animal model of spinal cord injury with similar clinical signs to syringomyelia will reduce behavioural signs of allodynia (Eaton, 2003, 2006).

Conclusion

Appropriate medical management of CM/SM in the dogs has yet to be established. Frusemide, non-steroidal antiinflammatory drugs, opioids, gabapentin and corticosteroids may all be appropriate drugs however the evidence for this is still anecdotal. Current thinking in the treatment of neuropathic pain in humans suggested that because the mechanisms of development of neuropathic pain are multifactorial, appropriate polypharmacy is likely to be more effective than treatment with single agents. This is supported by the existing few case reports detailing treatment of neuropathic pain in animals. Many other drugs such as amitriptyline and pregabalin may prove to have a significant role in pain control in these patients, but there are only very limited current data on their efficacy. More investigation is needed in this area and will require multicenter studies to determine appropriate drugs and drug combinations for optimal pain control.

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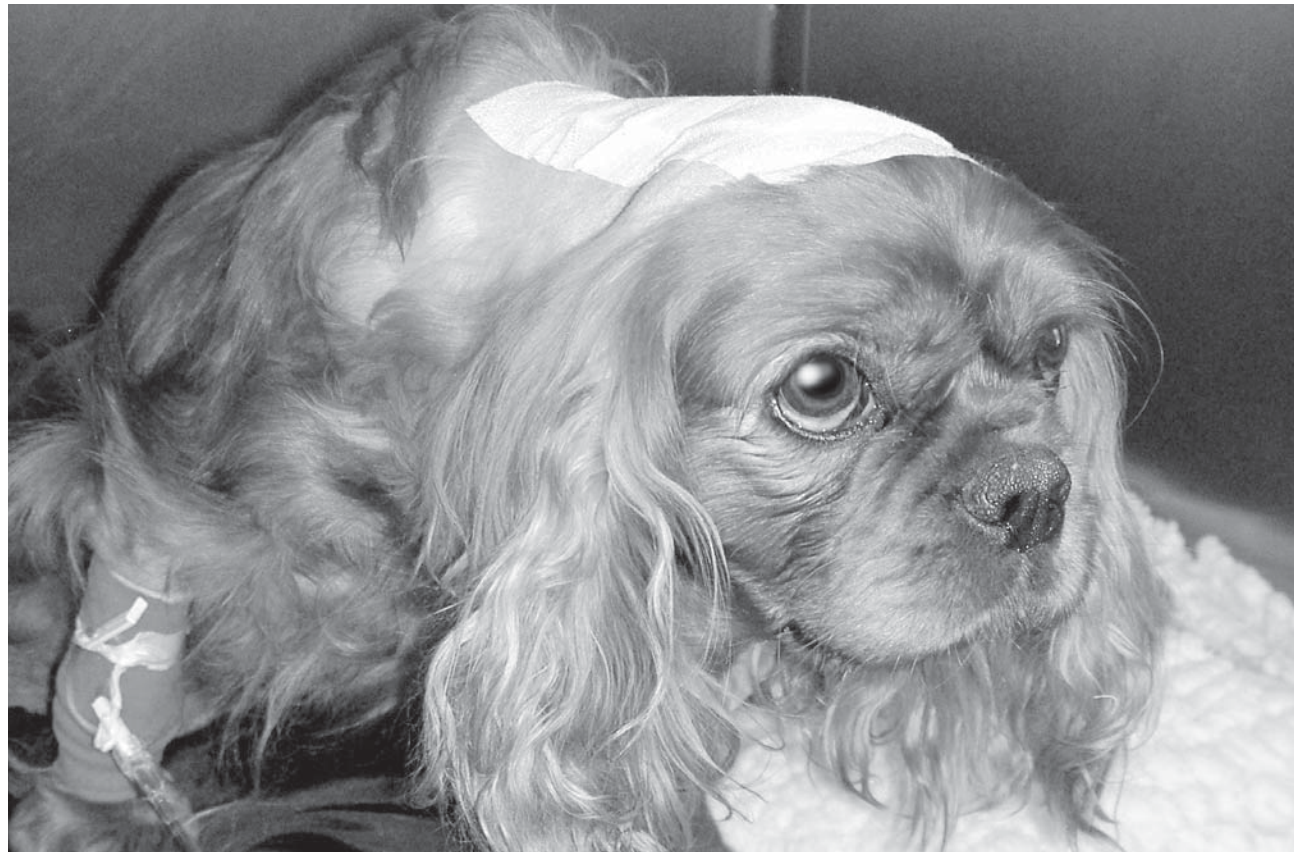

Section 6

Surgical management

Chapter 6.1

Chiari-like malformation with syringomyelia in the cavalier King Charles spaniel; long term follow up after surgical management

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Accepted – Veterinary Surgery

Introduction

Syringomyelia is a condition that results in fluid-containing cavities within the parenchyma of the spinal cord as a consequence of obstruction to cerebrospinal fluid (CSF) movement. It is increasingly recognised in the dog and one of the most common causes is Chiari malformation - defined as decreased caudal fossa volume with caudal descent of the cerebellum, and often the brainstem, into the vertebral canal[1]. Chiari-like malformation (CM) is particularly common in the cavalier King Charles spaniel (CKCS)[2, 3, 4]. The condition is characterized by a mismatch between the caudal fossa volume and its contents, the cerebellum and brainstem, and consequently there is insufficient room for the neural structures, which are forced caudally, obstructing the foramen magnum and the pressure wave of CSF emanating from the head during arterial pulsations. The pathogenesis of syringomyelia is much debated[1, 5]. There is increasing agreement that the syrinx fluid is not CSF and is most likely extracellular fluid that coalesces within the central canal and/or spinal cord substance as a consequence of abnormal pressure differentials between the spinal cord and subarachnoid space[5, 6].

Pain is a predominant feature of the disease in humans and animals with ~ 80% (human) and 35% (dog) respectively reported to experience discomfort[7, 8]. Owners may describe signs suggesting head, spinal or other discomfort. The pain may be difficult to localise on clinical examination as it is often intermittent. Common historical features include yelping after sudden posture change or being more uncomfortable in the evening or early morning. A recent study found that syrinx width is a predictor of pain and suggested that spinal cord dorsal horn damage may result in a neuropathic pain syndrome[8]. Affected dogs may show behavioural signs suggestive of 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). Dogs with a wide syrinx may also scratch, typically on one side only, while the dog is walking and often without making skin contact [1]. The behaviour is suggestive of dysesthesia - *i.e.* a spontaneous or evoked unpleasant abnormal sensation, described by some humans as an intense feeling of insects crawling on the skin or a painful burning itchiness[9].

Surgical therapy has been recommended[10] to improve the dog's quality of life and to retard clinical and radiographic progression of the syrinx. The most common procedure is cranial cervical decompression (also described as suboccipital decompression or foramen magnum decompression) in which most of the supraoccipital bone and dorsal laminae of the atlas are removed (with or without a durotomy) to decompress the foramen magnum[10,11,12]. In this study the case histories for 15 CKCS which had surgical management of Chiari-like malformation/syringomyelia (CM/SM) at least 12 months previously were reviewed retrospectively.

Material and methods

15 consecutive cases which had surgical management of CM/SM over a 6 year period and with at least 12 months follow-up were evaluated retrospectively (Table 1 and 2). Diagnosis was made on the basis of neurological examination and magnetic resonance imaging (MRI) of the brain and cervical spinal cord. The dogs also had haematology and biochemistry. CSF analysis was not performed in any case because of the perceived risk of doing this procedure in dogs with a cerebellar herniation and wide syringomyelia, because the brain and spinal MRI did not support a diagnosis of central nervous system inflammation and because CSF in cases with syringomyelia typically has an inflammatory pleocytosis [2] making interpretation difficult. Pain was determined by historical features such as yelping, scratching behaviour and/or apparent discomfort or avoidance of being touched over the ear, neck, shoulder or sternum together with clinical features such as spinal hyperaesthesia or abnormal head posture. The cases were assigned, retrospectively, a pre- operative pain score, as follows:

- 0 = No pain
- 1 = occasional (< 1 per week) signs of facial, ear (e.g. rubbing) or spinal pain and / or yelping
- 2 = Mild neuropathic pain - occasional shoulder scratching when excited, on waking and when touched.

Does not scream whilst scratching.

- 3 = – Moderate neuropathic pain - consistent shoulder scratching at exercise, when excited and when touched. May occasionally cry when scratching. May appear to dislike touch to certain body parts for example one ear. Owner considers a normal active dog in other respects.
- 4 = Severe Neuropathic pain - consistent shoulder scratching at exercise, when excited and when touched or at other times. Ears or other body parts cannot be touched and/or or groomed. Frequently screams. May adopt unusual body posture when sleeping. Owner feels dog's activity is compromised by the disease.

Other neurological signs e.g. scoliosis, long tract signs (ataxia and /or pelvic limb weakness), ventral horn signs (lower motor neuron signs thoracic limbs) and seizures were recorded. A decision was made for surgery based on severity of pain and lack of response to medical management (10 of 15 dogs) or because the owners were concerned that the dog's signs may be progressive (5 of 15 dogs) (Table 1).

A cranial cervical decompression was performed by the same surgeon in all cases. 30 minutes prior to surgery the dogs received a premedication of 100mg gabapentin (Neurontin Parke-Davis, Eastleigh, UK) per os (this drug was continued post-operatively starting 8 hours after the initial dose), 4mg/kg carprofen (Rimadyl, Pfizer Limited, Sandwich, UK) subcutaneously, 0.2mg/kg methadone hydrochloride (Physeptone, Martindale Pharmaceuticals, Romford, UK) intramuscularly, 0.02mg/kg acepromazine maleate (ACP, Vericore Novartis Animal Health, Royston, UK) intramuscularly. Anaesthesia was induced using 4mg/kg intravenous propofol (Rapinovet, Schering-Plough Animal Health, Welwyn garden City, UK) and maintained with isoflurane (1-3% in 100% oxygen). After induction, 20mg/kg Cephradine (Velosef, Bristol-Myers Squibb, Dublin, Ireland) was administered intravenously. A repeat dose was given every hour during surgery until 1 hour postoperatively (typically 3 doses including premedication dose). A pulse oximeter (Nonoin, Kruuse, A/S Denmark) and oesophageal stethoscope were used to monitor heart rate and adequacy of ventilation. Diastolic blood pressure was recorded using an ultrasonic Doppler flow detector and temperature using a rectal probe oesophageal thermometer. All dogs received intravenous fluids during surgery which was continued until 24 hours postoperatively. The dogs were positioned in sternal recumbency and the head was flexed over a vacuum support cushion (Buster vacu support, Kruuse, A/S Denmark). Tape was used to prevent movement (Fig 1).

Figure 1 CKCS positioned for cranial cervical decompression. The head was flexed over a vacuum support cushion and secured using tape.

A dorsal approach was made to the supraoccipital bone and atlas. The rhomboideus, splenius and occipital muscles were reflected aside and the supraoccipital bone and atlas was exposed. A supraoccipital craniectomy and partial C1 laminectomy was performed in all cases. The extent of the bone removal is depicted in figure 2.

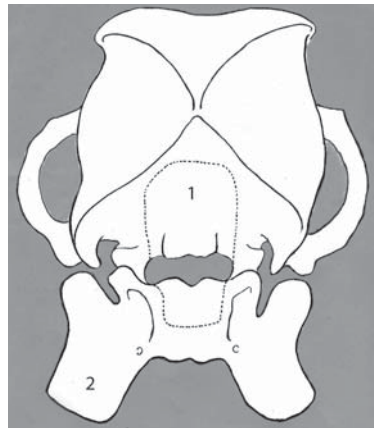

Figure 2 Cranial cervical decompression. The dotted line delineates the extent of bone removal from the supraoccipital bone and dorsal laminae of the atlas. 1. supraoccipital bone, 2 wing of atlas.

The bone was burred using a Hall Sugairtone 2 (Linivatec Corporation, Largo, Florida) until egg-shell thickness and then removed with rongeurs and dental instruments. Care was taken in the region of the vermiform impression as the bone was extremely thin and very little drilling was required. The atlantooccipital membrane was removed using a scalpel blade and bipolar electrocautery. Associated with the atlantooccipital membrane was a tight constricting band of connective tissue across the foramen magnum which was also removed. 8/0 Vicryl (Ethicon, Johnson and Johnson St Steven-Wolouwe Belgian) stay sutures were placed in the dura. Using the stay suture to identify and support the outer meninges (Fig 3), the dura and subarachnoid membranes were incised in a cross shape as depicted in figure 4.

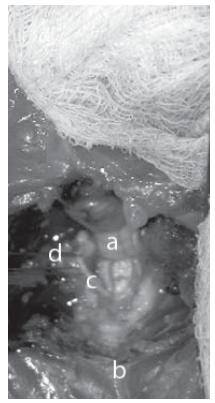

Figure 3 Cranial cervical decompression. The dura and arachnoid meninges have been incised and are supported by a stay suture. The spinal cord and the cerebellar vermis can be visualised though the meningeal defect. The dogs head is towards the top of the picture. a. caudally displaced vermis b. dorsal spine C2 c. dura and arachnoid meninges d. stay suture

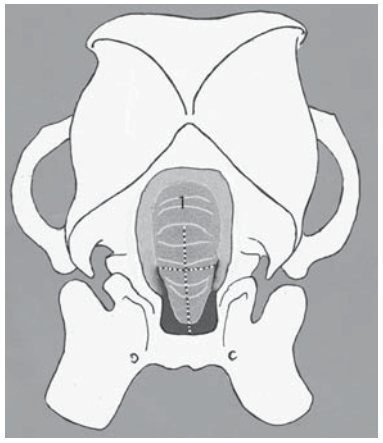

Figure 4 Cranial cervical decompression. The dotted line delineates the incision through the meninges. 1. cerebellar vermis.

This shape of incision was chosen because it allowed the best visual decompression of cerebellum and medulla. In some dogs bleeding occurred from the dural vessels which were controlled with bipolar electrocautery and / or micro-porous polysaccharide beads (Hemablock, Abbott Laboratories, North Chicago). The neural structures were inspected for adhesions which were removed if present. The C1 laminectomy was continued until ~ 3mm caudal to the tip of the cerebellar vermis; typically to the level of the attachment of the dorsal spinous process of C2. The resulting kite shaped defect in the meninges was either left open and covered with absorbable collagen sponge (Lysostypt Braun Aesculap, Rueeggisingerstr, Switzerland) (earlier cases listed in Table 1a) or expanded by patching with 2 layers of a biocompatible collagen matrix (Vet BioSIST, Cook/Global Veterinary Products, SurgiVet, Smiths Medical Pm inc N7 W22025 Johnson Road, Waukesha, WI USA 53186). If possible the patch was sewn to the dura using the Vicyl 8/0 stay sutures however in case 14 manipulation of the dura resulted in repeated excessive haemorrhage and so the patch was simply laid over the defect overlapping the dural edges by at least 1cm. To aid with haemostasis an absorbable collagen sponge (Lysostypt Braun Aesculap, Rueeggisingerstr, Switzerland) was then placed over the entire defect. The muscle layer was closed with 2/0 PDS, subcutaneous layer were closed with 2/0 Vicryl and the skin defect was closed with skin staples (Skin Mate Skin Stapler Animalcare Ltd Dunningtom York).

Postoperatively the dogs received 0.2mg/kg methadone (Physeptone, Martindale, Pharmaceuticals, Romford, UK) every 4 hours. When the dog had appeared consistently comfortable over an 8 hour period this was switched to 0.015mg/kg of Buprenorphine (Vetergesic, Alistoe Animal Health, Sheriff Hutton, UK) every 6 hours which then gradually withdrawn at a rate determined by the degree of pain behaviour displayed by the dog. Carprofen (Rimadyl, Pfizer Limited, Sandwich, UK) at 2-4mg/kg per day and gabapentin (Neurontin Parke-Davis, Eastleigh, UK) at 100mg every 8 to 24 hours were continued for at least 2 weeks post operatively then gradually withdrawn in all dogs with the exception of dog 12 who was continued on twice daily gabapentin and carprofen. All dogs also received 20-30mg/kg of Cefalexin (Ceporex 250mg; Schering-Plough Animal Health, Uxbridge, UK) twice daily for five days starting 8 hours after the last intravenous Cephradine (Velosef, Bristol-Myers Squibb, Dublin, Ireland). The dogs were reassessed 2, 6 and 12 months after surgery either by direct examination by the same veterinary neurologist or by telephone/email interview. Thereafter the dogs were assessed yearly. The nature of the post operative re-examination depended on owner preference and proximity to the hospital. Nine of 15 dogs had a neurological examination at all time points (unless euthanized). Dog 5 received veterinary neurologist examination at 2, 6, 12 and 23 months only. Dog 10 received veterinary neurologist examination at 2 and 12 months post operatively only. Dogs 3 and 15 received veterinary neurologist examination 2 months post-operatively only. Dog 13 received veterinary neurologist examination 2 months and 2.5 years post-operatively only. Dog 11 had no post-operative examination by a veterinary neurologist with all follow up information being obtained via telephone and email interviews with the primary veterinary surgeon and owner and examination of the primary veterinary surgeon's medical records. All the owners were asked whether they felt that the dog was improved after surgery and questioned on the degree of discomfort displayed by the dog. In the dogs that improved post-operatively the end point was taken as time at which new signs of pain had started to develop and / or additional analgesia was required. However if the post-operative improvement was sustained the end-point was taken as the time after surgery at the last post-operative assessment. In the dogs that were initially unchanged post-operatively an end point was taken as the time that the owner felt that the dog was worse than the preoperative status or if the status was stable as the time after surgery at the last post-operative assessment.

