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Seizure Management in Dogs: Going Beyond Standard Therapy

Seizure disorders are common in dogs, the most common etiology being idiopathic epilepsy. Most seizures are visibly upsetting to the pet owner, often causing the owner to suffer considerable emotional distress. This distress is often communicated to the family veterinarian. Managing seizure disorders presents a major challenge to the veterinarian, especially when a dog does not respond to standard (i.e., phenobarbital, bromide) therapy. Such refractory cases account for between 25-30 % of all epileptics. In a recent prospective investigation, it was determined that epilepsy in dogs does have a significantly negative impact on lifespan. The most common reason for euthanasia of an epileptic dog is lack of seizure control, and drug side effects also impact this decision. With information concerning antiseizure therapy readily available through the internet (much of which is either anecdotal or simply incorrect), clients often come to their veterinarian with preconceived notions concerning how their pet's seizure disorder should or should not be handled. I often encounter pet owners who refuse phenobarbital therapy, because it (according to what the owner has read) causes liver failure. Owners also often arrive at their veterinarian's office following their pet's first seizure, fully expecting their veterinarian to make their pet seizure-free. It is very important for the clinician to inform the pet owner that less than 30% of epileptics become seizure free; success is typically considered a reduction in the frequency and duration of seizures. Nonetheless, the goal of anticonvulsant therapy should be to eliminate seizure activity in the patient, or come as close to this goal as possible, without subjecting the patient to unacceptable side effects of drug therapy. A common misconception concerning seizure management is that the achievement of no more than one seizure per month should be the goal of therapy. Such a goal would be of little benefit to the dog presenting with a history of monthly seizure activity. Alternatively, a dog that seizures daily prior to drug intervention and experiences two seizures per month afterwards would be incorrectly considered a treatment failure, using such arbitrary criteria. Concerns over potential side effects of drug therapy are based primarily on the use of phenobarbital and bromide. With the advent of the newer anticonvulsant drugs to be discussed in this presentation, improved seizure control is often possible without concurrent adverse side effects. There are a number of so-called "new" drugs for dogs with epilepsy, and they are discussed below in order of my perception of most to least effective. I will also briefly discuss a drug called pregabalin for which we recently reported the results of a clinical trial in refractory epileptics. My opinion is that pregabalin is often an effective drug.

Zonisamide is a sulfonamide-based anticonvulsant drug recently approved for human use; it has been shown to be effective for the treatment of both focal and generalized seizures in people, with minimal side effects. Suspected anticonvulsant mechanisms of action include blockage of T-type calcium and voltage-gated sodium channels in the brain, modulation of dopaminergic metabolism in the central nervous system, scavenging free radical species, enhancing actions of GABA in the brain, and inhibition of carbonic anhydrase activity.

Zonisamide (ZNS) is metabolized mainly by hepatic microsomal enzymes, and the t ½ in dogs is roughly 15-20 hrs. In humans, it has been shown that the t ½ of ZNS is dramatically shorter in patients already receiving drugs that stimulate hepatic microsomal enzymes, in comparison with patients who are not receiving such drugs. A similar phenomenon appears to occur in dogs. When used as an add-on therapy for dogs already receiving drugs requiring hepatic metabolism (e.g., phenobarbital), I recommend an initial oral ZNS dose schedule of 8-10 mg/kg body weight, q 12 hrs. This dose regimen has been shown to maintain canine serum ZNS concentrations within the therapeutic range reported for people (10 to 40 ug/ml), when used as an add-on therapy. For dogs not concurrently receiving drugs that induce hepatic microsomal enzymes, it is recommended to start ZNS at a dosage of 5 mg/kg body weight, q 12 hrs. Trough serum ZNS concentrations are checked after approximately one week of treatment. Zonisamide has a high margin of safety in dogs. In one study, minimal side effects occurred in beagle dogs administered daily ZNS doses up to 75 mg/kg body weight per day for one year. In a clinical trial I published in 2004, ZNS was found to decrease seizure frequency by at least 50% in 7 of 12 dogs with refractory idiopathic epilepsy. In this responder group, the mean reduction in seizure frequency was 81.3%. In six of the 7 responder dogs, phenobarbital was reduced by an average of 92.2%. Mild side effects (e.g., transient sedation, ataxia, vomiting) occurred in six (50%) dogs; none of the side effects were considered severe enough to discontinue zonisamide therapy. In a more recent, similarly designed study, 9 of 11 refractory epileptic dogs treated with zonisamide were responders, with a median seizure reduction of 92.9%; transient ataxia and sedation occurred in six dogs. I have used zonisamide as a sole anticonvulsant drug in a large number of dogs. Zonisamide is usually effective as a sole anticonvulsant therapy, with few to no apparent side effects. I have also treated a number of cats with zonisamide for seizure control. The elimination half-life of ZNS in cats is quite long (about 33 hrs), so some cats can be dosed SID. The case numbers are small, but the drug does appear to be of some clinical utility in this species. I have had a few cats become anorexic on ZNS, necessitating drug discontinuation.

