A Falling Star

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Introduction

Caudal Occipital Malformation Syndrome (COMS), or Chiari-like malformation (CM), is a complex malformation resulting in caudal fossa overcrowding and displacement of the cerebellum into the foramen magnum. This condition typically results in craniocervical junction overcrowding, disturbing normal cerebrospinal fluid (CSF) dynamics. This alteration in normal CSF dynamics leads to formation of syringomyelia (SM), which is defined as fluid-filled cavities within the spinal cord. CM with secondary SM, is a painful, inherited disorder prevalent among brachycephalic toy breed dogs and considered ubiquitous among Cavalier King Charles Spaniels (CKCS), with CM and CM/SM having a prevalence of 95% and 46%, respectively. As a result of CM and SM being recognized as a substantial welfare concern by the Companion Animal Welfare Council and becoming more frequently diagnosed in predisposed brachycephalic toy breeds through the increased availability of MRI, this disease is of growing concern in veterinary medicine.

History and Presentation

Twinkle Star is a 10-year old, female spayed, Toy Poodle who presented to the Veterinary Specialty Center on July 8, 2019 for an approximately one-year history of stumbling in her forelimbs. Twinkle Star's owner first noticed her holding her forelimbs closer together when she walked approximately a year prior to presentation. Over time, her gait progressively worsened to the point where she would get one forelimb stuck behind the other, causing her to stumble and occasionally fall over. Twinkle Star was initially evaluated by an orthopedic surgeon who diagnosed her with bilateral patellar luxation and neurological deficits before referring her to the Veterinary Specialty Center for further neurological consultation.

Upon presentation to the Veterinary Specialty Center, Twinkle Star was bright, alert, and responsive. She weighed 3.9 kg with a body condition score of 8/9 (5/9 being ideal). On physical examination, her mucous membranes were pink and moist with a capillary refill time of less than 2 seconds. She appeared to be adequately hydrated. She had a normal temperature of 102.5 F, heart rate of 114 beats per minute, and respiratory rate of 48 breaths per minute. No murmurs or arrhythmias were appreciated upon cardiac auscultation. Normal bronchovesicular sounds were appreciated in all lung fields with no crackles or wheezes heard. Her abdomen palpated soft and non-painful. All peripheral lymph nodes palpated were small, soft, and symmetrical. Minor abrasions were observed on the dorsal aspect of her right thoracic paw believed to be a result of scuffing. An approximately 2 cm, raised, freely moveable mass was observed on the right dorsum just caudal to her right scapula. Bilateral patellar luxation was appreciated in both pelvic limbs with crepitus being appreciated in both shoulders. The remainder of the physical examination was unremarkable.

On neurological examination, Twinkle Star was ambulatory tetraparetic with proprioceptive deficits noted in all four limbs, appearing to be more severe on the right side. An intermittent menace response of the right eye was observed. The remainder of her cranial nerves appeared to be intact and within normal limits. A normal withdrawal reflex was elicited in all four limbs. Mild cervical discomfort was noted upon palpation. The remainder of the neurological examination was unremarkable.

Diagnostic Approach/Considerations

Due to Twinkle Star's year-long history of progressively worsening clinical signs and neurological localization to the brain and cervical spine, magnetic resonance imaging (MRI) was warranted. Since sedation and general anesthesia is required to obtain appropriate imaging, a

complete blood count (CBC) and biochemistry panel to assess blood cells and organ function was performed prior to the MRI. The CBC revealed no significant findings with all components being within reference range. The biochemistry revealed a mild hypernatremia, hyperchloremia, hyperglycemia, hypophosphatemia, hypercalcemia, hypercholesterolemia, and a mildly elevated creatinine kinase. These abnormalities were believed to have no significant contribution to Twinkle Star's condition, and she was deemed healthy enough to undergo sedation and general anesthesia.

On July 8, 2019, a computed tomography (CT) metal scan was performed to ensure that she did not have any metal in her body prior to undergoing the MRI. An MRI of the brain and cervical spine was performed. The MRI revealed a number of abnormalities. She had mild generalized ventriculomegaly. The caudal aspect of the cerebellum appeared flattened as a result of occipital bone malformation. The caudoventral aspect of the cerebellum extended into the foramen magnum, consistent with cerebellar herniation. Dilatation of the central canal of the spinal cord was also appreciated. After careful evaluation by the MSU-CVM Radiology Department, the official report from Twinkle Star's MRI findings were consistent with a diagnosis of Caudal Occipital Malformation Syndrome (COMS) with a Chiari-like malformation and secondary syringomyelia.