Results

Surgical management

Table 1 illustrates pre-operative information for the 15 CKCS with CM/SM. There were 6 male and 9 female and the age range at the time of first clinical signs of syringomyelia was 0.3-4.5 years (mean 2.2 years). The age at the time of surgery ranged from 0.8-8.1 years (mean 3.3years) and the dogs had clinical signs for 0.1-4.2 years (mean 1.1 years, mediam 0.7y) before surgery. The maximum width of the syrinx ranged from 0.6-0.9cm in 12 dogs (mean 0.7cm). For 3 dogs this information was not available as the MRI images were not in a DICOM ™ format thus preventing precise measurement. These dogs were either assigned wide (2 dogs) or narrow (1 dog) syrinx. Ten of 15 owners made the decision for surgery because they felt that their dog's quality of life was unacceptable; 5 of 15 owners made a decision for surgery in an attempt to avoid deterioration. 1 dog had a pain score of 2, 4 dogs had pain score 3 and 10 had pain score 4. All dogs had a cranial cervical decompression, 8 dogs had a durotomy alone and 7 dogs had durotomy with biocompatible collagen matrix patch (Vet BioSIST, Cook/Global Veterinary Products, SurgiVet, Smiths Medical Pm inc N7 W22025 Johnson Road, Waukesha, WI USA 53186). A decision had been made to change surgical technique because of concern about how the neural tissue bulged through the open dura and arachnoid layers.

Table 1 CKCS with surgical management of Chiari-like malformation / syringomyelia

Dog	Sex	Age onset signs SM (years)	Owner's primary reason for surgery	Pain score	Other neurological signs	Maximum width of syrinx (cm)	Duration clinical signs before surgery (years)	Age at surgery (years)	Surgical technique
1	M	2.6	1	4	Slight thoracic limb weakness	0.7	0.6	3.2	durotomy
2	F	0.3	1	4	Scoliosis, thoracic limb weakness,	wide	1.0	1.3	durotomy
3	F	0.7	2	2	Scoliosis	0.7	0.1	0.8	Durotomy and biocompatible collagen matrix%
4	F	1.5	2	3	Slight thoracic limb weakness	0.8	0.4	1.9	durotomy
5	F	1.7	1	4	Epilepsy, Mild pelvic limb weakness	0.8	1.5	3.2	durotomy
6	F	0.4	1	4	Slight thoracic limb weakness	0.8	1.0	1.4	Partial durotomy *
7	F	3.0#	2	3	none	0.8	1.4	4.4	durotomy
8	M	3.9	1	4	Scoliosis, pelvic limb ataxia, thoracic limb weakness,	0.7	4.2	8.1	Durotomy and biocompatible collagen matrix%
9	F	4.3	1	4	None	0.6	2.8	7.0	Durotomy and biocompatible collagen matrix%
10	M	4.5	2	3	single seizure	0.6	0.6	5.1	Durotomy and biocompatible collagen matrix%
11	F	2.9	1	4	Scoliosis	0.9	0.3	3.3	Durotomy and biocompatible collagen matrix%
12	F	1.3	1	4	Scoliosis	0.8	0.1	1.4	Durotomy and biocompatible collagen matrix%
13	M	3.3	1	4	None	0.7	0.7	4.0	durotomy
14	M	2.1	2	3	Pelvic limb ataxia	narrow	0.8	3.0	Durotomy and biocompatible collagen matrix%
15	M	1.0	1	4	Scoliosis, tetraparesis, ataxia	wide	0.7	1.7	durotomy
MEAN	60%F	2.2		3.6		0.7	1.1	3.3	

F – female, M - male
1. Quality of life unacceptable – pain uncontrolled by medical management.
2. Attempt to prevent deterioration
%-. Biocompatible collagen matrix (Vet BioSIST, Cook/Global Veterinary Products, SurgiVet, Smiths Medical Pm inc N7 W22025 Johnson Road, Waukesha, WI USA 53186).
- clinical signs present from day acquired from breeder at 3 years old
* - problems haemorrhage forced early closure
wide – maximum width of syrinx judged to be more than half diameter spinal cord,
narrow - maximum width of syrinx judged to be less than half diameter spinal cord

Table 2 Post operative follow-up in CKCS with Chiari-like malformation / syringomyelia

Dog	Immediate post operative complications	Apparent dis-comfort Improved after surgery	Pain score 2 months after surgery	Pre-operative neurological deficits improved after surgery	Time of deteriora-tion after surgery (years)	Time after surgery eutha-nasia (years) - reason	Post operative MRI- time (years)	Years since surgery (surviving dogs)	Addi-tional medi-cation #	Age surviving dogs at last follow up (years)
1	none	Y	2%	N	0.2	0.4 - SM	N		none	
2	none	Y	3	Y*	0.3	4.7 - SM	N		S	
3	none	N	2	Y	0.8		N	1.3	None	2.1
4	none	Y	2	N	1.5		Y- 1.0	1.9	F, G	3.8
5	status epilepticus	Y	2	Y	1.8		Y- 1.9	3.8	S	7.0
6	none	Y	2	N	2.0		Y - 2.1	2.4	S	3.8
7	none	N	3	n/a	2.3		Y- 3.8	3.8	G	8.2
8	none	Y	2	Y		0.9 - tonsillar carcinoma			none	
9	Slight ataxia and hypermetria	Y	3	n/a			Y- 0.3	1.0	none	8.0
10		Y	2	seizure 3-4 months post-operatively			N	1.0	F	6.1
11	none	Y	2	No post-operative examination			N	1.2	none	4.4
12	none	Y	2	Y			Y - 1.4	1.6	C,G,A	3.0
13	Slight ataxia and hypermetria	Y	3	n/a			N	2.5	none	6.5
14	none	N	3	Y			N	3.5	none	6.4
15	hypermetric left side, more ataxic	Y	3	Y			N	6.5	none	8.3
MEAN			**2.4**		**1.3**	**2.0**	**1.8**	**2.5**		**5.6**

% - deteriorated within days of this assessment * - improvement of scoliosis only , n/a – not applicable, # - medication dog is currently receiving or was receiving at time of death is detailed F- frusemide, G-gabapentin, C-carprofen, A-acupuncture, S – methylprednisolone or prednisolone , Y – yes, N- no, n/a – not applicable

Table 2 illustrates post operative data for the 15 dogs. The surgery had a low morbidity. One epileptic dog had status epilepticus after surgery and was managed with intravenous diazepam (Diazamuls, Dumex, Barnstaple, UK) at 0.5 mg/kg followed by intramuscular phenobarbitone (Martindale Pharmaceuticles Romford UK) at 6 mg/kg. Three dogs were slightly hypermetric and ataxic the day after surgery. This resolved within 48 hours. All the dogs made a quick recovery after surgery and were able to exercise normally within 4 weeks of the procedure. Six dogs had scoliosis prior to surgery. In 5 dogs this improved; one dog (case 11) had no post operative neurological examination. Four dogs had pelvic limb ataxia with upper motor neuron weakness; this improved in all dogs postoperatively. Six dogs had thoracic limb weakness; this improved in 2 dogs and was persistent in 4. The epileptic dog (case 5) with status epilepticus after surgery never had another seizure post operatively and was successfully weaned of anti-epileptic drugs. Case 10 had a single seizure prior to surgery and another single seizure approximately 3 months after surgery.

None of the dogs had a complete resolution of the signs of pain post operatively. At 2 months post operatively all 10 dogs with a pain score of 4 had improved to pain score 2 (6 dogs) or 3 (4 dogs). Two of the dogs with a pain score of 3 had improved to 2; the remaining 2 dogs were unchanged. The single dog with a pain score of 2 was unchanged post-operatively Overall of the 15 dogs, 12 (80%) had improved comfort after surgery and 7 of that 12 maintained that improvement for 1 – 6.5 years of follow up (mean 2.5 years, median 2.2 years). 1 dog was euthanized because of a tonsillar carcinoma 5 months after surgery; at the time of euthanasia he had maintained an improved status. 4 of the 12 improved dogs had deteriorated 0.2 – 2.0 years after surgery. 2 of these dogs were subsequently euthanized as a consequence of syringomyelia associated pain at 0.4 and 4.6 years after surgery. 2 of 15 dogs had an unchanged pain status postoperatively then subsequently deteriorated 0.8 and 2.3 years after surgery. 1 dog with an unchanged status has remained stable for 3.5 years. In summary all dogs had either an improved (80%) or unchanged status (20%) postoperatively. 7 dogs (47%) subsequently deteriorated 0.2 – 2.3 years after surgery (mean 1.3 years). 2 dogs had been euthanized as a consequence of the syringomyelia and 1 dog because of tonsillar carcinoma; 12 dogs were still alive 1-6.5 years after surgery.

6 of 15 dogs had a post-operative MRI, 0.3-3.8 years (mean 1.8 years) after surgery. Some examples of pre and post operative MRI scans are depicted in figures 5, 6 and 7. It can be appreciated that the shape of the syrinx had remained remarkably unchanged. 7 dogs received additional pain-relief medication after surgery (table 2). Dogs 10 and 12 had been maintained on medication since the time of surgery, the remaining dogs had been started after an increase in discomfort.

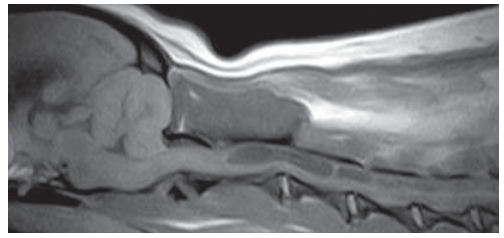

Figure 5a

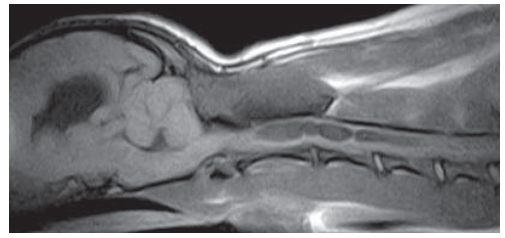

Figure 5b

Figure 5 Midsagittal T1-weighted image of the brain and cervical spinal cord from dog 9 a) pre operatively b) 4 months post operatively. The dog was clinically improved at the time of the MRI scan and described by the owner as no longer screaming. However she still displayed signs of a neuropathic pain syndrome.

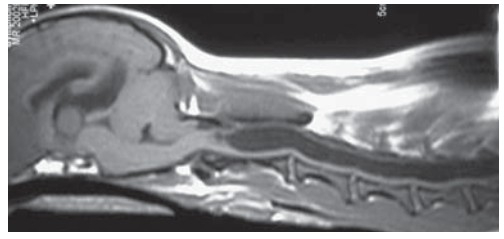

Figure 6a

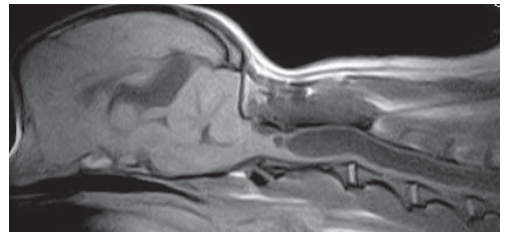

Figure 6b

Figure 6 Midsagittal T1-weighted image of the brain and cervical spinal cord from dog 4 a) pre-operatively b) 1 year post operatively. The dog was clinically improved at the time of the MRI scan however she deteriorated to her pre-operative degree of discomfort 6 months later.

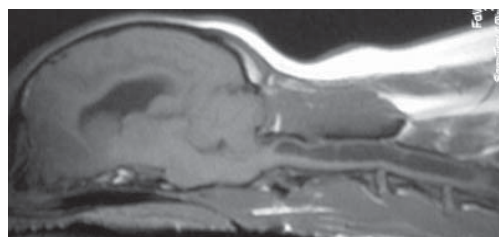

Figure7a

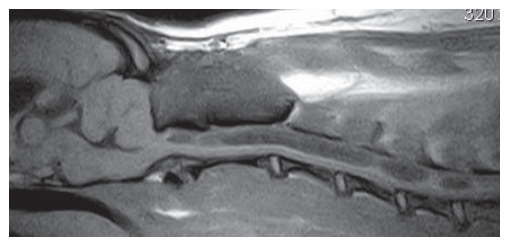

Figure7b

Figure 7 Midsagittal T1-weighted image of the brain and cervical spinal cord from dog 6 a) pre-operatively b) 2 years post operatively. The dog had recently deteriorated to her pre-operative degree of discomfort. The pain was unresponsive to NSAIDS and gabapentin and was somewhat improved on corticosteroids.

Discussion

Successful surgical management of syringomyelia could be defined as a procedure with a low mortality and morbidity where postoperatively the syrinx has resolved and the patient is free of clinical signs and the syrinx does not recur. Like previous reports, this study suggests that cranial cervical decompression is a safe procedure if performed by a surgeon with appropriate neurosurgical training [10, 11, 12]. Intra-operative complications were minimal and confined to meningeal vessel bleeding which was quickly controllable with cautery and haemostatic aids.

The surgery had a low morbidity. All the dogs made a quick recovery after surgery and all were able to exercise normally within 4 weeks after the procedure. 12 of 15 dogs were improved after surgery but all dogs continued to have signs suggesting a neuropathic pain syndrome. All of the dogs with a pain score of 4 improved, suggesting that surgery could be recommended for dogs in severe pain where medical management has been unsuccessful. However although 80% of the dogs showed a post operative improvement this surgical procedure does not appear to result in resolution of the syrinx. Similar findings were described by Vermeersch et al [11]. The reason for the failure for this surgical technique to adequately deal with syringomyelia is not clear. Da Costa, et al described successful management of acquired cerebellar herniation and syringomyelia secondary to brain stem tumour [13]. After treatment with radiation therapy, shrinkage of the tumour and presumably re-establishment of CSF flow through the foramen magnum the syringomyelia resolved indicating that reversal is possible in the dog. The failure of surgery to adequately treat the syrinx suggests that this surgery in the dog does not sufficiently improve CSF flow though the foramen magnum and it may be that in the dog, removing most of the supraoccipital bone and part of the dorsal laminae of C1 with durotomy is just not sufficient. The same situation does not exist for management of Chiari malformation in humans in which most reports suggest that cranial cervical decompression, whatever the technique, results in syrinx resolution in over 90% of patients [14, 15]. However due to anatomical differences it is possible to remove comparatively more bone laterally from both the occipital bone and atlas in the human. One further difference between the human and canine condition is that in the human, the cerebellar tonsils rather than the vermis is herniated through the foramen magnum[16]. The tonsils may be resected without compromise to the patient and consequently many surgeons partly or completely remove them thus creating more space[17, 18]. However, resection of the vermis in the dog could be expected to result in post-operative ataxia, dysmetria, and intention tremors[19]. It may be possible to perform a partial resection of the vermis without serious postoperative complication and this it may be worth considering as an adaptation of the surgery (Todd Axlund, personal communication).

Another possible explanation is that once formed a large syrinx may self perpetuate either because normal CSF flow cannot be re-established though the narrowed subarachnoid space or possibly because the CKCS spinal cord with chronic syringomyelia is not compliant enough to allow syrinx collapse and resolution. An alternative explanation is that pathogenesis of the syringomyelia in the CKCS is due to more than just overcrowding at the foramen magnum. Chiari malformation is extremely common in the CKCS [5,6]. Cerda-Gonzalez et al found that 51 of 59 dogs had cerebellar crowding at the foramen magnum[20]. However, not all dogs with a Chiari malformation develop syringomyelia and there is no significant difference in the caudal fossa volume between CKCS with and without syringomyelia.[20, 21] This suggests that there may be other anatomical factors involved; so far however, investigation has failed to indicate what these may be. In a study looking at vertebral canal diameter in the C1-C3 area, Carruthers et al [21] found that dogs with syringomyelia tended to have a larger vertebral canal diameter at the C2/C3 junction and at C3 and that dogs with syringomyelia and clinical signs of pain tended to have a narrower vertebral canal at C1/C2 although further study is required to establish if this truly is an important contributory feature in the pathogenesis.

It is possible that the surgery could be modified and improved. Dewey et al recently described a technique of cranial cervical decompression combined with a titanium polymethyl methacrylate plate over the bony defect. [22] It is not yet known whether this technique will be more successful in the long term. An alternative method of managing syringomyelia is direct shunting of the cavity. In humans this is not a preferred technique for management of CM/SM as long term outcome is poor due to shunt obstruction and/or spinal cord tethering.[23] However the short term results are reasonable with syrinx collapse occurring in a majority of human cases[24]. There has been a single report of syringo-subarachnoid shunting in a dog using an equine ocular lavage tube (Cook/Global Veterinary Products, SurgiVet, Smiths Medical Pm inc N7 W22025 Johnson Road, Waukesha, WI USA 53186). [25] However post-operative MRI revealed that the syringomyelia was still prominent although there was clinical improvement.