Felbamate is a dicarbamate anticonvulsant drug that has shown efficacy for both focal (partial) and generalized seizures in experimental animal studies and human clinical trials. The suspected mechanisms of action of felbamate include blocking of N-methyl-D-aspartate (NMDA)-mediated neuronal excitation, potentiation of GABA-mediated neuronal inhibition, and inhibition of voltage-sensitive neuronal sodium and calcium channels. There is also evidence that felbamate may afford some protection to neurons against hypoxic/ischemic damage. Approximately 70% of the orally administered dose of felbamate in dogs is eliminated in the urine unchanged; the remainder undergoes hepatic metabolism. The t ½ of felbamate in adult dogs is typically between 5 and 6 hrs (range, 4-8 hrs). An initial felbamate dose regimen of 15 mg/kg body weight, q 8 hrs is recommended. Felbamate has a wide margin of safety in dogs, with serious toxic effects usually not apparent below a daily dose of 300 mg/kg body weight per day. If the initial dose of felbamate is ineffective, I increase the dose in 15 mg/kg every 2 weeks until efficacy is achieved, unacceptable side effects are evident, or the drug becomes cost-prohibitive. The therapeutic range for serum felbamate concentration in dogs is thought to be similar to that in people (20-100 ug/ml). Serum felbamate assays are typically costly, and are typically not necessary (due to low toxicity potential). Side effects are infrequently encountered with felbamate use in dogs. A major advantage of felbamate over more standard anticonvulsant drugs is that it does not cause sedation. Because felbamate does undergo some hepatic metabolism, liver dysfunction is a potential side effect. In one study, 4

