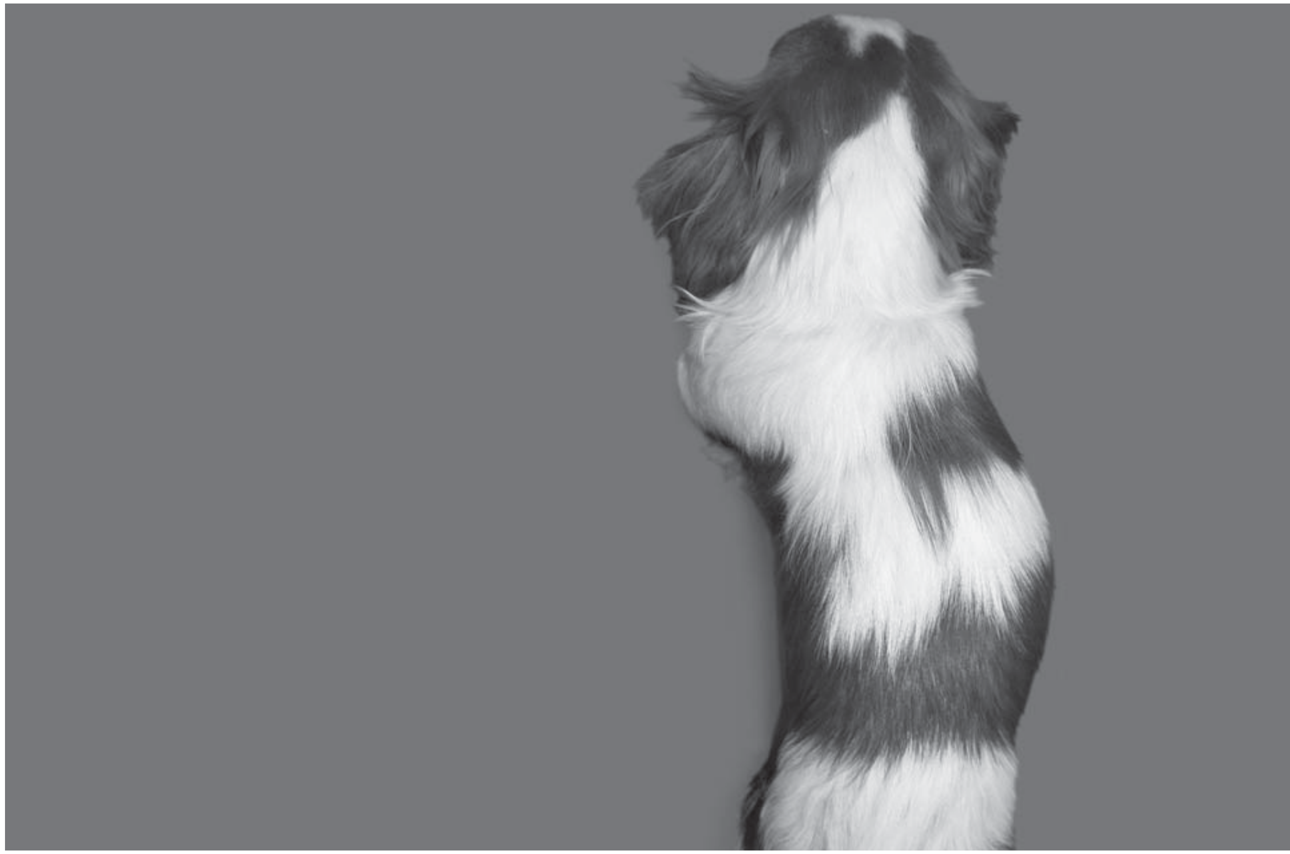

Section 5

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

C. Rusbridge [1] H. Carruthers [1] M-P Dubé [2] M Holmes [3] N. D. Jeffery [3]

1. Stone Lion Veterinary Centre, 41 High Street, Wimbledon Village, London, SW19 5AU, 2. Department of Medicine, Université de Montreal, and The Montreal Heart Institute, Canada, 3. Department of Veterinary Medicine, University of Cambridge, Madingley Road, Cambridge, CB3 OES

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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).

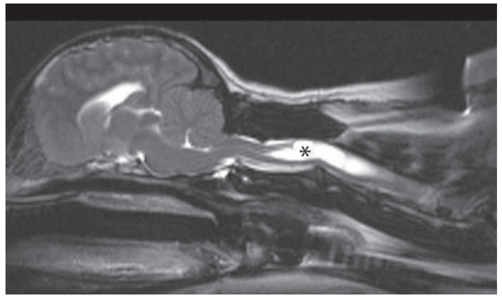

Figure 1 Midsaggittal T2 weighted MRI of the brain and upper cervical spinal cord from case 52, a 4.1 year old female neutered CKCS that had signs of pain from 1.7 years old. Clinical signs included yelping whilst scratching at the right shoulder area. This was more likely when she was excited. Note 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).