7 of 15 dogs (47%) deteriorated 0.2-2.3 years after surgery (mean 1.3 years). The follow up period of the remaining dogs ranged from 1 to 6.5 years (mean 2.5 years) so more cases could be expected to deteriorate given a longer follow up period. Similar results are reported by Dewey et al. [10] In a series of 16 dogs, 13 (81%) of affected dogs had improvement of clinical signs after surgery, but 25% had a recurrence within the follow-up period of 6-36 months.[10] It was not ascertained whether any of the improved dogs actually had resolution of the syrinx prior to deterioration or were in fact similar to the dogs in the current study i.e. clinical improvement without radiographic improvement. The deterioration was attributed to scar tissue adhering to exposed neural tissue thus preventing adequate CSF flow. [10] In the current study 1 of the 2 dogs that was euthanized after an early recurrence of signs was necropsied (Dog 1). Gross inspection revealed many layers of scar tissue adhered to the dorsal medulla, cranial spinal cord and cerebellum. This author suggests that the post operative improvement after cranial cervical decompression in canine CM/SM is attributable to improved CSF flow at the foramen magnum and the deterioration is due to subsequent obstruction.

It is possible that although cranial cervical decompression in the dog does not reverse the syrinx it may delay the progression of the disease. However due to the small numbers in this series it is not

possible any draw any conclusions as to whether the surgery did in fact achieve this objective. The post-operative MRI scans demonstrated little or no improvement in the syringomyelia but they also showed no progression. However it is naive to assume that because the syrinx had not increased in size and / or the dogs euthanized as a consequence of pain that the surgery was a partial success as the natural progression of CM/SM without surgical management has not been established. This also raises some ethical issues as syringomyelia results in a neuropathic pain syndrome [8] and according to human suffers, is an extremely painful condition. [7] Merely surviving does not give an indication of quality of life or whether the discomfort these animals experience is appropriately addressed.

The majority of the dogs in this study had high pain scores (mean score 3.6) and wide syrinxes. It is not known if this surgery may be more successful if performed on dogs with less severe disease. Due to small study size it was also not possible to draw conclusions as to whether performing surgery earlier in the course of the disease was advantageous however there was no correlation between favourable outcome and short clinical history of signs of syringomyelia.

As this is a small retrospective clinical study with many methodological problems, conclusions, if any, must be drawn with caution. One of the most important problems with this study is that pain is a subjective parameter and may have been inappropriately assessed. In particular interpretation of clinical history such as “scratching less intensely and less often” was very subjective and the pain score used in the study, although helpful, was not detailed enough. An improved (but simple) way of prospectively scoring neuropathic pain in dogs needs to be established (appendix 1). In an attempt to avoid bias the end point of this study was taken to be when the owners felt that the dog was starting to show new signs of pain, for example starting to scream more frequently. However this parameter is also subjective especially as owners may become more tolerant of clinical signs as they get used to them. Another limitation of this study is that not every dog had a postoperative MRI and with 3 dogs the last post operative assessment(s) was done distantly by telephone and/or email and examination of medical record.

Conclusion

Cranial cervical decompression surgery for CM/SM has a low mortality and morbidity and in cases with a high pain score the procedure can improve quality of life. The procedure does not appear to result in syrinx collapse and resolution possibly because other factors are involved in the development and/or persistence of syringomyelia. In addition the clinical improvement may not be sustained and a proportion can be expected to deteriorate from as soon as 2 months after surgery. The procedure may or may not delay progression of the disease. It is suggested that the postoperative improvement is attributable to improved CSF flow at the foramen magnum and the deterioration is due subsequent obstruction. It is also suggested that to properly evaluate the success of any surgical technique for CM/SM that there be a follow up period of at least 2 years and that post operative MRI scans be performed as clinical improvement does not necessarily imply radiographic improvement. Further study is needed to achieve better understanding of the pathogenesis and predisposing factors of CM/SM in the dog. As this condition is painful but does not necessarily result in euthanasia better medical treatment guidelines should be established.

Acknowledgements

The author is grateful to Penny Knowler who prepared Figures 2 and 4 and to the Goddard Veterinary group who part financed most of the post-operative MRI scans. I am also grateful to Professors Nick Jeffery and Jan Rothuizen who critically reviewed the manuscript.

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Chapter 6.2

Pilot Study: Chiari-like malformation with syringomyelia in the cavalier King Charles spaniel; long term follow up after conservative management

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Introduction

The progression of syringomyelia without surgical management has not been documented and without this background information it is more difficult to assess success or otherwise of surgery. A pilot study looking at the natural history of syringomyelia in a group of cavalier King Charles spaniels (CKCS) displaying signs of neuropathic pain syndrome was therefore performed.

Materials and methods

The medical records of all cavalier King Charles spaniels (CKCS) presenting to the Stone Lion Veterinary Centre neurology service over a 5 year period and with at least 2 years follow up (July 1999 to July 2004) were examined for a diagnosis of syringomyelia or suspected syringomyelia. The records were further searched for a clinical history of phantom scratching.[1] This clinical sign was chosen because it is specific for syringomyelia and is an indication of a wide syrinx with a neuropathic pain syndrome, thus ensuring that all the dogs in the group had disease of a similar severity[1] A further advantage was that this allowed a comparison with a similar group of CKCS that were managed surgically.[2] The owners and veterinary surgeons for this sub group of dogs were contacted by telephone and / or email and sent a questionnaire (Figure 1) detailing the dog's clinical signs and treatment. The veterinary surgeons also supplied a copy of their medical records for each dog. The end point was taken as the age at the point of death or the age at the conclusion of the study in July 2006.

Figure 1 Questionnaire sent to owners and veterinary surgeons (1 copy each) of dogs with clinical signs of syringomyelia-associated neuropathic pain ▶

The cohort included 6 dogs without MRI (magnetic resonance imaging) confirmation so as not to exclude dogs from a different socioeconomic group (i.e. owners that could not afford a MRI scan) and because the perception of suffering and decision making may be different between owners allowing and refusing investigation.

Results

Twenty eight dogs met the criteria for inclusion in the study, of which 11 were managed surgically and 17 conservatively. 3 of those conservatively managed dogs were lost to follow up because the owners had moved and the details of the 14 remaining dogs are detailed in Table 1. The age at which first signs of syringomyelia were seen was 0.4 – 6.8 years (mean 2.2 years) and the age of diagnosis was 1.3 – 9.1 years (mean 4.4 years). 8 of 14 dogs had the suspected diagnosis confirmed by MRI or post mortem.

Treatment included nonsteroidal anti-inflammatory drugs (NSAIDs), gabapentin (Neurontin Parke-Davis, Eastleigh, UK) and corticosteroids but some dogs received no drugs at all. There was great variation in the treatment regime between individuals at any given time but typically dogs were initially started on NSAIDs and then switched to gabapentin and / or steroids as their condition progressed. Five dogs were euthanized because of syringomyelia associated pain at 3.0-10.4 years old (mean 6.3 years), one dog was euthanized because of heart failure and the remaining dogs are still alive aged 4.1 – 10.3 years old (mean 7.1 years). By comparison in the group of 15 dogs managed surgically,[2] there was an post operative improvement in 80% with the remainder unchanged. Seven dogs (47%) subsequently deteriorated 0.2 – 2.3 years after surgery (mean 1.3 years) and 2 dogs were eventually euthanized as a consequence. Twelve dogs were still alive, 1-6.5 years after surgery (mean 2.5 years).

CKCS SYRINGOMYELIA STUDY GROUP

Aiming to prevent pain in our dogs

Pedigree Name / Registration Number _____

Dog's Date of birth: _____ Colour B B/T R T Gender M, MN F FN Date questionnaire completion_____

CLINICAL SIGNS

At what age did your dog first show signs of syringomyelia? _____

What were the initial clinical signs?

Shoulder scratching ☐; Scratching elsewhere☐ (specify)_____ ; Neck pain ☐ ; Pain elsewhere ☐ Specify _____ ; Signs of pain when scratching ☐, excited ☐, touched ☐, change of head position ☐, jumping ☐, no apparent reason ☐; Scoliosis (twisted spine esp. neck) ☐ Wobbly hind limb gait ☐ Weak forelimbs ☐

When was your dog diagnosed with syringomyelia?_____How old was your dog?_____

How was the diagnosis made? MRI ☐ Post Mortem ☐ Suspected on basis clinical signs only ☐

If possible, please attach a copy of the MRI or PM report / findings.

If applicable, what were the clinical signs before surgery?

Shoulder scratching ☐; Scratching elsewhere☐ (specify)_____ ; Neck pain ☐ ; Pain elsewhere ☐ Specify _____ ; Signs of pain when scratching ☐, excited ☐, touched ☐, change of head position ☐, jumping ☐, no apparent reason ☐; Scoliosis (twisted spine esp. neck) ☐ Wobbly hind limb gait ☐ Weak forelimbs ☐

Is your dog alive? Yes ☐ No ☐ **If dead, at what age did they die?**_____

If dead, what was the cause of death / reason for euthanasia?_____

_____

What are dog's clinical signs now (if dead indicate clinical signs at time of death)

Shoulder scratching ☐; Scratching elsewhere☐ (specify)_____ ; Neck pain ☐ ; Pain elsewhere ☐ Specify _____ ; Screaming when scratching ☐, excited ☐, touched ☐, change of head position ☐, jumping ☐, no apparent reason ☐; Scoliosis (twisted spine esp. neck) ☐ Wobbly hind limb gait ☐ Weak forelimbs ☐

TREATMENT☐ Please Complete Page 2 NO TREATMENT☐

Please return questionnaire to CKCS syringomyelia project coordinator Clare Rusbridge, Stone Lion Veterinary Centre, 41 High Street, Wimbledon, UK, SW19 5AU neuro.vet@btinternet.com Confidential fax 00 44 (0)20 87860525

CKCS SYRINGOMYELIA STUDY GROUP

Aiming to prevent pain in our dogs

Treatment	When / how old was dog	How long did your dog have this treatment	Was it effective? (PLEASE GRADE 0-5 WHERE 0 IS COMPLETELY INEFFECTIVE AND 5 IS COMPLETELY EFFECTIVE)	How long was it effective for	Is your dog still receiving this drug
NSAIDS e.g. Rimadyl, Metacam					
Steroids e.g. prednisolone					
Gabapentin (Neurontin)					
Opioid drugs e.g. pethidine or morphine					
Acetazolamide (Diamox)					
Shunt surgery (syrinx to subarachnoid shunting)		N/A			N/A
Decompression surgery (occipital craniectomy +/- durotomy, C1 laminectomy)		N/A			N/A
Repeat shunt surgery		N/A			N/A
Repeat decompression surgery		N/A			N/A
Acupuncture					
Homeopathy					
Other (please specify)					

If dog had surgery please indicate Surgeon's name:_____Phone:_____

Address:_____

Please return questionnaire to CKCS syringomyelia project coordinator Clare Rusbridge, Stone Lion Veterinary Centre, 41 High Street, Wimbledon, UK, SW19 5AU neuro.vet@btinternet.com Confidential fax 00 44 (0)20 87860525

Table 1 14 CKCS with signs of syringomyelia associated neuropathic pain

DOG	Sex	Age onset signs SM (years)	MRI / PM confirmed	Age diagnosis SM (years)	Age at death (years)	Reason for euthanasia	Years with clinical signs SM	Age surviving dogs at last follow up (years)
1	M	2.3	Y	2.7	3.0	sm	0.7	
2	F	1.0	N	3.0	5.2	sm	4.2	
3	F	1.7	Y	3.0	6.3	sm	4.6	
4	F	6.8	N	7.9	9.2	sm	2.4	
5	M	0.5	Y	4.0	10.0	heart failure	9.5	
6	M	1.5	Y	9.1	10.4	sm	8.0	
7	M	1.0	N	1.3			3.1	4.1
8	F	1.0	Y	2.2			3.2	4.2
9	M	1.4	N	1.9			3.1	4.5
10	F	0.4	Y	2.4			5.3	5.7
11	M	6.0	N	7.0			2.6	8.6
12	M	1.5	Y	5.2			5.7	9.5
13	M	1.0	Y	4.0			9.0	10.0
14	M	4.0	N	8.0			6.3	10.3
MEAN	**36%F**	**2.2**	**57% Y**	**4.4**	**7.3 (6.3 excluding case 5)**		**4.8**	**7.1**

M - male, F – female, Y- yes, N- no, SM- syringomyelia

Discussion

The age of onset and distribution of sex was similar to other studies [2] CM/SM was a cause of euthanasia in 36% of the cases. However 43% of the cohort had survived to be greater than 9 years of age. A recent study suggested that the mean age of death for CKCS is 10.7 years (standard deviation 2.9 years), [3] indicating that syringomyelia does not necessarily result in premature death and many dogs can achieve a normal lifespan for the breed. However, survival does not imply that the dogs enjoyed a good quality of life and the medical records of many of the dogs suggested that the pain was not adequately controlled all of the time. This observation is important when attempting to assess the success (or otherwise) of surgical management and also emphasises that surgery should not be considered a success because the dog has not been euthanized.

This study had serious methodological problems meaning that accurate conclusions cannot be drawn however it suggests that dogs with neuropathic pain from syringomyelia may survive for many years and are likely to benefit from better medical treatment guidelines. It also highlights the need for a prospective clinical study assessing which analgesics are the most appropriate for treating this disorder.

Acknowledgements

The author is grateful to Lisa Fox VN who spent considerable time coordinating much of the telephone and questionnaire follow up for the conservatively managed cases. Thanks are also due to Drs Pete Smith and Paul Mandigers who critically appraised this manuscript.

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Section 7

Genetics

Chapter 7.1

Hereditary aspects of occipital bone hypoplasia and syringomyelia (Chiari-like malformation) in cavalier King Charles spaniels

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Veterinary Record 2003; 153: 107-112

Introduction

Chiari-like malformation (occipital bone hypoplasia) resulting in caudal fossa overcrowding, obstruction of cerebrospinal fluid (CSF) pathways and secondary syringomyelia (figures 1 and 2) was first identified in Cavalier King Charles spaniels (CKCSs) in 1997 (Rusbridge and others 2000). After the condition was initially reported it became apparent that it was common in the CKCS breed. Affected CKCSs have now been identified across Europe, Australasia, and North America. The classic clinical sign in the CKCS is cervical and shoulder paraesthesia which results in the dog scratching at the neck/shoulders, especially when excited or on a lead. This is presumed to be a consequence of damage to the dorsal horn, decussating spinothalamic fibres and processing of sensory information. If there is ventral horn cell damage then the dog may have muscular weakness resulting in neck scoliosis or a thoracic limb paresis.

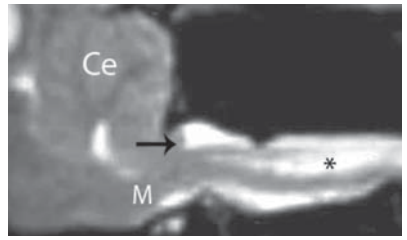


Figure 1a) Sagittal T2W magnetic resonance image of a four year old male CKCS with cervical and shoulder pain. The caudal fossa is small resulting in overcrowding of the cerebellum (Ce). There is a herniation of the caudal cerebellum into the foramen magnum (arrow), the medulla (M) is kinked and there is syringomyelia (asterisk). The cerebrospinal fluid (CSF) appears white.

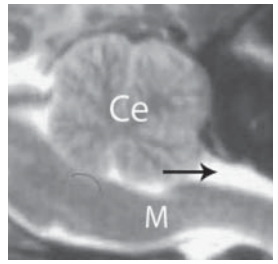


Figure 1b) Sagittal T2W magnetic resonance image of a Staffordshire bull terrier demonstrating the normal anatomy of the caudal fossa in a mesencephalic dog. Cerebellum (Ce), brain stem (M), the CSF appears white, note the large amount of fluid present in the foramen magnum (arrow) which is absent in figure 1a.

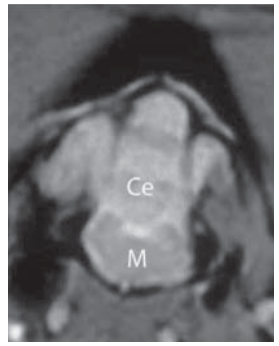


Figure 2a) Axial T2W magnetic resonance images through the cranial cervical junction of a four year old male CKCS with cervical and shoulder pain. The CSF pathways are obstructed, very little (white) CSF can be visualised around the central nervous system.