of 12 dogs receiving felbamate as an add-on therapy developed liver disease. However, all of these dogs were also receiving high doses of phenobarbital. In people, felbamate has been shown to increase serum phenobarbital concentrations in some patients receiving combination therapy. It is not clear whether felbamate, phenobarbital, or the combination of the two drugs is responsible for the reported hepatotoxicity in dogs. In people, serious hepatotoxicity is rarely encountered with felbamate use and is almost always experienced in patients receiving other anticonvulsant drugs concurrently. Aplastic anemia (due to bone marrow suppression) has been reported in people receiving felbamate at a rate of 10/100,000 patients; this uncommon side effect is also usually encountered with patients receiving combination anticonvulsant drug therapy. This devastating side effect does not appear to occur in dogs receiving the drug. In one report, however, reversible bone marrow suppression was suspected in two dogs receiving felbamate; one dog developed mild thrombocytopenia, the other mild leukopenia. Both of these abnormalities resolved with felbamate discontinuation. One patient in this report developed bilateral keratoconjunctivitis sicca (KCS); it is unknown whether or not this was related to felbamate use. However, I have had several felbamate patients that developed KCS. Generalized tremor activity in small breed dogs receiving high doses of felbamate has also been reported as a rarely encountered side effect. The limited published material concerning efficacy of felbamate mirrors my clinical experience with the drug. In one report of refractory epileptic dogs, 12 of 16 patients experienced a reduction of seizure frequency following initiation of felbamate therapy. In another report of 6 dogs with suspected focal seizure activity, all 6 dogs experienced a substantial reduction in seizure frequency when felbamate was used as a sole anticonvulsant drug; two of these dogs became seizure-free. In my experience, felbamate is very effective both as an add-on therapy and as a sole anticonvulsant agent for patients with focal and generalized seizures. Because of its lack of sedative effect, the author has found felbamate to be particularly useful as a monotherapy in dogs exhibiting obtunded mental status due to their underlying neurologic disease (e.g., brain tumor, cerebral infarct). I have found side-effects from felbamate to be very infrequent. However, because of the potential for hepatoxicity, it is recommended that serum biochemistry analysis be performed every 6 months for dogs receiving felbamate, especially if given concurrently with phenobarbital. It may also be prudent to evaluate complete blood counts (CBCs) every several months, in the unlikely event that a blood dyscrasia develops. To my knowledge, there is no clinical information regarding the use of felbamate in cats. Due to the potential for felbamate-associated hepatotoxicity and blood dyscrasias in dogs, felbamate is not likely to become a viable anticonvulsant option for cats. In recent years, felbamate has increased substantially in price, so I have been using it very infrequently.

Because of the problems of hepatoxicity and blood dyscrasias occasionally associated with felbamate use in people, a new derivative of the drug-fluorofelbamate-has been developed and is undergoing clinical trials for human use. A reactive aldehyde intermediate that is formed from felbamate metabolism has been linked to the drug's hepatic and hematologic side effects. This toxic intermediate is not produced during the metabolism of fluorofelbamate. In experimental animal epilepsy models, fluorofelbamate has been shown to have equal or superior anticonvulsant potency in comparison with felbamate.

Levetiracetam (LEV) is a new anticonvulsant drug that has demonstrated efficacy in the treatment of focal and generalized seizure disorders in people, as well as in several

experimental animal models. The mechanism of action for levetiracetam's anticonvulsant effects is not entirely clear, but appears to be related to its binding with a specific synaptic vesicle protein (SV2A) in the brain; unlike other anticonvulsant drugs, levetiracetam does not appear to directly affect common neurotransmitter pathways (e.g., GABA, NMDA) or ion channels (e.g., sodium, T-type calcium). Levetiracetam has demonstrated neuroprotective properties, and may ameliorate seizure-induced brain damage. Levetiracetam has also been reported to have an "anti-kindling" effect, which may diminish the likelihood of increasing seizure frequency over time. Orally administered LEV is approximately 100% bioavailable in dogs, with a serum t ½ of 3-4 hours. Levetiracetam seems to exert an anticonvulsive effect that persists longer than its presence in the bloodstream would suggest. Approximately 70% of the administered dose of LEV is excreted unchanged in the urine; the remainder of the drug is hydrolyzed in the serum and other organs. There does not appear to be any hepatic metabolism of LEV in either humans or dogs. The effective serum LEV concentration in people is 5 to 45 ug/ml. Since there is no clear relationship between serum drug concentration and efficacy for LEV, and since the drug has an extremely high margin of safety, routine therapeutic drug monitoring is not typically recommended for this drug in people. Based upon available pharmacokinetic information in dogs as well as clinical experience, I recommend an initial dosing schedule of 20 mg/kg body weight, q 8 hours. This dose can be increased by 20 mg/kg increments until efficacy is achieved, side effects become apparent, or the drug becomes cost-prohibitive. Long-term toxicity data for LEV in dogs confirm that the drug is extremely safe. In one study, dogs were administered oral LEV at doses up to 1200 mg/kg/day for one year. One of eight dogs receiving 300 mg/kg/day developed a stiff/unsteady gait. The remainder of side effects (salivation, vomiting) was confined to dogs receiving 1200 mg/kg/day. There were no treatment-related mortalities, and no treatment-related histopathologic abnormalities. In one small clinical study, oral LEV was found to decrease seizure frequency by over 50% in epileptic dogs, when used as an add-on therapy. Another more extended study found that oral LEV in dogs appeared to have a substantial "honeymoon effect", decreasing in efficacy after the initial 6-8 months of use. My clinical experience with this drug in dogs has been similar. My colleagues and I have prospectively investigated the use of oral levetiracetam as an add-on anticonvulsant therapy for epileptic cats refractory to phenobarbital. Levetiracetam appears to be very well tolerated in this species, usually with no apparent side effects, and no obvious "honeymoon effect". The t ½ of elimination is approximately 3 hours after oral administration. A dose of 20 mg/kg PO, q 8 hrs typically achieves a serum drug level within the therapeutic range reported for people. Two of 12 cats experienced transient inappetance and lethargy that resolved without dose adjustment within 2 weeks. Although there is some degree of variability among cats, the mean reduction of seizure frequency in cats receiving levetiracetam as an add-on drug is approximately 68%; this was found to be statistically significant when compared to the pre-levetiracetam time period. In addition, 7 of 10 cats evaluated for seizure frequency reduction were responders (i.e., reduction of seizure frequency of 50% or more), with a mean reduction of seizures of 92%. I consider levetiracetam to be the preferred add-on anticonvulsant drug for cats receiving PB, due to lack of serious side effects and evidence of efficacy. In terms of cost, levetiracetam is more expensive than zonisamide, but less expensive than felbamate.