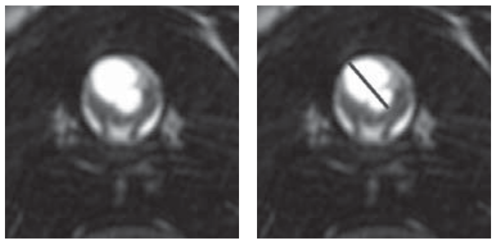

Figure 2 T2 weighted transverse image through the syrinx depicted in figure 1a) demonstrating the asymmetrical involvement of the right dorsal horn. If the spinal cord is transected in a dorsal plane into ventral and dorsal halves, then the spinal cord around the ventral syrinx is equal left to right. 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.

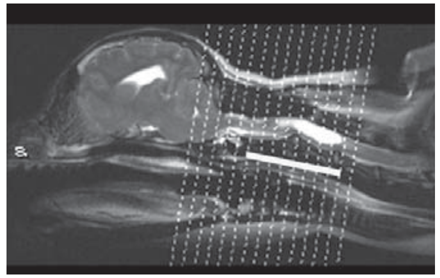

Figure 3 Scout view for the transverse images for case 52. The length of the asymmetrical dorsal grey column involvement was obtained by recording the image numbers through which there was a continuous asymmetrical syrinx then measuring the distance between the first and the last image on the scout view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

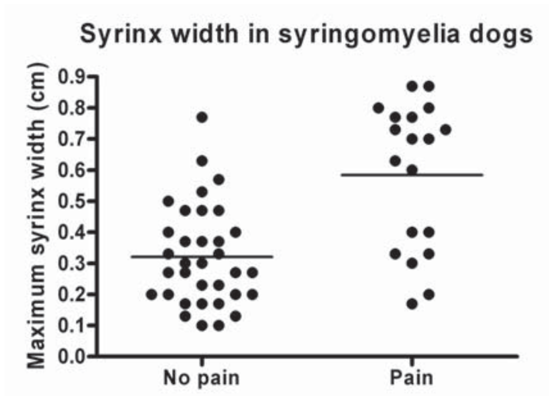

Figure 4 Scatter plot illustrating the relationship between maximum width of the syrinx and presence of absence of pain in dogs with syringomyelia. The horizontal line indicates the mean value

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.

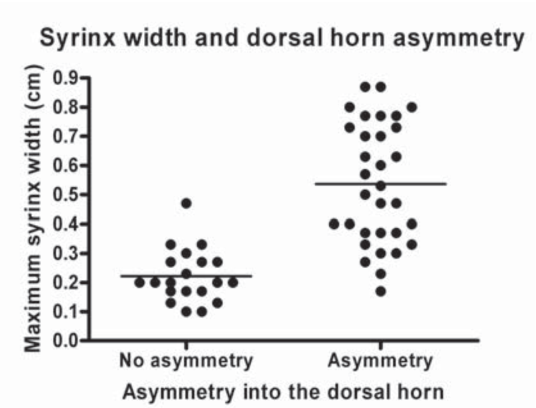

Figure 5 Scatter plot illustrating the relationship between maximum width of the syrinx and dorsal horn asymmetry. The horizontal line indicates the mean value.

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

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Chapter 5.2

Pathophysiology and treatment of neuropathic pain associated with syringomyelia

C. Rusbridge [1] N. D. Jeffery [2]

1. Stone Lion Veterinary Centre, 41 High Street, Wimbledon Village, London, SW19 5AU, 2. Department of Veterinary Medicine, University of Cambridge, Madingley Road, Cambridge, CB3 OES

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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).

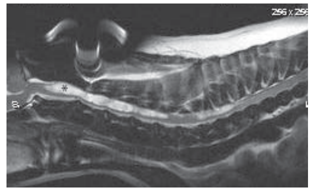

Figure 1 Mid-sagittal T2 weighted MRI of upper cervical spinal cord from a 2.6 year old female CKCS that had signs of pain from 1.9 years old. Clinical signs included yelping whilst scratching at the right shoulder area. This was more likely when she was excited. There is a syringomyelia (asterisk) secondary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

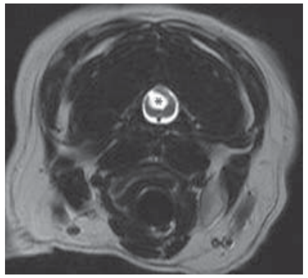

Figure 2 T2 weighted transverse image through a syrinx (asterisk) demonstrating the asymmetrical involvement of the right spinal cord dorsal horn

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).

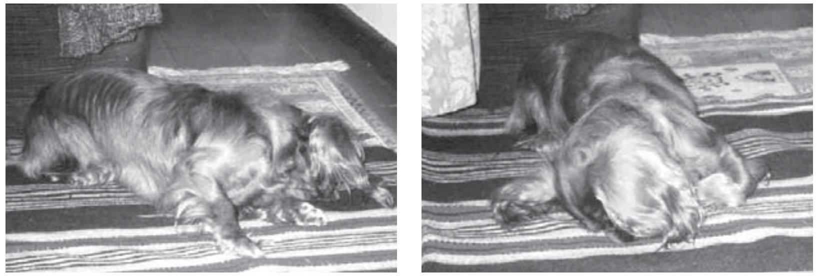

Figure 3 a, b A 2 year old female cavalier King Charles spaniel that was presented with persistent head rubbing that was most noticeable in the morning, when first getting up. The clinical signs were somewhat relieved by oral frusemide therapy and the dog subsequently was managed with a cranial cervical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