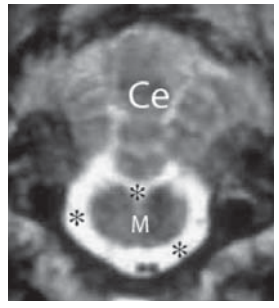


Figure 2b) Axial T2W magnetic resonance image through the cranial cervical junction in a Staffordshire bull terrier. The CSF pathways (asterisk) are unobstructed. Cerebellum (Ce) Medulla (M)

Cases with a very wide syrinx may have damage to the descending white matter tracts resulting in pelvic limb weakness and ataxia. Pain is a predominant feature of the condition and this may vary from a mild cervical hyperaesthesia to bouts of screaming after sudden changes in head position, excitement or being touched in the paresthetic region. Signs are usually recognised between six months and two

years however dogs of any age may be presented - the authors have had two ten year old dogs that were presented with neck pain and where investigation revealed cervical syringomyelia as the only explanation of the clinical signs. The condition occurs in both sexes and all coat colours. At present confirmation of the diagnosis is by MRI only. This is costly and not widely available. Many dogs have appropriate signs without confirmation of the diagnosis.

Mild cases may not require treatment or may be managed with non-steroidal anti-inflammatory drugs. A significant number of dogs have progressive signs and should be surgically managed e.g. by a suboccipital craniectomy (cranial cervical decompression) with durotomy relieving the obstruction at the foramen magnum. For dogs where surgery is not possible or successful, clinical signs may be improved by oral opioids, but by far the most effective drug is prednisolone at anti-inflammatory doses.

The modern CKCS breed was established in 1928 and in the 1930s six stud dogs were extremely popular. During the 1940s certain breed lines were extensively inbred with repeated grandfather to daughter, father to daughter, mother to son, half and full sister/ brother mating being the norm rather than the exception.

The defect in the CKCS is similar to Chiari type I malformation in humans which is characterised by underdevelopment of the occipital bone and posterior fossa with cerebellar tonsil herniation and obstruction of the foramen magnum (Karagoz and others 2002). Familial Chiari type I malformation with autosomal recessive or dominant inheritance patterns are reported with an incidence of about 2 % of total cases (Coria and others 1983, Zakeri and others 1995, Catala 1999). The Mhox gene or genes belonging to the Hox family control the development of the final shape of the occipital bone (Catala 1999). Ectopic expression of Hox-2.3 resulted in dysplasia/deficiency of occipital, basisphenoid and atlas bones in transgenic mice (McLain 1992).

This preliminary study investigated whether syringomyelia is inherited in the CKCS. The original report (Rusbridge and others 2000) had suggested a high frequency of certain names and lines within the pedigrees of affected dogs but it was not known whether this was because of the popularity of certain (champion) dogs or because these dogs passed on a genetic defect.

Materials and Methods

30 pedigrees of MRI confirmed cases (Group 1: dogs numbered 1-30) were initially scrutinised for common ancestral lines. The data was compiled on a computer programme for human genealogy - Generations C Grande Suite 8 (Sierra On-line. Inc. Bellevue, WA 98007). It generated individual pedigrees, descendant lines and enhanced hourglass pedigrees. Unlike other databases designed for dog pedigrees it had the advantage that all significant matings and relevant descendants can be viewed simultaneously. This permitted the complexity of the inter-relationships between dogs to be scrutinised. The computer programme used allowed direct descendants for any one individual to be marked so that a suspected 'founder' could be checked with reasonable accuracy.

The established population was augmented by an additional 15 cases (Group 2) with appropriate clinical signs (scratching at the shoulder/neck region, neck pain, absence of dermatological disease with or without scoliosis, thoracic limb weakness and pelvic limb ataxia) but without MRI confirmation. The sample (Group 1 and 2) included dogs from Britain, Finland, Tasmania, France, Ireland, Canada and the USA.

Information provided by the owners' pedigrees were for 3 to 5 generations. Additional pedigree information was obtained from the CKCS Book of Champions 1928-1999 (Thresh and others 2000) and The Kennel Club UK Breed Supplements -Small and Toy dog (1 Clarges Street, London, W1J 8A3). Finally a single, breed tree with affected dogs at the base and spanning 20 generations in relevant places was created. The number of dogs in the final family tree was over 1,300 CKCSs and extended back to the founder dogs for the breed. However when only 12 MRI confirmed dogs had been entered into the programme, there was sufficient framework to slot all subsequently confirmed cases to date. Pedigrees of 45 unaffected dogs were also studied (Group 3). These dogs were at least 10 years old with no clinical signs or known history of syringomyelia.

The degree of inbreeding meant that the information could not be represented meaningfully in a classic family tree for the purposes of this paper. Stud champions were sometimes used for over 12 years and sired large numbers of offspring spanning 2 or 3 generations within the same pedigree (i.e. one individual can be grandparent, great grandparent and great- great grandparent). Flow chart software (Flow chart maker; Cosmi Software. Cosmi Europe Ltd Unit 8a, Daimler Close, Royal Oak Industrial Estate, Daventry, Northants, NN11 5QJ) was used to illustrate selected information in a simplified form for this report.

Results

Analysis of the pedigree database indicated that syringomyelia had a high incidence in certain families and lines. Four key dogs, C, D, M and S, consistently occurred within the individual pedigrees but were not always present in the same pedigree. These represented four major breeding lines. Table 1 illustrates when affected dogs were descended from dogs C, D, M and S. Certain breeding lines were not represented in Dogs 5, 10, 13, 16, 18, 20, 23 and 29 from other countries, (highlighted in Table 1). This reflected the exportation of particular champion dogs from Britain. The pedigrees of dogs C, D, M and S were then studied to identify any common ancestry. All of the affected dogs could be traced back to a single common ancestor, bitch G (Figure 3). This dog died at eighteen months in 1958 and had only one recorded litter with two offspring. The direct descendants of bitch G were used to create a tree which provided a manageable tool with which to study the pedigrees. Aspects of the relationships between G, the four key dogs C, D, M and S and their descendants are featured in both Figures 3 and 4. A simplified pedigree of dogs A (non-champion) and B (champion) and their affected descendants are mapped in Figure 3. These dogs were selected because they illustrate some of the complexity of the family tree and have a high proportion of affected offspring.

Table 1

Case	Ancestor C	Ancestor D	Ancestor M	Ancestor S
1	YX	X	YX	
2		YX	YX	Y
3	Y		YX	YX
4	Y	YX	YX	YX
5*		YX	Y	YX
6	YX		X	
7	YX	YX	YX	X
8	Y	YX	X	YX
9	Y	YX	YX	YX
10*	YX	Y	Y	
11	YX			
12	Y	YX	YX	YX
13*	YX	YX	YX	X
14	YX	YX	YX	Y
15	YX	YX	YX	
16*			YX	Y
17	YX	YX	YX	X
18*	YX			
19	Y		YX	X
20*	YX		YX	
21	YX	YX	YX	YX
22	YX	Y	YX	Y
23*	YX		YX	YX
24	YX			
25	X	Y	YX	Y
26		YX	YX	X
27		Y	YX	X
28	YX	YX	YX	X
29*	YX	YX	X	
30	YX	YX	YX	X

Connection of MRI confirmed cases 1-30 to key ancestral dogs C, D, M and S.
Y- Sire of confirmed case is direct descendant, X - dam of confirmed case is direct descendant. * - non-UK dog. Note that both the dam and the sire can be traced back to C, D, S or M for each confirmed case

Figure 3 Pedigrees of two suspected carriers A and B showing relationship with G and their affected descendants

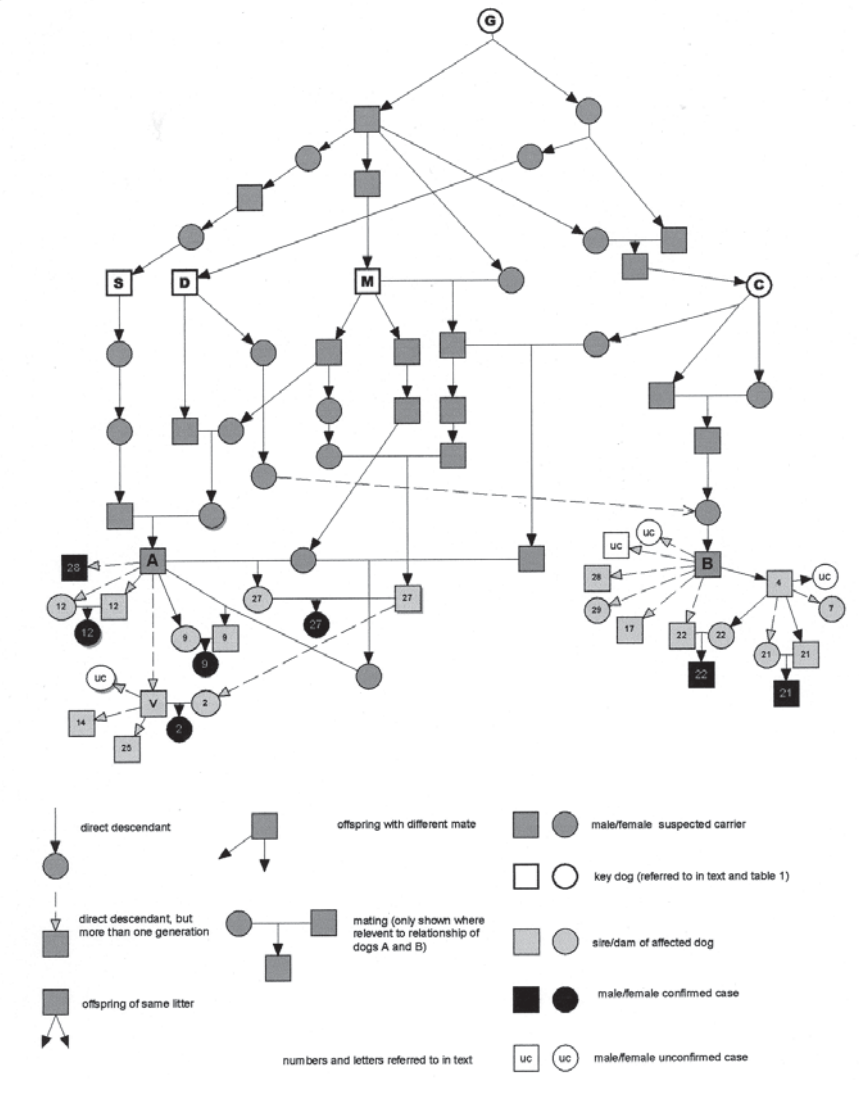
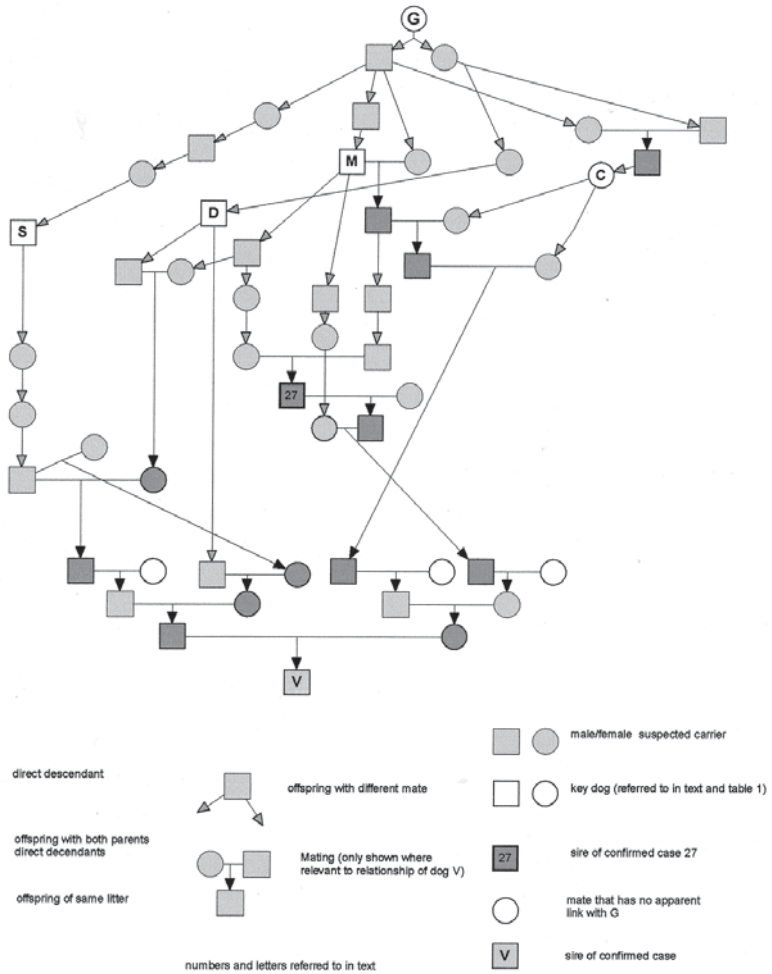


Figure 4 Pedigree of dog V showing relationship with G and "saturation" of suspected carriers in his first three generations.



The pedigree of Champion dog V is featured in Figure 4 and illustrates a phenomenon that occurs in 100% of the confirmed cases whereby all four of the grandparents are descendants of G. The degree of 'doubling up' of the descendants is colour-coded to highlight the trend. In confirmed cases the number of great-grandparents that were possible carriers range from 6 of the 8 to all 8. This was not found to be the case in control Group 3 where there remained a high degree of inbreeding but with different breeding lines (Table 2). Dog V is a suspected carrier that has sired two confirmed cases (dogs 2 and 25). He is also the grandsire of a confirmed case not included in Group 1 and an unconfirmed case. From 1989 to 2001 he had 57 recorded litters in the UK indicating how any defective gene might become widespread.

Table 2 Comparison between affected and unaffected dogs and the relationship to dogs C, D, S, and M. There are 45 dogs in each group

Descended from key ancestral dogs	Group 1 and 2	Group 3
Dam and sire	100%	60% (27/45)
All 4 grandparents	100%	17.7% (8/45)
6 Great-grandparents	100%	6.6% (3/45)
All 8 Great-grandparents	68.9% (31/45)	4.4% (2/45)

Discussion

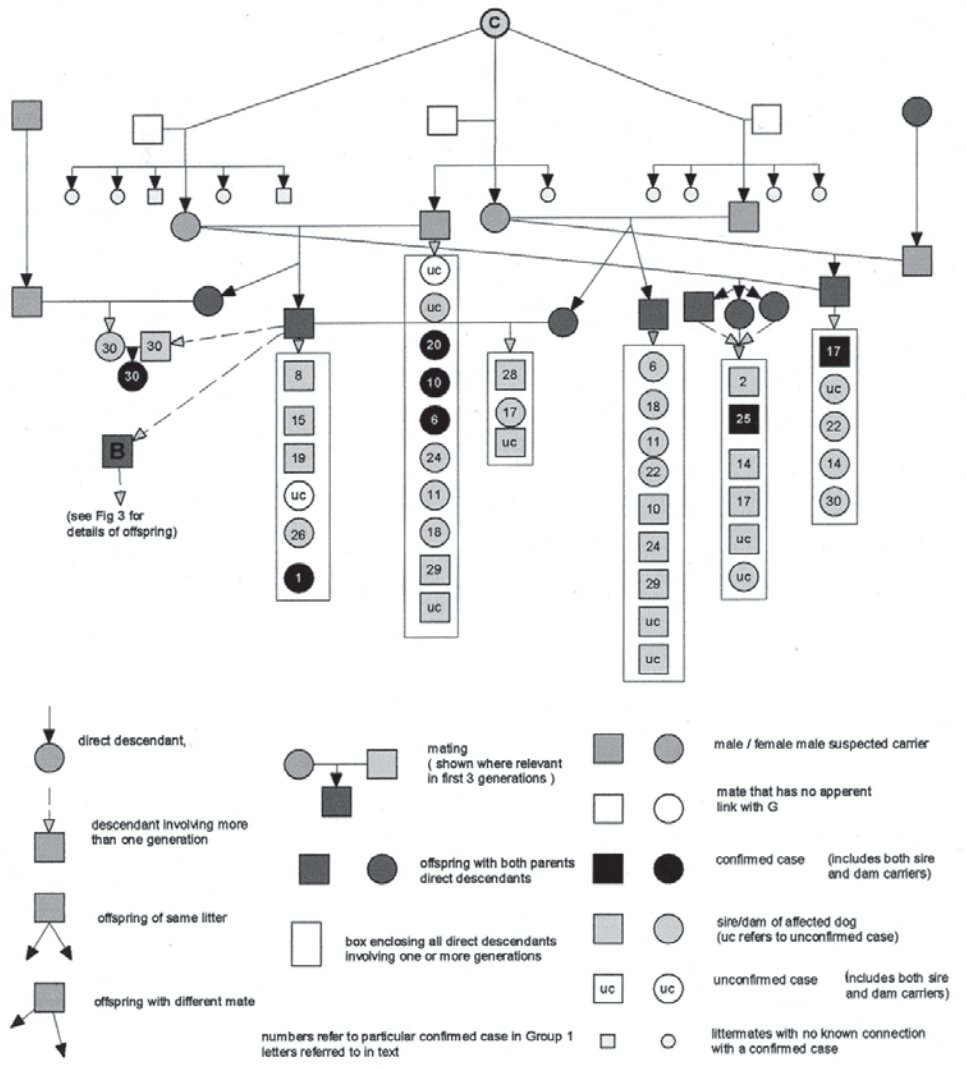
To investigate the inheritance of a disease, detailed information about an extended family is required. The ratio of affected to unaffected offspring in any given litter is usually collated to establish homozygous and heterozygous individuals and the likely mode of inheritance. In this study acquiring such information was not feasible since most puppies are sold to the pet owning public whereby they cannot be traced; additionally confirmation of the disease by MRI has only been possible in the last 7 years and has limited availability. However, analysis of the pedigrees of affected CKCS did suggest that syringomyelia had a high incidence in certain families and lines and therefore was likely to be an inherited genetic defect. All affected dogs could be traced back through both the dam and the sire to at least one of four significant ancestors – three champion dogs D, S and M and one non champion bitch C. These four dogs were descended from one bitch G. This bitch died shortly after producing her only litter of two pups and was thought a possible source of the defective gene(s) because 1) it was the earliest point in which the breed lines C, D, M and S came together, 2) it involved only one litter and 3) it offered an explanation for the high incidence of the disorder within certain parts of the extended pedigree

A number of other common ancestors were eliminated as possible 'founders' because they were successful stud dogs and therefore one would have expected an even more widespread problem earlier or because they were bitches that involved different mates and would require a more complex explanation to account for the phenomenon. For example, the sire of the single litter from bitch G had 38 recorded matings over a period of 6 years. These matings included 6 with G's dam who was matched every season for a period of 3 years resulting in twenty offspring

Aspects of the relationships between G, the four key dogs C, D, M and S and their descendants are featured in both figures 3 and 4. If bitch G carried a recessive gene(s) for occipital bone hypoplasia and this gene was passed down the generations to dogs C, D, M and S, and then to significant descendants for example dogs A, B and V, then the substantial inter breeding between descendants has the effect of increasing the chance of duplicating any defective gene(s). Figure 5 features the descendants of key bitch C (non-

champion). She died at 7 years and had 3 litters with different mates. Her family tree has been included to demonstrate how a recessive gene might build up a degree of homozygosity. This may account for the now common occurrence of cases compared to the past. The extent of inbreeding between the suspected carriers made it impossible to clearly illustrate C's family tree. In order to avoid confusion, suspected cases have been grouped into descendant boxes from stud dogs where large numbers of matings have occurred or closely bred dogs that have the same parents. The sire of affected dog 29 and dam of affected dog 22 can each be seen in two boxes because of close inbreeding. It is very possible that breeders using individuals arising from C's three different litters might not suspect any inbreeding because of the number of generations involved. In the pedigree of Case 6, Bitch C appears 6 times over a span of 5 generations.