Gabapentin is a structural analog of GABA. Gabapentin is thought to exert its antiseizure effects via binding to the α2δ subunit of voltage-gated neuronal calcium channels.

This binding decreases intracellular calcium influx, leading to decreased synaptic release of excitatory neurotransmitters. Gabapentin is well absorbed in both dogs and people, with peak serum concentrations occurring within 1-3 hrs after ingestion. In people, virtually all the orally administered dose of gabapentin is excreted unchanged in the urine (i.e., no hepatic metabolism). In dogs, however, 30-40% of the orally administered dose of gabapentin undergoes hepatic metabolism to N-methyl-gabapentin. Despite undergoing some hepatic metabolism in dogs, there is no appreciable induction of hepatic microsomal enzymes in this species. The t ½ for gabapentin in dogs and cats is between 3 and 4 hrs. The recommended dose range of gabapentin for dogs is 25-60 mg/kg body weight, *divided*, q 6-8 hrs. I use an initial dose regimen of 10 mg/kg body weight, q 8 hrs. The suspected therapeutic range for dogs is 4-16 mg/L. As is the case with felbamate, serum gabapentin concentrations are seldom pursued in dogs. Long-term toxicity trials for gabapentin have not been reported in dogs. However, the drug seems to be very well tolerated by this species, usually with no side-effects. Sedation does not appear to be a common problem with gabapentin use in dogs, but occasionally occurs. There are two clinical reports of gabapentin use as an add-on drug for dogs with refractory epilepsy. Overall, the responder rate of these dogs was between 41% and 55%. In the author's experience, gabapentin is moderately effective as an anticonvulsant drug in dogs. In people, gabapentin appears to be much more effective in the treatment of focal seizure disorders, compared with its efficacy for generalized seizures. Because of its short t ½, gabapentin probably needs to be administered at least every 8 hrs, and possibly every 6 hrs, in order to maintain serum gabapentin concentrations within the therapeutic range. The potential need for q 6 hr dosing can make it difficult for some pet owners to reliably administer gabapentin. Anecdotally, the author has found gabapentin to be useful for managing dogs with chronic pain or paresthesia. There is only anecdotal information concerning the use of gabapentin for cats with seizures. An oral dose of 5-10 mg/kg body weight q 8-12 hrs has been suggested, but is not based on any published data. To the author's knowledge, there is no information regarding either the safety or efficacy of chronic gabapentin administration to cats.

