Isabella's Cranium Conundrum

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Introduction:

Chiari-like malformation (CLM), also known as caudal occipital malformation syndrome (COMS), is a common abnormality of the caudal skull and brain parenchyma seen in Cavalier King Charles Spaniels (CKCS) and other small breed dogs. It is characterized by cerebellar overcrowding resulting in cerebellar herniation which can lead to secondary syringomyelia (SM). In SM, fluid-filled cavities, also known as syrinxes, form within the spinal cord, but the complete pathophysiology is unknown and multiple theories of its etiology have been proposed. It is thought that there is a strong heritable component to this abnormality in CKCS[12]. Common clinical signs include hyperesthesia of the head and neck, ataxia, and "phantom scratching." Although medical management can be used to control clinical signs of CLM, surgical intervention by way of foramen magnum decompression with cranioplasty is the current treatment of choice[7,11]. The pathophysiology of CLM with SM is not fully understood, but many theories have been presented and require further investigation as potential causes.

History and Presentation:

Isabella is a 2-year-old female spayed Cavalier King Charles Spaniel. At approximately one year of age, Isabella began to display clinical signs such as rubbing her face on the ground, head and neck pain, and phantom scratching. Her owners also noticed that Isabella was not as playful or energetic when taken to the dog park. Isabella was presented to her family veterinarian on September 10, 2019, due to her unusual pain and neurological symptoms. CLM was suspected by the veterinarian due to Isabella's clinical picture and on February 3, 2020, Isabella's family veterinarian referred her to Nashville Veterinary Specialists for a further work up of her suspect CLM. Isabella was seen by Nashville Veterinary Specialists on February 13, 2020, for her CLM work up, and an MRI was performed on February 24, 2020. Isabella was diagnosed with CLM along with severe SM. In order to help control her clinical signs, Isabella was medically managed with omeprazole and gabapentin prior to her surgery consultation with Mississippi State University's College of Veterinary Medicine. Isabella was presented

to Mississippi State University College of Veterinary Medicine's Neurology Service on June 23, 2020 for surgical correction of her previously diagnosed Chiari-like malformation.

On presentation, Isabella was bright, alert, and responsive. She weighed 8.5 kilograms with a body condition score of 6 out of 9. She had a heart rate of 132 beats per minute, a panting respiratory rate, and a temperature of 101.1 degrees Fahrenheit. Isabella's mucous membranes were pink and moist with a capillary refill time of less than 2 seconds. Her lymph nodes palpated normally. Upon cardiopulmonary auscultation, Isabella's heart and lungs were normal with no murmurs, arrhythmias, crackles, or wheezes heard. Her eyes were clear with no discharge, and her ears were clean with minimal debris bilaterally. The rest of Isabella's physical exam was within normal limits.

Upon neurologic examination, Isabella was ambulatory with no paresis or ataxia and had a normal, appropriate mentation. All of Isabella's cranial nerves were intact, and she had normal postural reactions in all four limbs. Isabella's history of hyperesthesia of the neck and head was noted. She had a positive jugular occlusion and phantom scratching was present. The rest of her neurologic exam was within normal limits.

On presentation, a complete blood count and serum biochemistry panel were performed in preparation for surgical correction of Isabella's CLM. Both the complete blood count and serum biochemistry revealed no clinically significant findings.

Diagnostic Approach:

Prior to presentation, an MRI was performed on Isabella by Nashville Veterinary Specialists. Sagittal and axial T2-weighted images of Isabella's head and cervical spine confirmed the presence of CLM, and a fairly large syrinx was found within Isabella's spinal cord. MRI is the advanced imaging modality of choice for the definitive diagnosis of CLM.[4,7,13] The goals of the MRI include assessing anatomical changes, attempting to determine the cause of a present SM, and determining the extent of the disease process.[11,13] CLM can be diagnosed by finding one or more of the following abnormalities: caudal

cerebellar herniation, caudal cerebellar compression from occipital dysplasia, atlanto-occipital overlap, and attenuation of CSF.[1,7] The MRI will also reveal if there is SM present causing clinical signs that may be observed in the patient. SM appears as linear areas of hyperintensity on sagittal images of the spinal cord, and syrinx width and dorsal horn involvement can be observed on axial images.[7,11] Syrinx width is the biggest predictor of SM associated pain and dorsal horn involvement may result in neuropathic pain.[3,4,7] The most common locations for SM to occur are between the C1-4 and T-L2 spine.[7] In CKCS with CLM, it is common for the central canal to be dilated up to 4 mm in diameter, whereas central canal dilatation is defined as having a transverse diameter of less than 2 mm.[13]