Figure 5 Descendants of key bitch C from all 3 litters showing aspects of inbreeding



Dogs D, M, S and certain descendants from bitch C were popular dogs for breeding and most CKCSs have genetic influence from one or more. However the significance of these dogs could not be explained by mere popularity. As illustrated in Table 2, 60% of unaffected dogs have both sire and dam descended from bitch G through C, D, M and S compared to 100% of affected dogs. However, 100% of affected dogs have 6 or more great-grandparents that were direct descendants compared to 6.6% of the unaffected dogs. Therefore, it did not seem important for the development of syringomyelia if the sire and dam were descendants of bitch G through C,D,M and S, however, it was important if the majority of the great-grandparents were. All subsequently confirmed cases also fitted this pattern. These results suggest that the inheritance is more likely to be autosomal recessive i.e. both dam and sire must carry the defective gene(s), however, it also suggests a more complex pattern e.g. a variable penetrance, or that there is more than one gene involved. Without knowing how many affected and unaffected offspring there are in a litter the actual mode of inheritance cannot be determined.

It is also possible that other diseases affect the development of clinical signs. Rapid changes in intrathoracic pressure are important factors in the pathogenesis of syringomyelia (Williams 1993). Therefore, diseases which cause increased respiratory effect, e.g. an over-long soft palate, could exacerbate the development of the condition.

As so many CKCS have genetic influence from dogs C, D, M and S it would be foolish to avoid these dogs, as the resulting gene pool would be too small, resulting in more problems. As the number of descendant great-grandparents appears to be critical, the author's recommendations for breeding is to aim for no more than 5 of the great-grandparents in a potential cross to be descendants of G via dogs C,D, M and S. To implement this requires detailed knowledge of CKCS breeding and pedigrees because of the number of generations involved.

The investigation is continuing to study the mode of inheritance and the possibility of second gene. The population of affected dogs is also being compared to CKCS with idiopathic epilepsy. The authors are still seeking pedigrees of CKCSs with suspected syringomyelia from before 1993, normal CKCSs with MRI confirmation of adequate occipital bone development and CKCS with confirmed idiopathic epilepsy.

Acknowledgements

The authors are indebted to Bet Hargreaves whose in-depth knowledge of the Cavalier King Charles spaniel breed and diligence at pursuing the authors' queries was greatly appreciated. The authors are also grateful for the assistance of Malcolm Burley, Janet Ireland and Outi Kuisma-Parwar. Thanks are also due to the staff of Stone Lion Veterinary Practice for dealing with the many telephone enquires about this project.

Footnote

After this paper was published Dog V was confirmed to have syringomyelia by post mortem examination and his case history is detailed in Section 3.

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Chapter 7.2

Inheritance of occipital bone hypoplasia (Chiari-like malformation) in cavalier King Charles spaniels

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Journal of Veterinary Internal Medicine 2004; 18: 673-678.

Introduction

Occipital bone hypoplasia (Chiari-like malformation) resulting in caudal fossa overcrowding and obstruction of the foramen magnum with secondary syringomyelia (SM) was first identified in cavalier King Charles spaniels (CKCS) in 1997 [1].Clinical signs are caused by damage to the cervical spinal cord and include shoulder and neck paraesthesia, forelimb weakness, cervical scoliosis and pelvic limb ataxia. A classical clinical sign is a tendency to scratch at the shoulder area especially when excited or on a lead. Pain is a predominant feature of the condition and may vary from a mild cervical hyperaesthesia to bouts of screaming after sudden changes in head position, excitement or being touched in the paraesthetic region. Most dogs also have secondary ventricular dilatation. Signs usually are recognized between 6 months and 3 years of age. However dogs of any age may be presented, and dogs with more severe disease tend to be presented earlier. The defect in the CKCS is similar to Chiari type I malformation in humans characterized by underdevelopment of the occipital bone and posterior fossa with cerebellar tonsil herniation and obstruction of the foramen magnum [2].

Like all breeds derived from a small number of individuals, the CKCS breed has little genetic variation. The problem is compounded by the repeated use of particular stud dogs; it is not unusual for a popular sire to produce over 50 separate litters and hundreds of progeny. This breeding practice encourages the emergence of recessive genetic diseases. Selection for coat colours imposes further pressures on the available CKCS gene pool. Phenotypically, 4 colour variations are recognized: ‘whole colours’, ruby (r) and black and tan (bt) where white colour is undesirable and ‘parti-colours’ – blenheim (b) (ruby and white) and tricolors(t) (black, tan and white). Red colour and parti-colors are recessive and if breeders desire these coat variations they only use particular lines. The breed has a predisposition to myxomatous mitral valve disease (MVD), [3] and breeders are advised to select for their breeding program systolic murmur-free CKCS over 2.5 years old that have systolic murmur-free parents over 5 years old[4,5]. A “clear list” is kept and published by the UK CKCS club. This practice further narrows the gene pool as dogs showing signs of MVD are removed from stud. Access to internet pedigree databases allows breeders to select for longevity.

Investigation of inheritance by segregation analysis has not yet been possible primarily because of inability to determine the number of affected versus unaffected siblings in a litter. Puppies generally are sold to the public making them difficult to trace. The disease is confirmed by magnetic resonance imaging (MRI) which has only been available routinely in veterinary medicine in the last decade, has limited availability and is expensive. It is not possible to be sure whether a dog is truly unaffected without MRI because clinical signs may not be recognized or acknowledged by the owner or breeder. Signs may be mild, develop late in a dog’s life or may not be present at all e.g. mild syringomyelia can be identified as incidental findings in CKCS having MRI for other reasons. Study of dog genetics also is made more difficult by close and repeated inbreeding. Family trees are extremely complicated, and there are typically many possible paths for the inheritance of any genetic defect. Many breeders are unwilling to admit that they have a problem in the belief that to do so damages their reputation. Response from key breeders to provide information about affected dogs in their lines, especially before 10 years ago, has been minimal. This reluctance makes it very difficult to determine the Mendelian inheritance of this trait.

Preliminary work investigating the heritable nature of this disease involved establishing a 20-generation family tree which linked 45 affected dogs. [6] All of the affected dogs had at least 6 of 8 great-grandparents that could be traced back to a common female ancestor born in 1956 whereas only 6.6% of unaffected individuals had this ancestry. These data suggested that occipital bone hypoplasia was hereditary in the CKCS and that inheritance was likely to be autosomal recessive. The aim of this study was to develop a better understanding of the inheritance of occipital hypoplasia in a defined population of CKCS.

Materials and Methods

A family tree of over 5,500 related dogs was constructed over a period of 4 years. The data was compiled

on a computer program [a] for human genealogy. Unlike databases designed for dog pedigrees, it had the advantage that all clinically relevant crosses and descendants could be viewed simultaneously when printed. This feature permitted the complexity of the inter-relationships among dogs to be more easily scrutinized. The computer program identified all directly descended individuals and generated individual pedigrees either as a tree chart or text. It also produced 'enhanced hourglass' reports for any single cross, showing other mates, with their associated offspring for any number of generations. Information provided by the owners' pedigrees was for 3 to 5 generations but these findings were enlarged to 10-25 generations with information published by the UK CKCS club [7] and UK Kennel Club[b]. Supplementary information for some dogs that involved foreign breeding lines was obtained from http://www.cavaliersonline.com. and http://www.worldpedigrees.com/xCavalier.htm. The data was analysed at various time points. The degree of inbreeding meant that the information could not be represented meaningfully in a classical family tree. Flow chart software [c] was used to illustrate selected information in a simplified form for this report. For clarity, the diagrams illustrate only those matings relevant to the investigation together with relevant descendants.

Investigation 1. Does the family tree for occipital hypoplasia with secondary SM or hydrocephalus involve a subset of, or the entire CKCS population?

Family trees for occipital hypoplasia and idiopathic epilepsy (IE) were compared. An occipital hypoplasia family tree was constructed from the pedigrees of 120 affected dogs (Table 1).

Table 1 Cavalier King Charles spaniels under study

group	characteristics
1	Confirmed SM cases 1-50
1i	Confirmed SM cases with parti-colored coats (39 cases)
1ii	Confirmed SM cases with whole-colored coats (11 cases)
2	Unconfirmed SM cases 51-120
3	40 cases diagnosed with idiopathic epilepsy (IE)
4i	10 SM cases born before 1991 (mostly deceased)
4ii	10 SM cases born after 1996

SM – syringomyelia secondary to occipital bone hypoplasia.

Group 1 (case numbers 1-50) with MRI-confirmed occipital bone hypoplasia and secondary SM (49 cases) or MRI-confirmed occipital bone hypoplasia and secondary hydrocephalus (1 case). The MRI characteristics of occipital bone hypoplasia have been described previously. [1, 6] The earliest known CKCS with MRI-confirmed SM was born in 1988. The age range of the SM population ranged from 10 months to 12 years. The dog with hydrocephalus was 3 months of age at the time of diagnosis. The dogs were born in the UK, Eire, Finland, Sweden, Canada, USA or Australia. Additional pedigree information from another 70 dogs suspected to have SM on the basis of the typical clinical signs but without MRI confirmation (Group 2 case numbers 51- 120) was used to enhance the evidence. An IE family tree was constructed from the pedigrees of 40 CKCS with IE and no clinical signs of syringomyelia (IE). The earliest pedigree dated back to 1967 (Group 3). The diagnosis of IE typically had been made by veterinary practitioners on the basis of history and clinical signs (i.e., the dogs had generalized seizures and received anti-epileptic medication).

Investigation 2. Does a relationship exist between coat colour and occipital hypoplasia?

In order to determine the influence of selection for coat variation, Group 1 was subdivided accordingly into Group 1(i) for parti-colours (b and t) and Group 1(ii) for whole-colours (r and bt). The association between coat colour and epilepsy also was examined.

Investigation 3. Has the age of onset of clinical signs changed?

Breeders claimed that when they first started to notice clinical signs of the condition 10-12 years ago, the affected dogs were older than 3 years of age. Now many dogs are less than 2 years when first presented. A subset was made up of 10 dogs born before 1991 for which full clinical information was available (Group 4i). This group was compared with the 10 youngest dogs in the study (Group 4ii) born after 1996. In addition, the natural occurrence of the disease was studied in an extended family of a dog (case number 110) identified in the previous study [6] as being a likely carrier for SM secondary to occipital hypoplasia.

Results

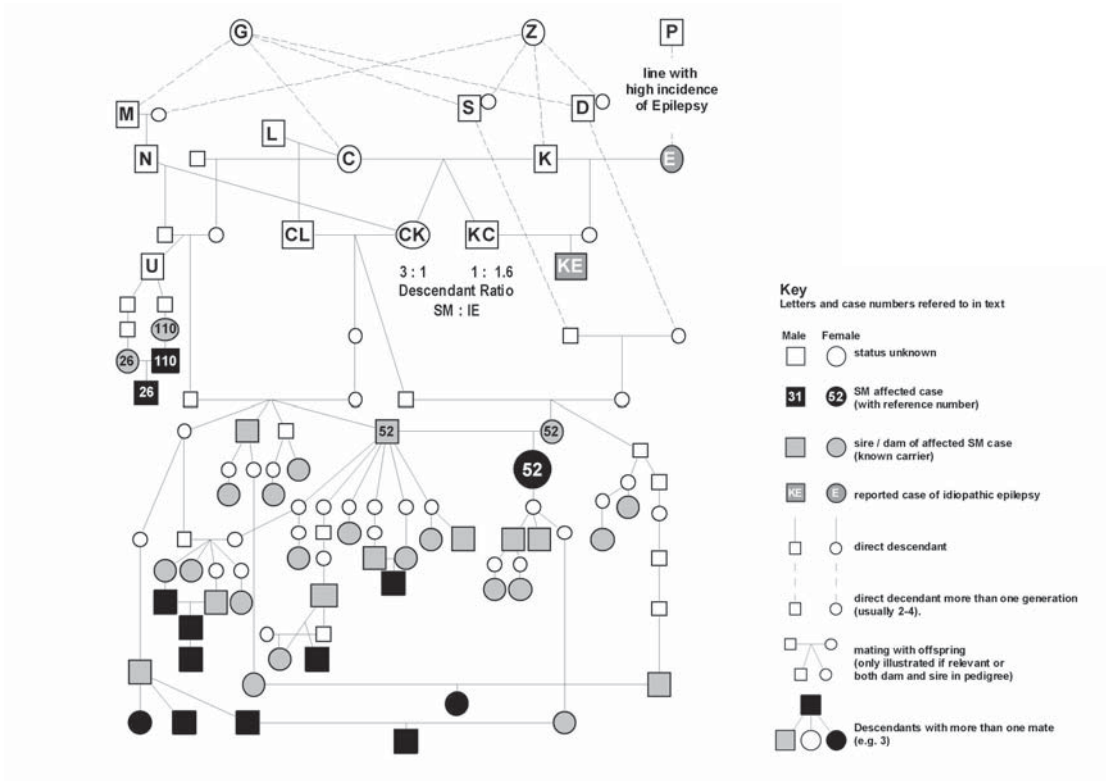
Investigation 1. Does the family tree for occipital hypoplasia with secondary SM or hydrocephalus involve a subset of or the entire CKCS population?

The CKCS breed has a narrower genetic base today than it did 15 years ago and can be traced back predominantly to a relatively small group of dogs and their closely bred descendants. All 120 dogs in this study with confirmed and suspected SM or hydrocephalus secondary to occipital bone hypoplasia could be shown to fit a similar pattern of inheritance as identified in the preliminary investigation [6] which highlighted 4 significant ancestors: C, D, M and S (Figure 1). All dogs with SM cases could be traced back through these 4 dogs, not only through both the dam and the sire, but through at least 6 of 8 great grandparents. Further investigation revealed that C, D, M and S in turn had common ancestors, namely Dam G and her mate. The study also showed another early common ancestor was Dam Z. At least 3 of 4 grandparents of all dogs with SM could be traced to Dam Z. The lines were sometimes independent from

descendant lines from Dam G. Thus, all 8 greatgrandparents of affected dogs were varying combinations of descendants of Dam G or Dam Z or (more usually) both.

All affected pedigrees fell into 2 broad groups: those descended from M with S or D; or those dominated by C. Only 1 confirmed case was descended from Dam C entirely. Dam C had only 3 different mates, which were not related to G but to ancestors common to D, M, S and Z. The relationship between G, Z, C, D, M and S is illustrated in Figure 1 which is the extended pedigree of Dam 52, the earliest known affected dog that was used in a breeding program. Two of Dam 52's sire's siblings were exported and account for affected dogs in Finland and USA. The CKCS population in these countries has a high incidence of disease as the gene pool is even smaller and the CKCS population is dominated by potential carriers of SM.