A new gabapentin analog, pregabalin, has recently been approved for human use. Pregabalin has an increased affinity for the α2δ-subunit of voltage-gated calcium channels, compared with gabapentin, and is suspected to be more effective in people than its predecessor as both an anticonvulsant and a pain-relieving drug. My colleagues and I have completed an oral pharmacokinetic study of pregabalin in both dogs and cats, and a clinical trial of pregabalin in refractory epileptic dogs. The median seizure reduction in the clinical study was approximately 50%.

Standard therapy for the dog with cluster seizures or status epilepticus in the hospital setting includes diazepam (and diazepam derivatives), barbiturates, and propofol. The main disadvantage of diazepam and similar drugs is that it is often ineffective in halting seizure activity in these patients. A disadvantage shared by all of these standard treatment options is sedation. The sedation caused by barbiturates and propofol is usually profound, requiring intubation. Levetiracetam (LEV) is now commercially available as a sterile intravenous solution. Levetiracetam does not cause sedation. Levetiracetam has been demonstrated to be tolerated well by normal dogs when administered intravenously as a bolus over 2 minutes; in addition, such administration results in serum LEV concentrations within or above the suspected therapeutic range. Since levetiracetam does not undergo hepatic metabolism in dogs,

it may be a useful drug for seizure management in postoperative portosystemic shunt patients. The dosing protocol and efficacy of intravenous levetiracetam has yet to be determined. We have been using it in our ICU for status/cluster patients for over a year and have been very pleased with the results.

Surgical options for epilepsy treatment are well established in humans, but are rarely considered in dogs. This is probably due both to the lack of functional brain imaging in veterinary medicine and the expense of equipment required for many of these procedures. Corpus callosotomy has been described in normal dogs, but there have been no reports of its use in clinical canine patients. Surgical implantation of a vagal stimulator has been described in dogs, but the procedure failed to demonstrate significant reduction of seizure activity. There has been recent work in the human epilepsy field dealing with the surgical implantation of stimulating electrodes into the thalamus. This deep brain stimulation (DBS) methodology has been effective for the treatment of Parkinson's disease, and has shown some preliminary promise for the treatment of epilepsy. Although the exact mechanisms of DBS in the amelioration of seizure activity are unknown, they are suspected to include depolarization blockade, synaptic inhibition, synaptic depression (neurotransmitter depletion with successive stimulation), and disruption of pathologic neuronal networks. This technology may hold some promise in the future for dogs with refractory epilepsy. At the present time, however, equipment costs alone exceed $10,000 per patient. We are currently investigating the possibility of a canine-specific DBS unit for use in refractory epileptic patients.

Chiari-Like Malformation in Dogs

Chiari-like malformation (CM), is the canine analog of Chiari type I malformation of people. It is typically associated with the development of fluid cavitations within the spinal cord-syringomyelia (SM)-so the combined condition is often abbreviated as CM/SM. Although only recently described in dogs, this is a very common neurologic disorder in this species. This disease is almost exclusive to small breed dogs, with the Cavalier King Charles spaniel (CKCS) being the most over-represented. The problem in the CKCS breed can be aptly described as a genetic crisis, with an estimate of up to 95% of the CKCS population having some form of the disorder. There is convincing evidence in the CKCS breed that CM/SM is a heritable disease, most likely autosomal recessive with incomplete penetrance. The disorder is a congenital malformation of the caudal occipital region of the skull, leading to overcrowding of the caudal fossa and compression of the cervicomedullary junction at the level of the foramen magnum. There is recent evidence that CM involves a malformation of the entire skull, with the intracranial volume being too small to accommodate the intracranial contents. The vast majority of dogs with CM have syringomyelia (usually in the cervical spinal cord), an accumulation of fluid within the spinal cord, as a consequence of the malformation. In patients with CM/SM, there tends to be some level of cerebellar compression as well as constriction of the cervicomedullary junction in the vicinity of the foramen magnum. With chronic bony compression at the cervicomedullary junction and probable turbulent CSF flow and pressure changes in this region, it is thought that the underlying meninges become hypertrophied with time. In CM/SM, as in Chiari type I of people, the caudal aspect of the cerebellum is often projecting into or through (herniation) the foramen magnum, contributing to obstruction of CSF flow between intracranial and spinal compartments. Progressive alterations in pressure