Another advanced imaging modality, phase-contrast MRI or cine MRI, combines electrocardiogram recording with MRI image acquisition to evaluate fluid dynamics of the CSF in the presence of an obstruction.[7] In CKCS, this technique has shown that CSF flow obstruction at the level of the foramen magnum is associated with the presence and severity of SM.[4,7] The movement of fluid within the syrinx was found to be associated with a progression in neurological clinical signs.[13] In a study utilizing cine MRI to compare CKCS with CLM and CKCS with CLM and SM, researchers found cerebellar pulsation to be greater in the CKCS with CLM and secondary SM.[4] Although cine MRI has been a reliable diagnostic tool in human medicine, its usefulness in veterinary medicine is still undecided.[4,11,13]

CT myelography is not typically recommended when attempting to diagnose a suspected case of CLM and SM. A CT may be indicated in cases where an MRI cannot be performed due to metal implants or in cases where vertebral abnormalities associated with SM are a concern.[13] Although CT cannot be used to definitively diagnose CLM or SM, it may have use as a screening tool for predicting future disease in purebred dogs.[13]

Although used in human medicine, ultrasonography appears to be of limited value in veterinary medicine when diagnosing CLM and SM. Ultrasonography of the atlanto-occipital joint may allow for visualization of cerebellar herniation but has a low sensitivity for its diagnosis.[1,13] SM cannot be

diagnosed by ultrasound as most syrinxes will develop caudal to the window of visualization found when scanning the atlanto-occipital joint.[13] Due to its inability to aid in the diagnosis of CLM and SM in dogs, ultrasonography is not utilized in the work up of suspect CLM and SM cases.

Additional diagnostics to evaluate CSF itself and post-mortem study of CLM and SM pathology can also be of use to diagnose CLM with SM when used in conjunction with MRI. The CSF in dogs with CLM and SM typically has a higher nucleated cell count, increased protein concentrations, neutrophilia, and lymphocytosis[7]. The CSF could also be completely normal. Post-mortem evaluation of dogs with CLM and SM that suffered from neuropathic pain often revealed an asymmetrical syrinx that had altered the dorsal horn along with the presence of glial and fibrous proliferations.[9]

Pathophysiology:

CLM with or without secondary SM is a very common abnormality seen in CKCS and less commonly in other small breed dogs. Although CLM can affect dogs of any age, clinical signs are most commonly seen in younger aged dogs, with an average age range of 2 to 4 years of age at the time of presentation.[9] Clinical sings are usually recognized between 6 months and 3 years of age, but dogs with more severe CLM and SM will often present earlier in life.[12] While CLM can be expected by a certain age, there appears to be no sex predilection currently described for CLM.[9]

On presentation, the most common clinical signs observed are hyperesthesia of the head and neck and “phantom scratching.”[2,12,15] Other clinical signs may include facial rubbing, exercise intolerance, inability to tolerate a neck lead, ataxia, and gait abnormalities.[4,7] “Phantom scratching”, the act of scratching at the neck or shoulder region often without making contact, has been shown to be associated with SM of the cervical region, which damages the fibers of the dorsal horn laminae causing neuropathic pain.[4,6,7,9] Another side effect often seen as a result of damage to the dorsal horn by a syrinx is scoliosis.[7,11,13] Pain associated with CLM is commonly found around the cervical spine but can be

difficult to localize as it is fairly non-specific and can result from other disorders.[11,13] These clinical signs are often intermittent and can fluctuate in severity in relation to stressful or excitable situations.[2,9,10]

CLM is thought to be the result of a combination of heritable bony and neural abnormalities. The selection and breeding of dogs with more desirable brachycephalic facial characteristics have inadvertently led to alterations in bony fusion of the skull, predisposing the offspring to CLM.[6] These inherited bony abnormalities seen in brachycephalic breeds alter CSF flow and drainage, further predisposing them to SM, ventriculomegaly, and increased intracranial pressure.[6] In order to produce offspring with desirable traits, male and female pairings are often selected from a smaller group of individuals who possess those traits. Like many other breeds of dogs, the CKCS breed has little genetic variation.[12] It is estimated that CLM arises in approximately 92% to 100% of the CKCS population.[9,15] CLM in some degree is found so often within the CKCS breed that the abnormality could be considered "normal".[12] In the CKCS breed, selecting for color or lack of another disease process, such as mitral valve disease, has narrowed the gene pool, making CLM more probable.[12] For example, secondary SM has been found in more Blenheim and ruby CKCSs than in other colors, as those are recessive coat colors and require breeding from a smaller gene pool.[12] While breeders are successfully breeding away from some undesirable diseases, these practices are making other diseases processes more prominent.[12]