Figure 1 Family tree of dog 52 and selected descendants demonstrating relationships with i) key SM ancestors G, Z, M, S, D and C ii) dogs P, K, E, L, CL, CK, KC and KE associated with IE iii) dogs U, 110 and 26 (figure 2).



Note – Dam Z introduced into the family tree via Sire K and females that were mated with Sires D, M and S

The family tree of IE appears to be a different subset of the CKCS population although some overlap was identified. The largest concentration of IE cases was associated with Dam C when bred to Sire K (Figure 1). When descendant lines from their 2 resulting offspring CK (b) and KC (b/t), were compared, the ratio of SM:IE was 3:1 with CK and 1:1.6 with KC. The descendants of Sire CL, an offspring of Dam C and Sire L, included 8 dogs with IE. Sire L was mated to 7 other dogs and none of these descendants, to the authors' knowledge, had IE.

Although the majority of the IE group 3 had Dam G in the ancestry, only 30% of cases were descended from Dam G via dogs C, D, M or S whereas 100% of the SM group had at least 6 of 8 great grandparents descended from Dam G via dogs C, D, M or S (Table 2).

Table 2 Percentage of grandparents and great-grandparents descended via dogs C, D, M or S. Comparison between Group 1 and 2 (SM) and Group 3 (IE)

Direct descendants	Group 1 and 2	Group 3
4 grandparents	100% (100/100)	35% (14/40)
6/8 g. grandparents	100% (100/100)	30% (12/40)

Table 3 illustrates that some ancestors appear to be more influential for SM than for IE. For example, Sire P (Figure 1) is an important ancestor for both SM and IE but sires M and D are more important ancestors for SM than for IE.

Investigation 2. Does a relationship exist between coat colour and occipital hypoplasia?

Table 3 also illustrates how some dogs appeared more influential through selection for coat colours. Sires K and C are important ancestors for whole-coloured dogs with SM and for IE and might have channelled genes for SM by selection for coat variation.

The effect of colour on IE and SM is illustrated by comparison between siblings CK (b) and KC (bt), offspring from Dam C and Sire K (Figure 1 and Table 4). KC was an important ancestor in the whole-coloured lines. Thus 67% of whole-coloured SM dogs and 23% of all dogs with IE had *both* sire and dam descended from this dog. However this individual had no influence on parti-coloured with SM. KC's offspring KE had EEG-confirmed IE. By comparison, sibling CK has more influence on parti-coloured pedigrees and less on the IE pedigrees.

Table 3 Percentage of affected individuals (group 1 and 3) that are descended though the sire or dam from selected ancestors

Group	1I		1II		1(I AND II)		3	
Coat Variation	*parti-colors (b, t)*		*whole Colors(r, bt)*		*all colors*		*all colors*	
	Sire	*Dam*	*Sire*	*Dam*	*Sire*	*Dam*	*Sire*	*Dam*
Dam G (b)	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**68%**	**88%**
Dam Z (b)	**100%**	**100%**	**100%**	**100%**	**100%**	**100%**	**68%**	**70%**
Sire M (b)	**100%**	**100%**	**73%**	**55%**	**94%**	**90%**	**43%**	**40%**
Sire D (t)	**80%**	**85%**	**64%**	**45%**	**76%**	**68%**	**20%**	**20%**
Sire P (bt)	**88%**	**39%**	**73%**	**91%**	**92%**	**85%**	**65%**	**73%**
Sire K (bt)	**62%**	**56%**	**100%**	**82%**	**70%**	**62%**	**50%**	**45%**
Dam C(t)	**69%**	**56%**	**100%**	**91%**	**76%**	**64%**	**48%**	**40%**

b- Blenheim, t-tricolour, r- ruby, bt – black and tan

Table 4 Percentage of affected CKCSs in group 1 and 3 *with both dam and sire descended* from siblings CK or KC demonstrating the relationship with coat variation and for idiopathic epilepsy.

Group	1i	1ii	1 (i and ii)	3
Characteristics	SM: Parti-colors (b,t)	SM: Whole Colors(r, bt)	SM: all colors	I.E. all colors
Dam CK (b)	**54%** (21/39)	**18%** (2/11)	**46%** (23/50)	**15%** (6/40)
Sire KC (bt)	**0%** (0/39)	**67%** (7/11)	**14%** (7/50)	**23%** (9/40)

Note - This gives the ratio of descendants from CK 3 SM:1 IE and KC 1SM:1.6IE
b- Blenheim, t-tricolor, r- ruby, bt – black and tan

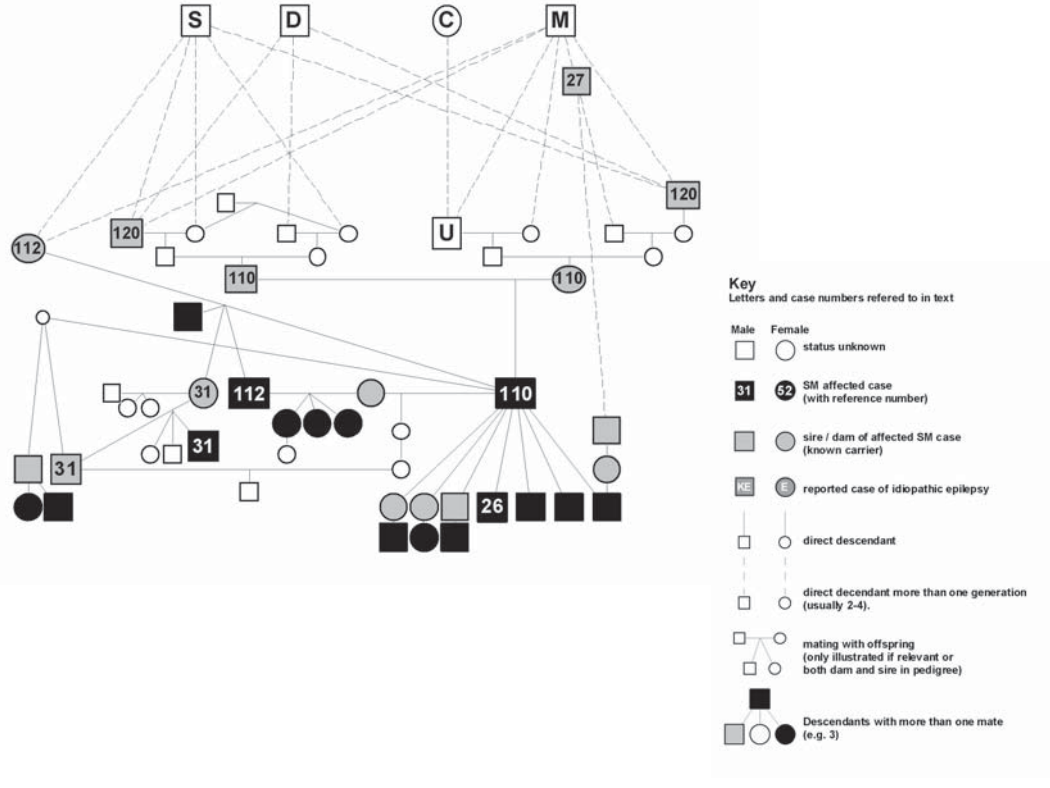
Investigation 3. Has the age of onset of clinical signs changed?

The average age of onset of the disease for Group 4i was 4.8 years (range, 3-7 years) compared to 8.9 months for Group 4ii (range, 3-15 months). Many owners with older SM dogs not included in group 4i were unsure of age of onset because it appeared to be a gradual process or the condition only was detected incidentally. Increased awareness of SM accounted for the earlier diagnosis in some dogs.

There was a tendency for increasing clinical severity and earlier onset with increased inbreeding. For example, case 47 was a severely affected female showing signs of disease from 18 months. Her sire had milder disease and was confirmed with SM at 32 months. It was common for the sire or dam to develop signs after the offspring had been diagnosed. For example dog 46 developed scoliosis at 10 months, her dam (dog 37) and her maternal aunt (dog 33) developed shoulder scratching and pain at 5 and 2 years respectively. The earliest onset of disease was in dog 41, a 3-month-old CKCS euthanized because of hydrocephalus secondary to severe occipital bone hypoplasia and foramen magnum obstruction. This bitch had 32/32 great-great-great-grandparents descended from the clinically relevant lines, which included champions known to have a tendency for shoulder scratching while walking.

Figure 2 is a case study of a family centred on dog 110 which developed mild signs of shoulder paraesthesia at approximately 18 months of age. This dog was mated to a female of unclear status. Clinical records indicate that she had a head tilt for which the cause was not determined. The consequence of the mating was a litter of 2. The male (dog 112) developed signs at 10 months and when mated to an allegedly unaffected female, the resultant puppy (dog 14) was severely affected with SM and euthanized at 6 years of age. According to the breeder, dog 112's sister had no signs consistent with SM; she was mated with a half-brother and produced dog 31 which showed signs of SM from 30 months of age. Two other matings have produced unaffected offspring so far. Other known affected dogs in the family are illustrated.

Figure 2 Family tree of dog 110 illustrating relationship with i) ancestral dogs C, D, M and S ii) Sire U and sires of affected dogs 27 and 120 iii) 12 affected descendants from 10 different matings



Discussion

The study is unusual because the complete pedigrees of dogs affected with SM secondary to occipital hypoplasia are known from the time of derivation of the breed from King Charles Spaniels in the 1930's. The investigation had many limitations that were a consequence of studying a naturally-occurring disease in a pet population. Segregation analysis has not been possible so far because of difficulty identifying whether a dog is truly affected or unaffected. In addition, the diagnosis of IE in group 3 was made, for the majority of cases, by general practitioners with limited diagnostic equipment. Therefore, conclusions on the inheritance of both diseases are limited. It is possible that SM secondary to occipital bone hypoplasia is recessive because affected individuals may be produced from apparently unaffected individuals. From a study of the extended CKCS family tree we conclude that the disease occurs as a result of repeated close breeding between 1 or more key descendants, C, D, K, M, and S - themselves descended from two dams, G and Z. All of the affected dogs born in the last 5 years are descended from C, D, K, M and S via known or suspected carriers through at least 6 of 8 great grandparents. It has not been established why, in every case, the number of potential carrier grandparents is always 3 or 4. The disease seems to require this high degree of inbreeding before becoming obvious, and this observation in turn suggests that the inheritance may be more complex than a single autosomal recessive gene. Sex-linked inheritance has not been ruled out. The ratio of male to female affected dogs is roughly equal, and the sex ratio of the database is 0.65:0.35 female:male. However in a study of 30 random selected cases it was possible to trace a possible line of inheritance to the key dogs without involving any male-to-male transmission.

Selection for coat variation and the avoidance of some lines because they carry certain diseases (e.g., heart and cataract disorders) have narrowed the CKCS gene pool. As a result, descendants of C, D, K, M, and S dominate modern CKCS pedigrees compared to 10 years ago. Occipital hypoplasia currently is so common in the breed that it could be considered "normal" for a CKCS to have some degree of occipital hypoplasia, with SM and hydrocephalus occurring in the most severely affected dogs. In ideal circumstances, a group of MRI-confirmed normal dogs would also be studied. To do so would depend on a chance finding of a normal animal that is having a diagnostic MRI for another reason and a large enough group of animals in that category has not yet been collected. In the original study [6], 45 dogs affected with SM were compared with a control group of 45 dogs over 10 years of age that showed no clinical signs of the disease. These older dogs used lines that were not as popular as those found in the pedigrees of current champions. Currently, avoiding descendants of C, D, K, M and S in a breeding program would be extremely difficult.

The SM pedigrees were compared to pedigrees of CKCS with IE because there was a concern that SM was so widespread in the population that it was possible that the whole, rather than a subset, of the CKCS population was being studied. There also was a concern that occipital hypoplasia may be directly associated with IE becasue several dogs had both diseases. Both diseases were found to be distinct subsets of the population although there was overlap especially associated with the intensely inbred lines from Dam C and Sire K where there were many half brother and sister matings. SM secondary to occipital hypoplasia is most common in blenheim and rubies which are recessive coat variations and must be bred from a more restricted gene pool. Selection for color affected the natural history of the disease because some of the champion dogs that are important ancestors for SM were popular for their tendency to "throw" a certain color. CKCS whole-color breeders commented that 15 years ago, tri-colors such as Sire D and Dam C were introduced to the ruby lines in an attempt to widen the gene pool but still deliver some whole-colors. This event appears to have been important in the history of SM by increasing the cohort of dogs with genes from both G and Z.

The disease has a tendency to be more severe in each generation (i.e. breeding mildly affected dogs can result in offspring with more severe disease with an earlier onset). There appeared to be 3 forms of the disease based on severity and age of onset: 1) neonatal form (less than 6 months of age) presenting with clinical signs relating to hydrocephalous; 2) juvenile form (6-15 months of age) initially presenting with scoliosis secondary to SM; 3) adult form (8 months-10years of age) initially presenting with shoulder scratching and pain secondary to SM.

The implications for the breed are serious. Pedigrees of the 25 top stud dogs for the last 5 years showed that not only were many very closely related, they all were descendants of suspected carriers for SM. Thirteen of these top stud dogs were directly associated with affected dogs.

The widespread tendency for heart disease in the breed must also be considered.[3,4] MVD has affected the development of SM as breeders have selected for dogs with ancestral history of longevity and late-onset systolic murmur. Unfortunately, many of these dogs had or carried a tendency for SM. Our clinical observation is that surviving dogs with SM have late onset heart disease (i.e., do not developing clinical signs until after 8 years of the age). In other words, the breeders' attempts to breed away from one disease appear to be making another disease more probable. It seems unlikely that CKCS breeders will be able to select against SM and MVD by pedigree analysis because both diseases are widespread in the population. Even if they could do so, the gene pool would be further narrowed, possibly encouraging the emergence of another disease. An appropriate way forward is to attempt to identify the causal genes in both diseases. If possible, carriers or even affected dogs then could be mated to unaffected dogs thus preserving genetic variation while reducing disease incidence.

Occipital hypoplasia with secondary SM is a valuable model of Chiari I malformation in humans both for studying the development of the disease and investigating its genetics. Chiari I malformation in humans occurs in up to 0.77% of individuals, and 75% of people with this malformation are symptomatic [8]. Familial Chiari type I malformation is reported with an incidence of about 2 % of total cases with autosomal recessive or dominant inheritance patterns [9, 10, 11] but a higher incidence is suspected [12]. The Mhox gene or genes belonging to the Hox family control the development of the final shape of the occipital bone

[11]. Ectopic expression of Hox-2.3 resulted in dysplasia or deficiency of occipital, basisphenoid and atlas bones in transgenic mice [13]. The Pax group of genes (especially Pax-1) also has been suggested as a candidate for Chiari I malformation[12]. The Pax-1 gene plays an important role in the cervico-occipital transitional zone [14].

In conclusion, the study findings support the hypothesis that occipital hypoplasia with secondary SM in CKCS is a hereditary condition. Further study is required to establish the inheritance, which is likely to be more complex than simple autosomal recessive. Selection for colour and against other diseases influences the incidence of the malformation in the population. With the advances in the canine genetic map, this family tree should be useful in further research to identify the genes contributing to the malformation in the dog, and may be useful in for research on the genetics of human type I Chiari malformation. Future studies should involve collection of DNA from extended 3 or 4 generation CKCS SM families with a view to genotyping, linkage analysis and positional gene cloning

Footnote

[a] Generations C Grande Suite 8 (Sierra On-line previously at Inc. Bellevue, WA 98007). The licence for this product has been withdrawn following a change in company ownership.

[b] The Kennel Club UK Breed Supplements -Small and Toy dog 1 Clarges Street, London, W1J 8A3

[c] Flow chart maker; Cosmi Software. Cosmi Europe Ltd Unit 8a, Daimler Close, Royal Oak Industrial Estate, Daventry, Northants, NN11 5QJ

Acknowledgements

The authors are indebted to Bet Hargreaves whose in-depth knowledge of the Cavalier King Charles spaniel breed and diligence at pursuing the authors' queries was greatly appreciated. The authors are also grateful for the assistance of the Margaret Carter Health Secretary of the UK CKCSC and Randi Rosvoll, the Past President of the CKCSC, USA and CKCSC, USA Health Foundation and to the many dog owners, breeders and veterinary surgeons who provided information. Thanks are also due to the staff of Stone Lion Veterinary Practice for dealing with the many telephone enquires about this project and to Dr Berge Minassian, Hospital for Sick Children, Toronto for his many helpful comments.

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Chapter 7.3

Inherited Chiari-like malformation/syringomyelia in the cavalier King Charles spaniel – experiences in setting up a worldwide DNA collection

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Journal of Heredity 2005: 96: 745-9

Introduction

Like most purebred dogs, the cavalier King Charles spaniel (CKCS) has a small and decreasing gene pool. The breed was established in 1928 in response to a reward offered for recreating a spaniel similar to those depicted in portraits of the era of King Charles II (Figure 1) and the modern breed is predominantly descended from six dogs (Rusbridge and Knowler 2003).

Figure 1. CKCS (from left to right) with tricolour, blenheim and ruby colour types. The black and tan variety is not illustrated. Selection for colour affected the natural history of syringomyelia in CKCS because some of the pivotal ancestors were popular for their tendency to "throw" a certain colour.