dynamics between the intracranial and spinal compartments are believed to be responsible for the development of clinical signs of CM/SM.

The "intramedullary pulse pressure" theory is currently the most accepted explanation for the formation of syringomyelia cavities in CM/SM. This theory proposes that the spinal cord parenchyma distal to the foramen magnum compression is subjected to distending forces that tend to pull the tissue in an outward or centrifugal direction. The combination of transmittal of the systolic pulse pressure wave to the spinal cord parenchyma (due to obstruction of the subarachnoid space) and decreased subarachnoid space pressure in the spinal cord region (due to obstruction of the subarachnoid space rostral to the foramen magnum) lead to this mechanical distension. Over time, the distension leads to a cavity formation (syrinx), which is filled with extracellular fluid. The "Venturi effect" describes a similar mechanical spinal cord distension caused by increased CSF velocity distal to an obstruction. The obstruction (i.e., foramen magnum occlusion in CM) causes a narrowing of the subarachnoid space and a resultant increased fluid velocity distal to the obstruction. This increased velocity lowers the hydrostatic pressure, producing a centrifugally directed suction effect, leading to spinal cord distension. This theory also assumes that the accumulated fluid in the syrinx is extracellular fluid and at a higher pressure than the subarachnoid space, two observations that other theories have failed to explain.

The typical age range at presentation appears to have changed over time, with many dogs developing clinical signs within the first year of life. In general, though the age range at clinical presentation is broad, most dogs present by the time they are 4 years old. Dogs that are presented at less than 2 years of age often have more severe clinical signs than older dogs. In recent years, we have seen an increasing number of younger patients (< 1 year of age); whether this trend reflects an increasing severity of the disorder with subsequent generations, increased awareness of the veterinary community and hence earlier diagnosis, or a combination of these two factors is unknown. Similar to Chiari type I of humans, there is a wide spectrum of possible neurologic presentations for dogs with CM/SM, including cervical myelopathy, cerebellovestibular dysfunction, and forebrain dysfunction (e.g., seizure activity). By far, evidence of cervical dysfunction and cerebellovestibular dysfunction are the most common and are often both present (e.g., multifocal CNS disease). Most of the CM/SM cases that the author encounters are presented for signs referable to the cervical region (e.g., neck pain, scratching activity) and subtle signs of central vestibular dysfunction are apparent on neurologic examination. Occasionally, dogs with CM and cervical syringomyelia present with a specific variant of cervical myelopathy called *central cord syndrome*. In this syndrome, the outwardly expanding syrinx causes more LMN damage to the thoracic limb musculature than white matter damage (to pelvic limbs); the result is thoracic limb paresis (often LMN in nature) that is notably worse than pelvic limb paresis. In some cases, the pelvic limbs may appear normal. Some specific clinical findings in dogs with CM/SM include cervical and cranial hyperesthesia, decreased menace responses with normal vision, positional ventrolateral strabismus, thoracic limb weakness, pelvic limb ataxia, persistent scratching (at the head, neck, and shoulder region-often without making skin contact), scoliosis, facial nerve paresis/paralysis (unilateral or bilateral), and hearing abnormalities. The persistent scratching activity and scoliosis are fairly unique clinical signs associated with syringomyelia. In the author's experience, these are more commonly encountered in the CKCS breed than in other