Another consideration of CLM is the embryologic factors involved in the development of this disease. Paraxial mesoderm insufficiency during embryogenesis is believed to be a contributor to skull inadequacy and overcrowding of the cranial caudal fossa.[3,13] Two problems are thought to occur during embryogenesis that predispose to CLM: first, craniosynostosis, and second, a lack of communication between occipital bone precursors and the closing neural tube.[4] In a recent MRI study, it was discovered that the growth plates of CKCSs closed earlier when compared those of other brachycephalic and mesocephalic dogs.[4] On average, 80% of CKCS experience closure of the spheno-occipital synchondrosis by 8 months of age, while other brachycephalic breeds closed at 12 months of age and mesocephalics at 16 months of age.[7]

The premature suture closures that occur during embryogenesis manifest as a variety of skull abnormalities. The features associated with CLM include suboccipital and occipital hypoplasia, reduced cranial caudal fossa (CCF) volume and rostroentorial, caudotentorial, and craniospinal overcrowding.[4,6,7,13] In addition, the cerebellum itself of CKCSs appears to be larger relative to the volume of the entire brain.[6] It has been hypothesized that a volume mismatch exists between the CCF and hindbrain parenchyma of CKCSs, as they possess the CCF volume of other small breed dogs but also have a parenchyma volume proportionally similar to that of mesocephalic breeds .[3,4,7,15] The amount of overcrowding present determines the degree of obstruction at the level of the foramen magnum as well as the chances of syrinx formation.[15] A correlation has been found between the degree of brain and skull mismatch with development or presence of syrinxes. However, reduced CCF volume on its own does not predispose one to SM.[3]

SM is a condition that can be described as fluid-filled cavitations found within the spinal cord.[7,11] On average, 50% of CKCS over 4 years of age have developed some degree of SM.[15] In a normal central nervous system, CSF flows from the ventricles to the subarachnoid space. From there, CSF relies on cardiac systole and the associated intracranial arterial pulsations to move from the subarachnoid space within the skull to the spinal cord.[7] SM occurs when the normal flow of CSF is obstructed, causing a build-up of fluid within the spinal cord. However, the full pathophysiology of SM is not fully understood, and many theories have been proposed as to why it occurs.[7] One of the more widely discussed theories centers around osseous abnormalities of the skull, such as hypoplastic supraoccipital bones, decreased CCF volume, and narrowed jugular foramina, which all contribute to overcrowding of the CCF and reduction of CSF within the subarachnoid space.[4] The other major theory revolves around soft-tissue abnormalities within the skull, such as proportionally larger cerebellums, ventriculomegaly, and decreased venous sinuses, which lead to altered CSF dynamics between the cranial and spinal compartments.[4] CLM is thought to be the most common contributor to the development of SM in dogs, but not all dogs who have CLM develop secondary SM, suggesting that its pathogenesis is

multifactorial.[10,13] Other factors that may contribute to SM development include poor venous drainage, intracranial hypertension, alterations in CNS compliance, and conformational changes of the spinal cord.[13] The most common clinical sign seen associated with SM is chronic pain, which is caused by a combination of CSF obstruction and spinal cord damage, specifically to the dorsal horn laminae.[11] Damage to the dorsal horn of the spinal cord causes pain because it is a relay center for the transmission of sensory information to the brain.[11]