CKCS breeders practice linebreeding which is understood (Rasmussen 2005) as a method to create a desired appearance and/or avoid known inherited diseases. A desirable ancestor is identified and descendants are often repeatedly bred together so that the common ancestor may appear several times on both maternal and paternal sides of a five generation pedigree. Once a "breeding line" is established, line- breeding is continued generation after generation with no or occasional "outcrosses" i.e. crosses to dogs with no common ancestors within a five generation pedigree. A popular stud dog can have over fifty matings to consanguineous bitches and produce hundreds of offspring which are then line-bred. Thus one individual can have a significant influence on a gene pool. While father-daughter, mother-son and full sister-brother matings are no longer acceptable more distant relationships e.g. grandfather-granddaughter, are allowed.

The complexity of the family tree makes study of canine inherited disease difficult. On the other hand, the strong familial relationships within purebred dog populations has also led to the accumulation of certain inherited diseases in nearly each breed, and the eradication of other diseases, so that many inherited diseases occur with high frequency in a breed specific manner. Recognition of the genetic background of a disease is therefore often possible in dogs, but not in other species.

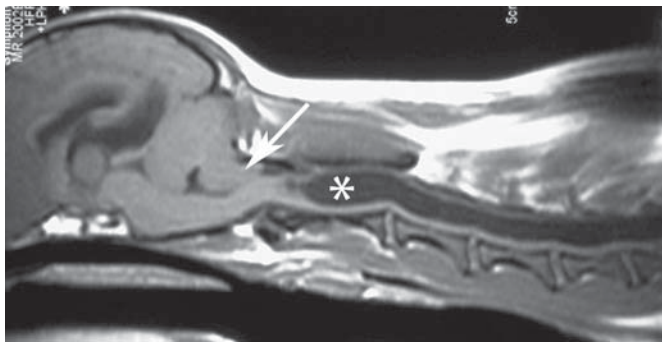
The CKCS breed has a high incidence of Chiari-like malformation (occipital hypoplasia), a condition similar to Chiari type I malformation in humans (Rusbridge et al 2000). The consequence of inappropriately small occipital bones is reduced volume of the caudal fossa i.e. the part of the skull which accommodates the cerebellum and brainstem. Cerebrospinal fluid flow is obstructed by the overcrowded cerebellum (often herniated through the foramen magnum) and brain stem. The obstruction results in fluid coalescing in cavity/cavities (syringomyelia) within the spinal cord. Some cases also have ventricular dilatation. The degree of syringomyelia is quite variable. The most severe cases have considerable spinal cord damage and are significantly disabled by 12 months of age. In contrast, some have a small subclinical syringomyelia which is only detectable by MRI or post mortem.

The classical clinical signs of syringomyelia are scratching at the neck/shoulders when walking (para-

esthesia/dyskinesia) and pain with or without cervical scoliosis, paresis and ataxia (Figure 2). At present, confirmation of the disease can only be made by magnetic resonance imaging (MRI) (Figure 3)

Figure 2 Scoliosis in a 16 month old CKCS. There is syringomyelia extending into the dorsal grey column over a number of spinal cord segments. Presumably this results in an imbalance of afferent information from the cervical neuromuscular spindles. The neck bends away from the side of the lesion.

Figure 3 Midsagittal TW1 weighted image of the brain and cervical spinal cord. Syringomyelia (asterixis) secondary to Chiari-like malformation in a 21 month female CKCS presenting with a 3 month history of yelping and a tendency to scratch at the right shoulder area. There is cerebellar herniation through the foramen magnum (arrow). This malformation is very similar to Chiari I malformation in humans



Recent data has suggested that Chiari-like malformation in the CKCS is inherited (Rusbridge and Knowler 2003, 2004). The disease has a tendency to be more severe in each subsequent generations, i.e. breeding mildly affected dogs can result in offspring with more severe disease and an earlier onset. An early observation from study of an extended CKCS family with a high incidence of syringomyelia suggests that apparently normal parents of clinically affected offspring have mild Chiari-like malformation /syringomyelia detectable by MRI only (unpublished data). A consistent observation is that all clinically affected dogs have 3-4 grandparents and 6-8 great grandparents descended from pivotal ancestors which anecdotally had produced affected offspring, some over 30 years ago (Rusbridge and Knowler 2003, 2004). Selection for colour and against other breed related diseases influences the incidence of the malformation in the population; for example, many of the pivotal ancestors were extensively used as stud dogs because they did not have early onset hereditary mitral valve disease (Rusbridge and Knowler 2004).

Identification of the causal gene(s) for Chiari-like malformation would be invaluable because it would allow development of a test to detect subclinically affected dogs and carriers for breeding purposes. It could also be useful in furthering understanding of the embryological development of occipital bone and the pathogenesis of Chiari type I malformation in humans.

Materials and Methods

After initially describing the disease, we established a database of affected dogs and their relatives. Due to the complexity of the family tree it was difficult to use existing canine genetic software. A basic program for human genealogy was used (Generations C Grande Suite 8; Sierra On-line previously at Inc. Bellevue, WA 98007) which allowed the inter-relationships among dogs to be more easily appreciated as all clinically relevant crosses and descendants could be viewed simultaneously (the licence for this product has subsequently been withdrawn following a change in company ownership). The database generated GEDCOM files (Genealogical Data Communication; Church of Jesus Christ of Latter Day Saints Family History Department) which were eventually transferred to a specifically designed program based on Microsoft Access (Microsoft Corporation USA). This database had the ability to record phenotypic variables to enable statistical and linkage analysis. The phenotypic variables included: sex; coat colour; severity of syringomyelia; clinical signs and age of onset; and presence/absence of other inherited disease.

We subsequently established a DNA collection program. Initially this was started in the UK with the support of the DNA Archive for Companion Animals, the University of Liverpool (held within the Integrated Genomic Medical Research, The University of Manchester). After initially being contacted by phone or letter, veterinary surgeons in general practice were provided with sample pots, tick-box forms detailing phenotypic information (Figure 4) and postage paid envelopes ensuring that they had an easy means by which DNA samples could be submitted (with owner consent). The DNA collection was later extended to the Netherlands, USA, Canada and more latterly Germany and France. The inclusion and exclusion criteria for DNA collection are detailed in Table 1.

Table 1

Inclusion criteria for DNA collection

1. Syringomyelia secondary to Chiari-like malformation as confirmed by MRI
2. CKCS with a normal occipital bone and no syringomyelia as confirmed by MRI
3. Selected Cavalier King Charles spaniels closely related to affected dogs and identified by project coordinators as important for linkage analysis. MRI status may not be known
4. Dogs with the stereotypical signs of syringomyelia (i.e. scratching at shoulder/neck/ear when excited or walking on the lead with or without cervical scoliosis, cervical hyperaesthesia, lower motor neuron signs thoracic limbs and pelvic limbs paresis/ataxia) but where MRI diagnosis is not possible either because of owner financial constraints or because prerequisite anaesthesia unadvisable.

All cases should have details of:

5. Clinical signs including time of onset and severity
6. Severity of MRI changes (if MRI available)
7. Presence / absence systolic heart murmur/ previous heart failure (i.e. development pulmonary oedema) and any heart medication
8. Pedigree

Exclusion criteria for DNA collection

1 Inadequate clinical records
2 Any evidence of skin disease (for cases without MRI confirmation)
3 Traumatising skin when scratching (for cases without MRI confirmation)

Results and Discussion

The family database is currently 24 generations and details over 8500 related individuals across 3 continents (North America, Australasia and Europe). MRI status is known for 193 dogs (160 affected with syringomyelia, 33 clear) and in a 12 month period we have collected over 500 DNA samples including ~ 90% of the dogs with known MRI status. It is focused around one pivotal affected stud dog and ranges over 4 generations. Ultimately genotyping, linkage analysis and positional gene cloning is planned.

Support from the breed clubs is essential in establishing a successful DNA collection program. This can be difficult to achieve as some breeders believe that highlighting health issues may reduce puppy sales and/or compromise their breeding program and thus endanger their livelihood. One of the key elements is support from senior committee club members. The election of less or more sympathetic individuals can significantly influence the ongoing success of a scheme. We found that the most successful way to ensure continuing support for research was to guarantee confidentiality and allow the breed clubs to control publicity about the disease and adopt a positive approach. This was achieved by keeping breeders and owners informed by quarterly newsletters and educational videos. E-mail was pivotal for ensuring communication both for dissemination of information and in provision of support for owners and breeders affected by the disease. Various internet support groups, some with membership of over

Figure 4 Phenotype form

DNA for Healthy Cavaliers

Syringlomyelia - Mitral Valve disease - Epilepsy

Phenotype Form

ID#_____

Send to: Clare Rusbridge- Confidential Fax: (011-44) 208 786-0525 or email: neuro.vet@btinternet.com

Pedigree Name: _____

Date of birth: _____ **Case No** _____ Owner's name _____

Color B B/T R T Gender M MN F FN Vet name/practice (practice stamp)

Sire's pedigree name _____

Dam's pedigree name _____

Date of Sampling - _____ Referring Clinician _____

Syringomyelia (please tick appropriate box)

No clinical signs ☐ Age of onset (if appropriate) – ____yrs ____mths

Shoulder scratching ☐ Neck pain ☐ Scoliosis ☐ Pelvic limb ataxia ☐ Thoracic limb weakness ☐

Was **MRI** carried out Yes ☐ No ☐ Was surgery carried out ? Yes ☐ No ☐ Date _____yrs _____mths

Occipital hypoplasia Yes ☐ No ☐
Cerebellar herniation Yes ☐ No ☐
Syringomyelia Yes ☐ No ☐
Area of spinal cord affected _____
☐ <1/3 diameter spinal cord
☐ 1/3-2/3 diameter spinal cord
☐ > 2/3 diameter spinal cord
Medullary kinking Yes ☐ No ☐
2° ventricular dilatation Yes ☐ No ☐
☐Neurologists notes attached

Details of any affected relatives _____

Mitral Valve Disease (please fill in/tick appropriate box)

Grade of murmur /6 Age of last heart clearance ____yrs _____mths Age murmur first diagnosed ____yrs ____mths

Stage of heart disease Age diagnosed _____yrs _____mths Examined by ☐Board Cert. Cardiologist ☐General Practitioner

☐Normal (0) *no murmur*
☐Mild (1) *Evidence of heart disease (i.e. murmur) but no clinical signs (heart normal size on x-ray / scan and no pulmonary oedema)*
☐Moderate (2) *As 1 plus mild cough and / or evidence of left atrial enlargement on xray/scan; no pulmonary oedema.*
☐Severe (3) *As 2 but has needed or still requires frusemide for pulmonary oedema (heart failure). Has or had clinical signs of coughing, breathlessness at exercise, some exercise intolerance*
☐Very severe (4) *On multiple drugs to control clinical signs of heart failure; unable to exercise.*

Heart medication currently receiving _____
☐Cardiologists notes / ultrasound scan results attached

Details of any affected relatives _____

Primary Epilepsy☐ Episodic Falling ☐ Compulsive disorder ☐ (e.g. fly-catching)
Age diagnosed above – Medication received -

Other (please specify) -

If applicable: Age at death_____ yrs _____mth **Cause of death** _____**age previous phenotype form** ____ yrs ___mths

I consent to DNA being extracted from my dog's sample and that this will be used entirely for research in the field of animal disease and genetics by *bone fida* scientists. I can reclaim my dog's sample at any time. **Please sign below**

200 individuals, have proved to be invaluable especially with regard to identifying other breeds with spontaneously developing Chiari-like malformation/syringomyelia. Project coordinators proved essential to focus collection of DNA by identifying particular offspring and relatives, answering queries and ensure that valuable data was not lost (Figure 5).

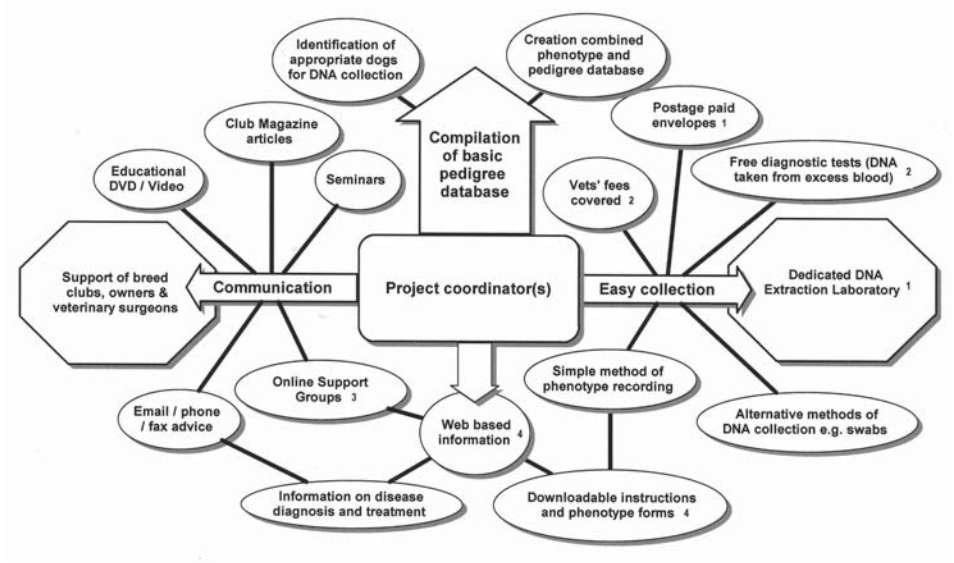


Figure 5 The key features which have ensured a successful DNA collection. Project was supported by the [1] UK DNA Archive for Companion Animals (www.liv.ac.uk/animalDNAarchive) and [2] Boehringer Ingelheim.

Internet sites / groups relating to the project

[3] http://uk.groups.yahoo.com/group/ArnoldChiari_dogs/ http://www.ourchad.20m.com

[4] http://www.cavaliers.co.uk/ http://www.thecavalierclub.co.uk/

Chiari-like malformation/ syringomyelia is a valuable model of Chiari I malformation in humans both for studying the development of the disease and investigating its genetics. Chiari I malformation in humans occurs in up to 0.77% of individuals, and 75% of people with this malformation are symptomatic (Meadows 2000). Familial Chiari type I malformation is reported with an incidence of about 2% of total cases with autosomal recessive or dominant inheritance patterns (Coria et al 1983, Zakeri et al 1995, Catala 1999) but a higher incidence is suspected (Speer et al 2000). There are a number of proposed candidate genes. Mhox gene or genes belonging to the Hox family control the development of the final shape of the occipital bone (Catala 1999) and ectopic expression of Hox-2.3 results in dysplasia or deficiency of occipital, basisphenoid and atlas bones in transgenic mice (McLain 1992). The Pax group of genes, especially Pax-1, which plays an important role in the cervico-occipital transitional zone, have also been considered as possible candidates for causative defects in human Chiari I disease (Speer et al 2000, Wilting et al 1995). However, to date it has not been possible to identify any mutations associated with Chiari I disease using human populations. The canine pedigrees being assembled here should yield crucial genetic information applicable to this very common human disease.

Acknowledgements

The authors are grateful to Simon Swift for his help with hereditary mitral valve disease and to the support of the DNA archive for Companion Animals; Boehringer Ingelheim Vetmedica; Margaret Carter; C. Anne Eckersley; Dana Schuller-Kuyper; and Angela Baker.

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Chapter 7.4

Preliminary results from syringomyelia (SM) genome wide scans in cavalier King Charles spaniel kindred and directions for future research

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Introduction

Chiari-like malformation (CM) represents an abnormality of the craniocerebral junction characterized by small volume caudal fossa with foramen magnum obstruction and secondary syringomyelia (Rusbridge and Knowler, 2003). This condition is particularly common to the cavalier King Charles spaniel (CKCS) as compared to other breeds, suggesting the involvement of genetic factors in the aetiology of this disease. Current studies suggest that syringomyelia (SM) occurs in at least 50% of dogs affected with CM and varies in severity from being asymptomatic to a severe neuropathic pain syndrome with paresis, ataxia and scoliosis. The disease has a tendency to be more severe in each subsequent generation. At present, confirmation of the disease can only be made by MRI (Rusbridge and Knowler, 2004). Pedigree analysis in a large database of over 5500 CKCS has suggested that CM in the CKCS is inherited where all clinically affected dogs share a small number of common ancestors. In fact, it has been shown that 6 out of 8 great-grandparents of all affected dogs can be traced back to two female ancestors. This small number of founders along with strict breeding criteria has led to reduced genetic variation in the CKCS breed (Rusbridge and Knowler, 2003).

In humans, while CM can be acquired following insults to the brain and cervical spine such as trauma and tumours, most cases of CM in the dog are due to a developmental defect thought to be the result of underdeveloped occipital bone(s) and caudal fossa. Morphometric studies in human patients have suggested that the fundamental defect may involve under-development of the occipital somites originating from the para-axial mesoderm (Speer et al. 2003). In hamsters, CM can be experimentally induced by administration of a single dose of vitamin A on embryonic day 8. Results from these studies suggest that the developmental defect in CM is thought to involve the somitic mesoderm at the basicranium and craniovertebral junction where a possible para-axial mesoderm insufficiency after the closure of the neural folds could lead to underdevelopment of the basichondrocranium resulting in a caudal fossa that is too small and shallow. The consequence would be overcrowding and subsequent herniation of the cerebellum into or below the foramen magnum (Marin-Padilla and Marin-Padilla, 1980).