breeds with CM/SM. The scratching activity is believed to be due to the syrinx interfering with spinothalamic tracts and/or dorsal horn neurons, resulting in abnormal sensations (dysesthesia/paresthesia). Scoliosis (torticollis) is most likely due to asymmetric syrinx damage to sensory proprioceptive neurons innervating cervical musculature; an alternative, less likely hypothesis is syrinx damage to LMNs innervating cervical musculature. Scratching activity and neck discomfort often are exacerbated by abrupt weather changes, stress or excitement, and physical contact with the neck/shoulder region (e.g., collar). It is important to realize that, especially in the CKCS breed, other conditions may account for some of the clinical signs. An enigmatic ear problem of the CKCS breed, called primary secretory otitis media (PSOM) has been described. Clinical signs of PSOM include apparent pain around the head and neck area, scratching of the head and neck, facial paralysis, and head tilt. Idiopathic epilepsy is also a prevalent disorder in the CKCS breed. Seizures have been reported to occur in 10% to 12% of humans with Chiari type I malformation; in the author's experience, seizure activity is an infrequent concurrent occurrence in CM/SM cases, and it is usually not possible to distinguish whether this is due to CM/SM or concurrent idiopathic epilepsy. Congenital deafness is also well-described in the CKCS breed. The severity and rate of progression of CM/SM in dogs is variable, ranging from asymptomatic (i.e., finding evidence of CM/SM while imaging for some other reason) to extreme pain and debilitation with rapid worsening. In addition, some dogs with CM/SM have other concurrent disorders (e.g.,disk extrusion, inflammatory brain disease) that could explain observed clinical signs. In such situations, it may be difficult to discern if the CM/SM is the main problem, contributory, or an incidental finding.

Diagnosis of CM is made by MR imaging. Magnetic resonance imaging is also the preferred imaging modality for diagnosing syringomyelia. The malformation is best visualized on a midsagittal view (preferably T2-weighted), which includes the caudal fossa and cranial cervical cord. Consistent findings on MR imaging indicative of CM are attenuation/obliteration of the dorsal subarachnoid space at the cervicomedullary junction and rostral displacement of the caudal cerebellum by the occipital bone. Other common MRI findings in CM include syringomyelia (usually C2 level caudally), herniation of the caudal cerebellum through the foramen magnum, and a "kinked" appearance of the caudal medulla. Recently, the width of cervical syrinxes as measured on axial MR images was positively correlated with presence of pain in CKCS dogs with CM/SM. Occasionally, dogs with MRI findings consistent with CM/SM will have evidence of other congenital disorders such as intracranial arachnoid (quadrigeminal) cyst, malformation of the C1 and or C2 vertebrae, and hydrocephalus. In the author's opinion, most small breed dogs normally have large lateral ventricles as a breed characteristic (ventriculomegaly) and are not hydrocephalic. In the absence of concurrent disease processes, CSF analysis is usually normal; occasionally, however, a mild mononuclear pleocytosis will be apparent.

Treatment of CM/SM can be divided into medical and surgical therapy. In people with symptomatic Chiari type I malformation, surgical therapy is considered the treatment of choice, with foramen magnum decompression (FMD) being the preferred surgical procedure. Although there is a high degree of success in surgical management of Chiari type I malformation in people, there is a re-operative rate varying from 8%-30% for FMD; the most common problem necessitating re-operation is excessive scar tissue formation at the FMD site causing compression at the cervicomedullary junction, effectively recreating the original