Pathophysiology

In order to understand the pathophysiology behind COMS, one must first define and understand these terms. CM is defined as a decrease in volume of the caudal fossa causing compression of the cerebellum, resulting in cerebellar herniation into or through the foramen magnum. This malformation typically results in overcrowding at the region of the craniocervical junction, disturbing normal cerebrospinal fluid (CSF) dynamics, ultimately resulting in the

formation of fluid-filled cavities within the spinal cord known as syringomyelia (SM).[1,2] This phenomenon is considered ubiquitous in Cavalier King Charles Spaniels (CKCS), with CM and CM/SM having a documented prevalence of 95% and 46%, respectively.[4] Other sources suggest these numbers are even higher with claims of CM being a breed-specific characteristic with an incidence of 100% in CKCS and 50-70% of these developing SM.[2] Though CKCS are the posterchildren for CM and SM, many other brachycephalic small and toy breeds such as American Brussels Griffons, Yorkshire terriers, Toy poodles, French bulldogs, Chihuahuas, Pugs, and Maltese have been diagnosed with this disease.[1,2,3,4,5]

Due to the high prevalence of CM and SM in brachycephalic breed dogs, particularly CKCS, there is reason to suspect that a strong genetic component is involved. In recent years, the primary focus in understanding the genesis of this complex disorder has centralized around skull morphology, presence of concurrent anomalies, and alterations in CSF flow dynamics. CM in brachycephalic dog breeds has been associated with premature closure of the spheno-occipital synchondrosis (growth plate), which in normal dogs would be responsible for longitudinal growth of the skull. Thus, early spheno-occipital synchondrosis closure is the primary contributing factor for the short, wide, brachycephalic skull conformation. Premature closure of the intersphenoidal synchondrosis in combination with premature closure of spheno-occipital synchondrosis results in overall shortening of the basicranial axis.[1] However, this premature closure of the intersphenoidal and spheno-occipital synchondrosis defines the canine brachycephalic skull, and CM does not affect all brachycephalic dogs. This suggests CM is much more complex and likely involves other premature suture closure, such as the lamboid.[3] One study performed in CKCS neonates found that the lamboid suture closed earlier in CKCS when compared to Beagles. This premature closure of the lamboid suture is a known contributing

factor in the reduction of posterior fossa volume in human Chiari malformation.[1] Additionally, studies have shown that CKCS have a larger cerebellar volume when compared to other small breed dogs, yet no reported differences in the caudal cranial fossa volume. [2,4,5] Overcrowding of the caudal cranial fossa with a greater volume of neuroparenchyma has also shown to be associated with the development of SM.[1,2,3]

Another skull deformity resulting from brachycephalicism, especially among CKCS, is narrowing of the jugular foramen as a result of a shortened skull base. This narrowing of the jugular foramen is believed to be responsible for intracranial hypertension and impairment of CSF absorption. By virtue of jugular foramen narrowing, a reduction in venous sinus volume also occurs. Secondary venous congestion resulting from jugular foramen narrowing and reduction in venous sinus volume, theoretically, influences CSF pulse pressures potentially causing a mismatch in the timing of arterial and CSF pulse waves, predisposing them to formation of SM.[1]

Occipital hypoplasia, the underdevelopment of the occipital bone, has been a key feature in identifying SM secondary to CM. Histological results from CKCS neonates have shown evidence of marked apoptosis of the chondrocytes that would result in decreased growth potential. Histomorphometric analysis of these CKCS neonates have further shown reduced numbers of trabeculae, which is a key factor in the meshwork of the skull. In other words, the quality of the supraoccipital bone in these CKCS neonates was diminished when compared to different breeds of the same age class.[1] However, it is now being suggested that occipital hypoplasia is not congenital but rather acquired over time. Concern is now being given to the idea that caudal fossa overcrowding, which typically causes cerebellar herniation into or through the foramen magnum, is responsible for supraoccipital bone resorption as a result of pressure

necrosis. Indeed, studies have shown a positive correlation between foramen magnum size and cerebellar herniation, suggesting a dynamic loss of the supraoccipital bone and a marker for disease progression. Perhaps a more fitting term would be occipital dysplasia rather than hypoplasia since this is an acquired change secondary to pathology; however, it may also be a combination.[1,2,3]

Medullary elevation, or “kinking”, is considered a major component of CM that occurs in conjunction with this disease. Medullary elevation has a reported prevalence of 40-68% in small/toy breed dogs and of 66-100% in CKCS. It can be visualized via MRI and appears as a ventrally concave and elevated appearance of the caudal medulla at its junction with the cranial cervical spinal cord (cervicomedullary junction). Obstruction of the subarachnoid space is a common finding associated with medullary elevation and has been reported in approximately 70% of cases. Earlier studies suggested a possible association between the presence of medullary elevation and more clinically affected dogs. In more recent years, a medullary kinking index has been described as an objective measure of medullary elevation at the craniocervical junction. A study of 36 CKCS was performed using this medullary kinking index. The medullary kinking index and the medullary elevation angle (angle formed between the ventral and caudal margins of the medulla) were used to quantitate medullary elevation at the cervicomedullary junction. For evaluation of the brainstem’s position in relation to the foramen magnum, an obex measurement (distance between caudal most aspect of 4th ventricle and foramen magnum) was calculated. Results from this study were conclusive of a higher medullary kinking index being associated with neurological signs, yet had no relationship to SM. Instead, lower obex measurement were associated with the presence and severity of SM.

