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.

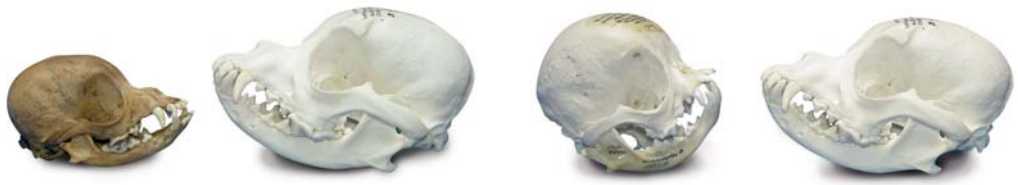

Figure 4a Figure 4b

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

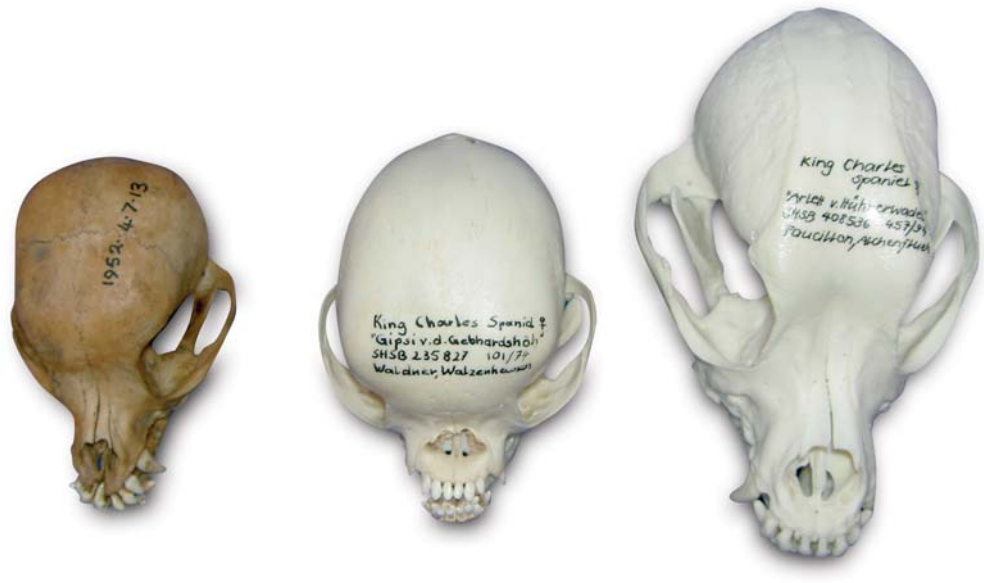

Figure 4c Left to right: early King Charles spaniel, modern King Charles spaniel and cavalier King Charles spaniel

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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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).

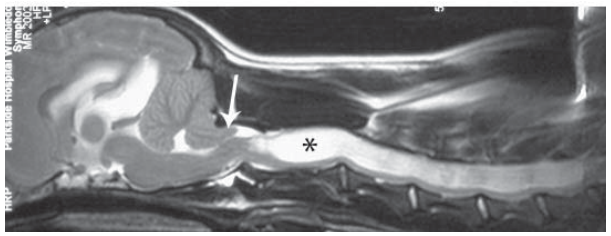

Figure 1 Midsagittal TW2 weighted image of the brain and cervical spinal cord. Syringomyelia (asterisk) secondary to Chiari-like malformation (occipital hypoplasia) in a 21 month female CKCS presenting with a 3 month history of yelping and a tendency to scratch at the right shoulder area. There is cerebellar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