disease state. Medical therapy for dogs with CM/SM generally falls into three categories: analgesic drugs (implies relief of dysesthesia/paresthesia also), drugs that decrease CSF production, and corticosteroid therapy. By far the most useful drug available for relief of scratching activity associated with syringomyelia has been gabapentin (10 mg/kg body weight PO, q 8 hrs). It has been shown that neuropathic pain is accentuated over time due to up-regulation of the α2δ-1 subunit of voltage-gated calcium channels in dorsal root ganglion neurons and dorsal horn nociceptive neurons of the spinal cord. Gabapentin, and the newer gabapentin analog, pregabalin, are believed to exert their antinociceptive effects by selectively binding to the α2δ-1 subunit and inhibiting calcium influx in these neurons. Side effects of gabapentin are minimal, usually restricted to mild sedation, pelvic limb ataxia, and weight gain. At Cornell, we have been using pregabalin more frequently to treat the pain and scratching activity associated with CM/SM. The drug has a much longer half-life of elimination than gabapentin (7 hrs vs 3-4 hrs) and appears to be more potent than gabapentin. We dose this drug initially at 2 mg/kg q 12 hrs. Orally administered opiate drugs are sometimes helpful in alleviating neck and head pain in CM/SM dogs. I have also had success using oral tramadol (2-4 mg/kg, q 8-12 hrs). A number of drugs aimed at decreasing CSF production have been used in CM/SM patients, in an effort to diminish the CSF pulse pressure. All information regarding efficacy of these drugs is anecdotal. They include omeprazole (a proton pump inhibitor), acetazolamide (a carbonic anhydrase inhibitor), and furosemide (a loop diuretic). More specific information regarding these drugs is covered in the congenital hydrocephalus discussion. Corticosteroids are often used in medical management of CM/SM. Potential benefits include anti-inflammatory effects, decreased CSF production, and decreased substance P (a nociceptive neurotransmitter) expression in spinal cord dorsal horn neurons. An initial antiinflammatory dose of 0.5 mg/kg PO, q 12 hrs is often effective in controlling clinical signs. This dose should be tapered, if at all possible, to an every other day schedule within the first month of therapy.

The preferred surgical procedure for treatment of CM/SM in dogs is FMD. However, surgical success in dogs appears to be less predictable than that reported for people. In one report, the success rate (resolved or improved) was 81.25%. Unfortunately, there was a 25% re-operative rate due to scar tissue formation in this study. This report also found an inverse relationship between the length of time clinical signs were present prior to surgical intervention and the extent of post-operative improvement. In another report, the ultimate surgical failure for FMD in CKCS dogs was near 50% with long-term (>1 year) follow-up. In most cases, clinical signs of pain are routinely relieved with surgery, but scratching activity tends to persist. Recently, Dr. Dominic Marino (surgeon) and I adapted a cranioplasty procedure used in human FMD surgery to prohibit excessive post-operative scar tissue formation. This procedure entails affixing a plate formed from titanium mesh and polymethylmethacrylate to the caudal occiput with titanium screws. So far, we (Cornell and Long Island Veterinary Specialists) have operated over 100 dogs with this procedure. The recurrence rate using the titanium plate procedure, based on this large group of dogs, is approximately 7%. There is recent evidence that the malformation in CKCS dogs is not restricted to the caudal fossa, and that the disease may represent a relative volume deficiency of the entire intracranial compartment. If this is correct, part of the reason for surgical failure in these dogs may be due to inadequate decompression with a suboccipital approach. There is also growing evidence that "other" malformations of the craniocervical junction may be present that are being mistakenly

labeled CLM and treated as such, or occur in conjunction with CLM but are not being specifically addressed surgically in many cases.

There is little information regarding the prognosis for CM/SM in dogs. Most dogs with CM/SM will respond favorably to medical therapy, although in many cases this response is temporary. In one group of 10 CM/SM dogs treated medically, 5 dogs (50%) were euthanized within 2-3 years due to disease progression and diminished responsiveness to therapy. In another report, 5 of 14 dogs (36%) with the disorder treated medically were eventually euthanized due to disease progression. Although the surgical success rate is generally favorable for CM/SM in dogs in the short-term, the recurrence rate due to excessive post-operative scar tissue formation is unacceptably high. Hopefully, refinements in surgical technique, such as cranioplasty, will ameliorate this problem. In general, the overall prognosis for CM/SM in dogs is guarded to good for sustained improvement in clinical signs.