CKCSs with SM secondary to CLM are thought to have narrower jugular foramina and larger cerebellar parenchyma, both which contribute to the development of SM.[4,15] The resulting compression that occurs at the level of the foramen magnum causes turbulent CSF flow, leading to SM and ventricular dilatation.[3,4] An association has been found between the dimensions of ventricles and syrinxes, supporting the hypothesis that SM may result from altered fluid dynamics.[3,6] One study found that in dogs with SM, 94.4% of cases had a form of moderate to severe ventriculomegaly.[3] Another proposed theory for the pathogenesis of SM formation is the intramedullary pulse pressure theory. Obstruction of normal CSF flow can potentially cause a mismatch between the timing of arterial and CSF pulse waves.[1,6] When the cerebellum falls in systole, a high-pressure pulse wave is created.[6] A pressure difference is created between the subarachnoid space and the spinal cord leading to centrifugal forces that are applied distal to a blockage, forming a syrinx.[3,4,15] Repeated distention of the spinal cord over time dilates the central canal, extracellular fluid accumulates, and eventually causes coalescing cavities.[11] Although plausible, a cause and effect relationship between cerebellar pulsation and SM development has yet to be proven.[4]

Reduced CCF volume and other abnormalities of the skull and spine are the most widely discussed causes of SM. More severe occipital hypoplasia and overcrowding compresses the subarachnoid space, resulting in syrinx dilatation.[3,6] It has also been found that CKCSs with SM have reduced venous sinus volume, indicating that reduced venous drainage may also be a contributor to SM.[6] All of these factors reduce craniospinal compliance, or the ability of the CNS to accommodate for changes in the brain parenchyma, blood, or CSF volumes. Reduced craniospinal compliance in CLM

cases can manifest as ventriculomegaly, as a result of retained CSF within the skull, or as a pressure shift between blood and CSF, which can lead to turbulent CSF flow at the foramen magnum.[7] Additional craniocervial junction abnormalities commonly seen in toy breeds can further predispose dogs to SM. These CLM associated abnormalities include atlantoaxial subluxation, dorsal angulation of the dens, and potentially occipital dysplasia.[6] Along with osseous variations, soft tissue abnormalities and alternations in fluid dynamics could also contribute to the development of SM, making its pathophysiology multifactorial. Further research is required in order to help pinpoint all of the contributing factors to the pathophysiology of SM.

Treatment and Management Options:

CLM can be controlled by two methods: medical management and surgical intervention. Medical management is used to control clinical signs but will not prevent progression of the disease.[7] Multimodal medical therapy is recommended over single drug therapy in order to provide pain relief and reduction in CSF production.[7] A combination of NSAIDs, drugs that reduce CSF production, corticosteroids, and antiepileptics are used to help manage the clinical signs of CLM.[9,11] The cyclo-oxygenase inhibition activity of NSAIDs may be helpful in alleviating neuropathic pain in mild cases.[7] Corticosteroids are thought to have an effect on sympathetic pain by reducing the expression of substance P in addition to anti-inflammatory effects, however, the complete mechanism is not fully understood.[7,11] Proton pump inhibitors, such as omeprazole, and carbonic anhydrase inhibitors are thought to be useful in reducing CSF production and, as a result, decrease CSF pulse pressure.[7,11] However, long-term use of proton-pump and carbonic anhydrase inhibitors is not recommended[11]. The prolonged use of proton pump inhibitors causes chronic gastric acid suppression increasing the risk of developing gastric cancers, while continued use of carbonic anhydrase inhibitors has been associated with abdominal pain, lethargy, and generalized weakness.[11] Through interaction with voltage-gated calcium channels at the dorsal horn, gabapentin is thought to reduce neuropathic pain by decreasing the release of glutamate and substance P.[7] Alternative therapies, such as acupuncture and low-level laser therapy, have also been used to help control the pain

associated with CLM.[7] In a study tracking CKCSs that were medically managed for their CLM and SM for 39 months, researchers found that 75% of dogs had a progression in clinical signs.[7] As a result of these findings, the statement can be made that although not all cases of CLM will require surgical intervention initially, those who do not undergo surgical intervention are more likely to experience a progression in clinical signs.[7] For this reason, medical management of CLM should be reserved for cases of mild pain, cases where surgical intervention is not financially feasible, and cases in which surgical intervention has failed.[11]

Surgical correction is the treatment of choice for CLM. When medical management can no longer provide proper pain control or when neurological signs worsen, surgical intervention is warranted.[11] Foramen magnum decompression (FMD) is a relatively safe procedure that has been shown to increase the patient's quality of life while slowing the progression of clinical signs.[10] FMD is the most commonly used technique for correction of caudal fossa overcrowding and combines a suboccipital craniotomy with a dorsal laminectomy of the first cervical vertebra.[7,11] Surgical intervention is indicated in cases where a patient's syrinx measures > 3mm in diameter on axial T2-weigted images or when clinical signs progress to a point where the patient's quality of life is deteriorating.[8]