The likelihood of a genetic basis to CM in humans is supported by many lines of evidence including familial aggregation and co-segregation with known genetic syndromes. Familial clustering has been reported in some families with CM where both vertical and male-to-male transmission was described, consistent with an autosomal dominant mode of inheritance (Speer et al. 2003). Other pedigree studies have implicated autosomal recessive mode of inheritance for CM. Most likely, the pattern of inheritance of CM is oligogenic with variable penetrance. CM has been associated with a variety of known genetic disorders including achondroplasia, Klippel-Feil syndrome, primary basilar impression and Goldenhar syndrome. The majority of these disorders affect mainly bony structures supporting the hypothesis that CM is mesodermal in origin (Speer et al. 2003).

The cellular and molecular mechanisms leading to CM are poorly understood. A number of biologically-plausible candidate genes have been proposed. The *Hox* gene family controls the development of the occipital bone and ectopic expression of Hox-2.3 results in dysplasia or deficiency of occipital, basisphenoid and atlas bones in transgenic mice (McLain et al. 1992). The *Pax* group of genes, especially *Pax-1*, plays an important role in somitic segmentation and proper sclerotomal differentiation in the cervico-occipital transitional zone (Speer et al. 2000). *Noggin* is required for growth and differentiation of the somites in the paraxial mesoderm and Noggin knockout mice show various defects affecting neural and axial-skeletal defects. *Noggin* was analysed in 33 cases of CM and no variants were identified suggesting that this gene is not a common genetic factor involved in CM (Speer et al. 2003).

The number and identity of genes predisposing to CM and associated SM have not been determined yet.

Our goal is to identify the genetic factors leading to the development of these conditions. Our specific aims are (1) genetic mapping of the CM and SM gene(s) by linkage disequilibrium analysis in the CKCS breed and in other related breeds; (2) identification of candidate genes for CM and SM using the positional candidate gene approach and (3) molecular characterization of the gene(s) mutated in CM and associated SM.

Experimental Plan and Preliminary Results

1. Genetic mapping of the CMI and SM gene(s) in the CKCS breed by linkage disequilibrium (LD) analysis:

We have constructed a genealogy of more than 10000 related CKCS dogs spanning 24 generations across 3 continents (North America, Australia and Europe). The data is stored in an Access database containing phenotypic descriptors, DNA availability, and filial relationships. Samples were ascertained through a veterinary clinic specializing in neurological diseases of dogs and also by voluntary participation of dog owners alerted of the ongoing collection effort in this breed. Once a dog was seen at the clinic for CM/SM, the owner provided pedigrees of 3 to 5 generations. When necessary the breeder was contacted to obtain the extended pedigree information. As is standard for dog breeders, dog records were tracked by using unique dog names. The collected filial data was matched to dogs in the genealogy database as well as to publicly available pedigrees of CKCS published by the UK CKCS club and UK Kennel Club. Supplementary information of some dogs of foreign breeding links was obtained from http://www.cavaliersonline.com and from http://www.worldpedigrees.com/xCavalier.htm/.We have established a wide DNA collection of over 1000 samples including mainly the CKCS breed and 30 samples from 10 other breeds affected with CM of various degrees of genetic relatedness to the CKCS (King Charles Spaniels, Brussels Griffon, Yorkshire Terrier, Staffordshire Bull Terrier, Boston Terrier, Chihuahua, Maltese terrier, a Miniature dachshunds, a Boston terrier, a Pug and a French bulldog).

Founder events and stringent breeding practices have made the CKCS breed, like other purebred dogs, a closed genetic pool, equivalent to isolated human populations used advantageously in genetic mapping studies such as the Finns, Icelanders and Bedouins. Isolated populations have limited variation in their gene pools which reduces the chances of disease heterogeneity. The higher inbreeding in isolated population also has the effect of leading to larger physical regions of genetic identity shared on chromosomal segments involved in disease expression (Varilo and Peltonen 2004). As a result, LD mapping is a promising strategy for gene mapping studies in the dog (Hyun et al. 2003). We will use this mapping strategy to identify genes predisposing to CM and to SM in the dog.

1.1. Genetic mapping of the gene(s) predisposing to CMI

CM is present in variable degrees of expression in nearly 100% of the CKCS dogs, making association studies in this single breed not feasible. CM/SM does occur with a lower frequency in other (mostly toy) breeds; however, since diagnosis is confirmed only by MRI, the exact incidence of CM in these breeds is not known. Closely related breeds are more likely to share ancestral chromosomes and hence carry the same disease allele. Studies of the evolutionary history of the dog have shown that dog breeds define distinct genetic units divided into at least 4 hierarchical groupings (Ostrander et al. 2005, Parker et al. 2004). The CKCS are clustered with mostly modern breeds including other spaniels, gundogs, hounds and terriers. Ongoing studies are focusing on defining clusters within this group. This kind of structure analysis of the dog population provides a genetic guide to the design of LD whole-genome scans. We will initially conduct a whole genome scan using dogs from the CKCS breed and other relatively modern and closely- related breeds. Studies have shown that LD in purebred dogs is ~100 times more extensive than in humans (Sutter et al. 2004). We will use allele sharing, homozygosity mapping and association testing to pinpoint a candidate region. We will next try to narrow down and delineate the minimal genetic interval containing the CM gene(s) by LD mapping and haplotype association studies using a dense SNP (single nucleotide polymorphisms) coverage between historically older but related breeds affected with CM as necessary. Analyses will be conducted by using SAS 9.1 including SAS/Genetics (SAS Institute Inc., Cary, NC, USA), as well as DMLE for LD mapping (Reeve and Rannala 2002).

1.2. Genetic mapping of the genes predisposing to SM associated with CM

Currently studies suggest that SM is present in over 50% of dogs affected with CM (Rusbridge and Knowler, 2004) making whole genome association and linkage-based studies feasible within this breed. Due to the complex inbreeding in the CKCS, a preliminary genetic analysis was necessary to evaluate the informativeness of the genetic markers and hence the feasibility of a whole genome scan in such breed. Consequently, 10 dogs were selected for genotyping with 122 markers distributed among the 38 autosomes and X chromosome. Next and with the support of the Marshfield genotyping services from the NIH, we have recently completed the genotyping of 173 CKCS dogs over 249 microsatellite markers distributed over the 38 autosomes and the X chromosome. The dogs are distributed over 34 dog pedigrees including multiple affected and unaffected sibs and half sibs with parents. The data was analysed for linkage using the program SAGE (Statistical analysis for genetic epidemiology) using the LODPAL analysis tool which allows for affected relative pair and discordant pair linkage computations. We also analyzed the genotyping data using a statistical approach testing association in the presence of linkage methods implemented in the computer program FBAT (Abecasis et al. 2000). FBAT (family based association test) provides a class of conditional tests that includes many of the established tests described for specific family structures. It handles missing parents, missing marker data, uncertain phase, continuous and discrete phenotypes as well as covariates. The main motivation for using the FBAT approach is to control for the multiple inbreeding loops present in the CKCS genealogy. This approach allows the detection of both linkage and association. Empirical evaluation of the study- specific genome wide significance criterion was conducted

using simulations with the program. Preliminary results have suggested six interesting regions on six associated chromosomes which warrant further investigation.

2. Identification of candidate genes in the minimal CM and SM interval(s)

We will search the minimum candidate genetic interval(s) for the presence of transcribed genes. As most of the dog sequence data is available *in silico*, we will define our candidate genes and their precise sequence using mostly three public databases: UCSC (http://genome.ucsc.edu), NCBI (http://www.ncbi.nlm.nih.gov) and Ensembl (http://www.ensembl.org). Comparative genomics between multiple species including human, mouse, dog and chimp is another powerful tool in identifying genes via analysis of sequence conservation. Novel genes will be analyzed for secondary structure predictions, specific sequence motifs and sequence homology to known proteins and nucleic acids. This analysis will provide some clues on the structural and functional aspects of the cloned gene and encoded protein. We will screen candidate genes chosen according to the following criteria: (1) position within the definite candidate region, (2) expression in the affected tissues and (3) predicted/known function. Candidate genes based on function are chosen if they are thought or known to be implicated in the morphogenetic processes involved in formation of the craniocerebral junction. We will first focus on sequencing the coding exons where most of the disease-associated mutations are found. We will examine promoter, untranslated and intronic regions to detect splice-site and regulatory mutations by sequence analysis. To further assess any detected splice-site or regulatory mutation(s), cellular or animal models will become necessary.

3. Molecular characterization of the gene defective in CM and in SM

Our goal is ultimately to determine the normal function of genes implicated in CM and in SM and how mutations in these genes cause the CM and SM phenotype. A mouse model (if not already available) will be generated to further study the biology of the disease. Expression studies will be performed at the RNA and protein level, both at the tissue (Northerns, RT-PCR, Westerns) and cellular levels (*in situ*, immunohistochemistry). The protein will be studied for subcellular localization and post-translational modification.

Conclusion

Identification of the genes responsible for CM with or without SM will help better understand the underlying pathogenic mechanisms 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.

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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.

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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,
Wimbledon,
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:

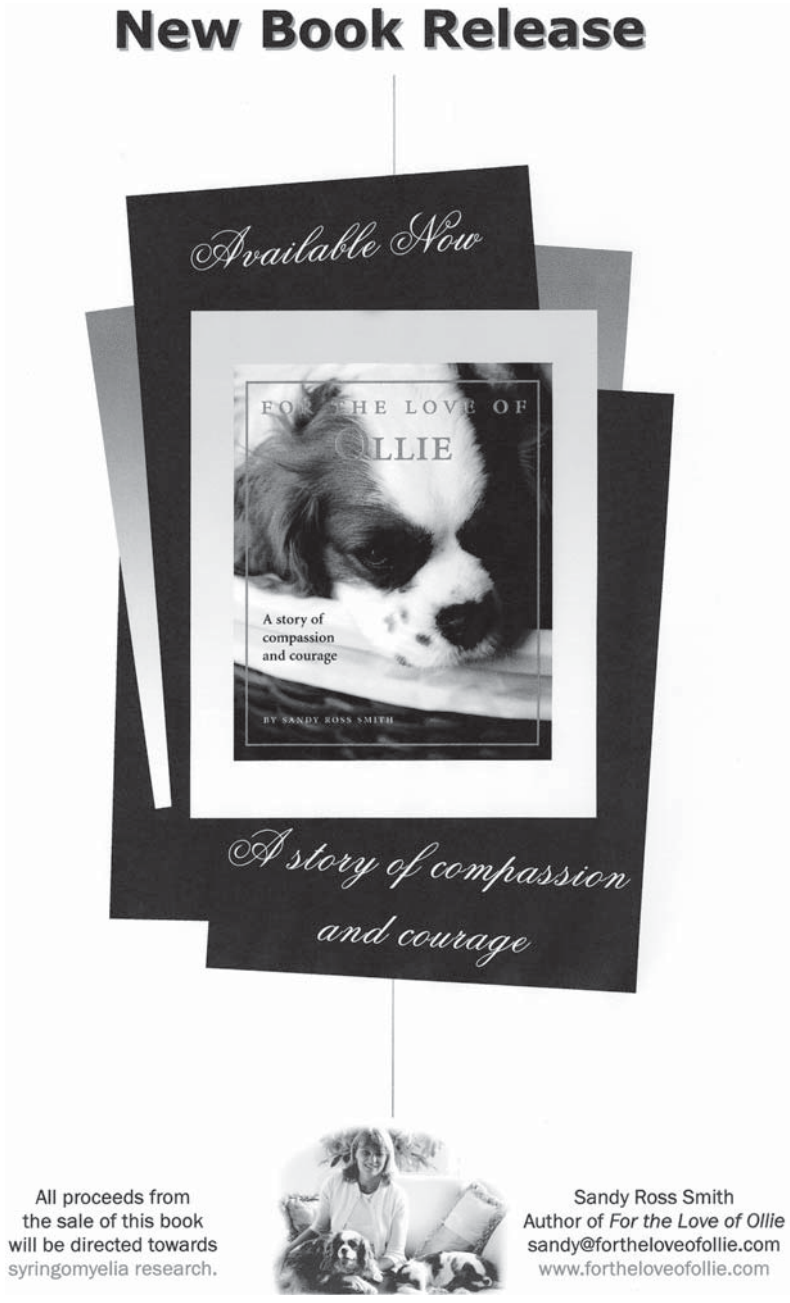
Chiari-like malformation of the caudal skull	**YES / NO**
Dilatation of the central canal	**YES / NO (region)**
Syringomyelia in the cervical spinal cord	**YES / NO (maximum width)**
Ventricular dilatation	**YES / NO**

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

Dankwoord / Acknowledgements

This thesis would not be possible without the contribution of all the **dedicated cavalier lovers,** worldwide, who have given their support in so many different ways – information, time, energy, money and expertise to help the dogs.

In particular I should like to thank

My family, especially **Penny Knowler**, my co-author, research assistant and mother who also coordinated the international DNA research project and made an educational DVD (the sales of which funded some of our research). My love and thanks to **Mark,** my husband and soul mate, for his encouragement and patience especially when I was under pressure. My daughter, **Jill**, who enabled me to keep my sense of perspective and delighted me with her creations while keeping me company 'down the office'. Thanks also to my father, **Professor John Knowler,** who tolerated (not always quietly) the invasion of "Cavalier spaniels' into family life.

Paul Mandigers, if it were not for you I would have never had the courage or opportunity to do a PhD. You constantly encouraged me to "have something to show" for my research and went beyond to call of duty to see that I achieved it with the considerable assistance of **Professor Jan Rothuizen** my supervisor and support of **Utrecht University**.

The **Goddard Veterinary Group** in particular the all the **nurses and receptionists** at the **Stone Lion Veterinary Centre.** I am also grateful for the support of practice owner **Phillip Goddard**, practice manager **Ray Girotti** and head vet **Harvey Carruthers.** It is not easy doing research from a referral practice setting and you were always encouraging.

Simon Wheeler for his initial encouragement – in 1996 he said "I think you may have got something important" - when I excitedly explained my theories for the phantom scratching. I am also very grateful to **Professor Nick Jeffery** and **Cambridge University** (in particular the Clinical Research Outreach Program) for providing me with the opportunity of their resources and for supervising my projects in such a professional and enthusiastic manner.

Professor Guy Rouleau, Zoha Kibar, Marie-Pierre Dubé at Montreal University (CHUM) and **Berge Minassian** in Toronto, Canada for their collaboration with the genetic research and for their expertise. There is still a great deal to do but together we have made amazing progress over the past few years.

For their help with the collection of samples and extraction of DNA, I should like to thank **Natasha Olby** at **North Carolina University, Ohio University** and the **UK DNA Archive.** If it had not been for the latter, it would have been impossible for general practitioners to store DNA. I would also like to thank **Andy Torrance** and **TDDS laboratories** for their professional support.

The Cavalier King Charles Spaniel Club, UK and all the breeders who contributed to 'DNA for Healthy Cavaliers' in particular **Margaret Carter** – a breeder who cares. Thank you for all your support and for your bravery in tacking the problem of CM/SM in the CKCS. Also to **Bet Hargreaves** whose initial support is still appreciated.

Dana Schuller-Kuyper for your courage and dedication to breed healthy CKCS, establishing the Cavalier Guild in the Netherlands and supporting for the research with the help of the **Dierenartsenpraktijk Hoogeveen Veterinary Practice** and the **Diaconessenhuis Meppel** CKCS syringomyelia screening program. Your continued work with **Pirkko Blijham-Keckman** is very important for our sustained understanding of the natural history and inheritance of CM/SM.

Randi Rosvoll and **Anne Eckersley** of the Cavalier Club of the USA. **Pat Barrington** and the Cavalier Club of Canadian, **Sue Shidler**, and all the other breeders in North America who contributed information and DNA.

To the many pet owners (and their dogs), in particular: **Janet Ireland** for first raising awareness to SM in 1996; **Sandy Smith**, owner of two SM affected CKCS and author of "For the love of Ollie" a book that made CM/SM easier to understand for many owners (**appendix 5**). Thank you for donating profits of this book to our research and for being such an amazing host and special person; **Carol Fowler**, the owner of two SM affected CKCS who has tirelessly campaigned for the improved welfare of this breed. You have

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.

The interaction and collaboration with human neurologists has been especially valued – in particular with members of the **Ann Conway Trust, the American Syringomyelia Alliance (ASAP)**, **Atkinson Morley Hospital** and **Parkside Hospital.**

Finally thanks are also due to **Daphne Hills** Curator Mammals, The Natural History Museum, Cromwell and **Marc Nussbaumer** Curator Albert-Heim Foundation for Canid Research Natural History Museum, Bern. Thanks for all your time and patience dealing with my many requests and for permitting me access to your valuable specimens.

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

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