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

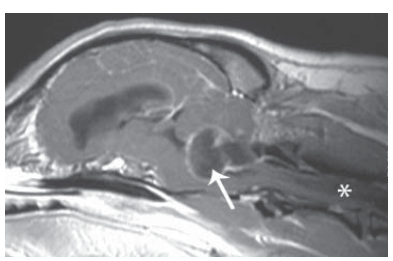

Figure 2 Midsagittal gadolinium enhanced TW1 weighted image of the brain and cervical spinal cord in a seven year female CKCS with syringomyelia (asterixis) secondary to a dermoid sinus (arrow). The dog presented with central vestibular signs that were slowly progressive over several months. The mass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

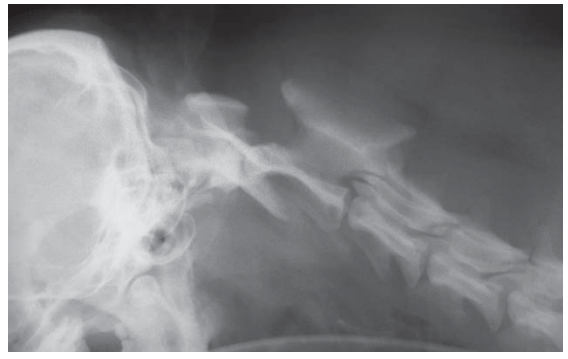

Figure 3 Lateral cervical radiograph with ventriflexion of the atlantoaxial joint in an 18 month old female CKCS that was presented with tetraparesis and had pain on ventriflexion of the neck. The dens is absent and there is atlantoaxial subluxation illustrated by dorsal widening between C1 and C2.

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.

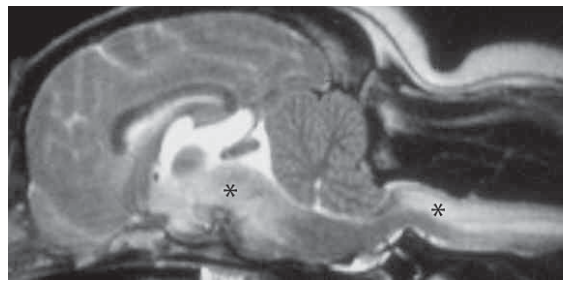

Figure 4 A midsagittal TW2 weighed image of the brain and cervical spinal cord in a 5 year old female CKCS presenting with cervical pain and depression. Note the high signal through the midbrain and spinal cord suggestive of inflammation (asterisk). CSF analysis revealed a mononuclear pleocytosis.

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.

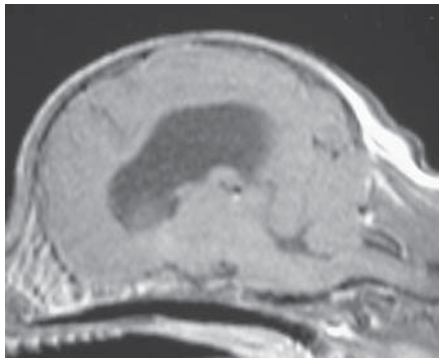

Figure 5 Midsagittal TW1 weighted 9 week female CKCS that was presented after a generalised tonic clonic seizure. There is marked dilation of the lateral ventricles and the skull shaped is more domed than normal. The mesencephalic aqueduct appears patent but there is severe caudal fossa overcrowding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

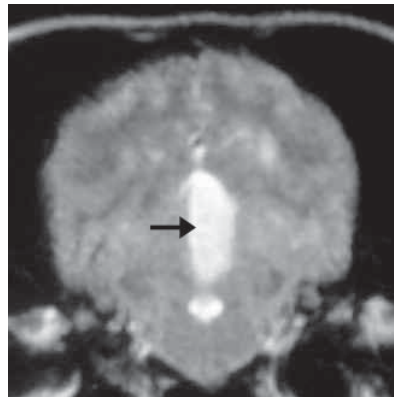

Figure 6 Transverse TW2 weighted image at the level of the rostral cerebellum. A 3 year old male CKCS that presented following acute onset intention tremor, depression and tetraparesis with a right sided head tilt, facial nerve paresis and lateral strabismus. MRI reveals a sharply delineated wedge shaped 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).

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