In past studies evaluating dogs that had undergone FMD alone, it was found that 80% of dogs experienced initial improvement or resolution of clinical signs, but the presence and size of the cervical syringes did not change.[2,7,9,11] Despite the initial success of the FMD procedure, 25-47% of these dogs experienced recurrence of clinical signs within a mean time of 1.3 years post-surgery and required a second operation.[2,7,9,11] These patients exhibited behaviors suggestive of neuropathic pain.[9] The recurrence of clinical signs post-surgery was thought to be linked to compressive scar tissue formation.[7] FMD with cranioplasty is a surgical method first used to treat CLM in humans but is now suggested as a technique to use in veterinary medicine in an attempt to lessen the incidence of this post-operative complication. Cranioplasty has been shown to help reduce surgical failure due to compressive scar tissue formation in short-term following FMD procedures.[2] The clinical signs associated with this surgical

complication are typically seen within 3 months of the initial surgery.[2] The scar tissue that forms following FMD compresses the spinal cord at the level of the foramen magnum, mimicking the initial abnormality. In a 2007 post-surgery study following dogs that underwent FMD with a cranioplasty, researchers found the initial post-surgical success rate to be 81% and none of the participants required a second surgery.[2] Another study conducted between 2007-2010 evaluated post-surgical success of CLM patients with secondary SM that underwent a FMD, durotomy, duraplasty, and autogenous fat graft placement, an alternative method to avoiding scar tissue formation.[8] Based on owner surveys, 94% of participants were found to have improvement in quality of life after surgery, and none of the patients' clinical states had deteriorated to a level below that noted prior to surgery.[8] At the 1-year follow up, researchers found that none of the study participants required a revision procedure.[8] Future research is required to determine the long-term efficacy of these procedures and to decide if further surgical modifications need to be made.[2,8] Although the majority of dogs that undergo a FMD show clinical improvement, most patients still require some level of medical management following surgery.[2]

Despite the clinical success of most FMDs, there is little to no resolution of syrinxes. There are many theories as to why the syrinxes remain. One theory is that large syrinxes persist because normal CSF flow can no longer occur through the narrowed subarachnoid space or that in CKCSs with chronic SM the spinal cord will not allow for syrinx drainage and resolution.[10] Another theory states that since the complete pathogenesis of SM is not understood, factors other than overcrowding abnormalities may be contributing to syrinx formation.[10] In comparison, over 90% of humans that undergo decompression to correct their CLM experience syrinx resolution.[10] This resolution is thought to occur because of anatomic differences that exist between dogs and humans. In human medicine, surgeons are able to remove more bone from the occipital bone and atlas and have the option to resect the cerebellar tonsils, which herniate through the foramen magnum in human CLM, creating more space.[10] It has been shown that surgical intervention performed early in the course of disease correlates with a more successful surgical

outcome.[7,11] It is also recommended that patients follow up with a post-operative MRI to properly assess surgical success, as clinical improvement does not indicate radiographic improvement.[10]

Case Outcome:

A foramen magnum decompression (FMD) surgery with fat graft was performed on Isabella on June 24, 2020. Surgery went well with no major complications encountered during surgery or recovering from anesthesia. Isabella was discharged from MSU CVM on June 28, 2020, with instructions to restrict her activity, to monitor her incision site, and to monitor Isabella for pain, lethargy or worsening of her current clinical signs. She was sent home on a short course of Tylenol 4, and her owners were instructed to continue her Gabapentin and Omeprazole administration. A recheck appointment was to be scheduled with Nashville Veterinary Specialists 14 days following discharge from MSU CVM for neurological reevaluation and suture removal.

Conclusion:

Chiari-like malformation with secondary syringomyelia is a debilitating and painful disease process seen in nearly all Cavalier King Charles Spaniels. Although the complete pathophysiology of syringomyelia is still unknown, it is thought to be a result of caudal fossa abnormalities.[11] MRI is the diagnostic tool of choice to fully evaluate the craniocervical junction and potential syrinx width.[7,13] While medical management can be useful in alleviating pain in some cases, surgical intervention is the treatment of choice and has been shown to improve clinical signs and help slow the progression of disease in the majority of dogs.[7] Since there is a heritable component to CLM, phenotyping will be essential for future genetic investigation, selective breeding, and development of prophylactic therapies in an effort to eliminate this abnormality from the CKCS breed.[6]

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