Treatment and Management

CM/SM can be treated medically or surgically. The primary goal of medical management is to alleviate intracranial/intraspinal pressure. Medical management of CM/SM is typically instituted for managing neuropathic pain and decreasing CSF production; however, studies have shown no benefit in preventing disease progression and typically only provides temporary relief from clinical signs. In a study of CKCS medically managed for CM/SM over a 39-month period, 75% of cases had progression of clinical signs. In contrast, 3 studies evaluating surgical treatment of CM/SM with greater than a 1-year follow-up showed clinical improvement in over 80% of patients. Taking into consideration these observations, not all dogs need surgery; however, most will progress clinically without surgical intervention.[2,5,9]

Several drugs have been used in the medical management of CM/SM in dogs. The three big categories of drugs used in the medical management of CM/SM are drugs that decrease CSF production, analgesics, and corticosteroids.[9] Proton pump inhibitors, such as omeprazole, are considered a mainstay of therapy in the medical management of CM/SM. Omeprazole works by decreasing CSF production via reduction in the Na+ K+ ATPase activity in the choroid plexus. By decreasing CSF production, the belief is that this decreases CSF pressure, thus preventing progression of SM. Its rationale is based on an observed 26%-50% decrease in CSF production immediately following IV administration. However, whether or not a similar decrease occurs during long-term PO administration is questionable.[2,5,9] Anti-epileptics such as gabapentin, pregabalin, and topiramate are commonly used for their analgesic properties in the management of neuropathic pain. Gabapentin and pregabalin are believed to exert their effects by preventing the release of glutamate at the dorsal horn of the spinal cord by binding alpha-2-delta subunits of voltage-gated calcium channels and also decreasing the release of substance P. Anecdotal

evidence suggest pregabalin is effective in cases of CM/SM dogs refractory to high doses of gabapentin; however, its cost usually limits its current utility as a first line treatment. Topiramate is another antiepileptic drug used in the management of neuropathic pain.[2,5] Other drugs such as tricyclic antidepressants (TCAs), NMDA receptor antagonists, NSAIDs, and opioids have been considered for their analgesic properties in the management of neuropathic pain; however, evidence of their efficacy in veterinary patients is either currently limited or based on extrapolation from human literature.[2] Corticosteroids, such as prednisone, are believed to have multidimensional benefits in the treatment of CM/SM and work by ultimately preventing the release of a host of proinflammatory mediators as well as decrease the release of substance P. They also have the added benefit of decreasing CSF production, which is one of the primary goals of medical management. Due to corticosteroids unfavorable side-effects in long-term usage, perhaps pulse dosing only during flare-ups of CM/SM-related pain is the best rationale for their usage.[2,5,9]

Surgical intervention should be considered in patients that are refractory to medical management or have continued to worsen clinically despite medical treatment. Surgical decompression of the foramen magnum is considered the treatment of choice and has been shown to improve clinical signs in 80-94% of patients. Surgical intervention does not typically result in the resolution of the existing syrinx. However, the primary goal of surgical decompression is to prevent further progression of syrinx size and to improve quality of life by decreasing both the frequency and intensity of pain-related behaviors. In the long term, patients that have undergone foramen magnum decompression (FMD) alone have experienced a 27-47% relapse rate due to scar tissue formation at the surgical site. However, studies suggest the addition of a cranioplasty to FMD decreases reoperation rates due to scar tissue formation. An

FMD typically consist of a suboccipital craniotomy with a dorsal laminectomy of C1. The FMD is then followed by a durotomy over the atlanto-occipital and atlantoaxial regions for re-establishment of CSF flow through the region.[2,5,9] Variations of the FMD procedure include FMD and durotomy, FMD with titanium-mesh cranioplasty and durotomy, and FMD with a durotomy and duraplasty with lyophilized swine submucosa coupled with a free autogenous adipose tissue graft (FAATG) implanted over the duroplasty. While all of these procedures have been successful in the treatment of CM/SM, long term follow-up evidence remains limited. One study involving 23 dogs (CKCS, Yorkshire terriers, Chihuahuas) that had undergone an FMD, durotomy, duraplasty consisting of swine intestinal submucosa (SIS), and a FAATG demonstrated a 100% rate of clinical improvement observed one month post-operatively, with 94% still showing clinical improvement one year after surgery. These findings suggest this modified surgical technique is clinically most effective in treating CM, while other methods involving titanium-mesh or screws may contribute to tissue trauma and offer no advantage to CM patients.[7]

The congenital and progressive nature of CM was discussed with Twinkle Star's owners, along with medical and surgical treatment options. The owners elected to pursue surgical treatment for correction of Twinkle Star's cerebellar compression. Twinkle Star was discharged for 2 weeks prior to surgery with instructions to walk her with a harness rather than a neck collar to not only support her while walking but also to decrease pressure on her neck. During this time, Twinkle Star was also prescribed prednisolone (5 mg tablets) at 1.0 mg/kg and instructed to give 1 tablet orally every 24 hours for 7 days, followed by 0.5 tablet orally every 24 hours for the next 7 days, and then 0.5 tablet orally every other day for 7 doses. In addition to the prednisolone, Twinkle Star was sent home with omeprazole (5 mg capsules) at 1.0 mg/kg and instructed to

give 1 capsule orally every 24 hours until directed otherwise. Surgery was scheduled on July 24, 2019 for Twinkle Star to undergo a foramen magnum decompression with a free autogenous adipose tissue graft procedure to address her Chiari-like malformation.

Twinkle Star presented to Mississippi State University College of Veterinary Medicine on July 23, 2019 to have bloodwork and her neurological status reassessed the day prior to surgery. A CBC revealed a segmented neutrophil % of 86% (60-77), lymphocyte % of 4% (12-30), and lymphocyte count of 365 /ul (1200-6500). A neurochemistry panel was performed, revealing a CO2 of 19.8 mEq/L (20.0-28.0), ANGAP of 22 mmol/L (10-20), glucose of 135 mg/dl (75-125), and calcium of 11.4 mg/dl (8.8-11.2). Upon neurologic examination, Twinkle Star was still ambulatory tetraparetic but with proprioceptive deficits only being observed in the right thoracic and right pelvic limbs. All cranial nerves appeared to be intact and normal spinal reflexes were observed. She appeared non-painful upon palpation along her cervical spine with no signs of pain being observed throughout the remainder of the neurologic examination. Routine thoracic radiographs were also performed for evaluation of any possible metastasis prior to surgery, which no evidence of nodular pulmonary metastatic neoplasia was reported.

On July 24, 2019, Twinkle Star underwent general anesthesia and placed in sternal recumbency with her head ventroflexed at a 90-degree angle and held in place using 1-inch white tape. The skin on her dorsal neck, caudal skull and right hip were clipped and prepped aseptically. She was then draped in a standard fashion. An approximately 2 cm skin incision was made over the right hip for harvesting adipose tissue for the fat graft. The subcutaneous layer of the incision was closed using a continuous pattern, and a cruciate pattern was used for closing the skin. A skin incision was then made along dorsal midline extending from just cranial to the occipital protuberance to the middle of the C2 spinous process. Dissection was then performed

through the soft tissue, fascia, and muscles down to the level of the occipital bone, C1, and C2 vertebrae. The craniodorsal aspect of C1 was removed, exposing the meninges. The natural defect in the caudal aspect of the occipital bone was deemed adequate for decompression. The dura was then carefully incised, and CSF flow was observed. Fibrous adhesions to the cerebellum were then broken down. A cell graft, consisting of swine intestinal mucosa, was placed over the durotomy site and sutured to the surrounding dura and musculature in a simple interrupted fashion. The previously harvested adipose tissue graft from the right hip was then placed over the top of the cell. The muscle layer was closed using a cruciate pattern with the subcutaneous layer sutured in a buried simple continuous pattern. Finally, the skin layer was closed using an intradermal continuous pattern. A Telfa pad and Suresite bandage were then placed over both incision sites. No complications were associated with anesthesia and Twinkle Star recovered uneventfully.

Following surgery, Twinkle Star recovered in the ICU where she was continued on LRS fluids at 10 ml/hr and a fentanyl CRI at 3 mcg/kg/hr (0.2 ml/hr). She appeared to be nonpainful and recovered well overnight, so her fentanyl CRI was decreased to 2 mcg/kg/hr (0.1 ml/hr) before being discontinued. During this weaning process she was transitioned to oral medications, which consisted of Tylenol 3 (30 mg/ml) oral suspension at 2 mg/kg q8h for pain and gabapentin at 10 mg/kg PO q8h for neuropathic pain. She also continued her tapering dose of prednisolone at 0.5 mg/kg EOD. Twinkle Star appeared to recover well in the ICU and was discharged on July 26, 2019, two days post-operatively. Twinkle Star was discharged with her previously prescribed Tylenol 3, gabapentin and omeprazole. She was scheduled for a 2 week recheck examination at the Veterinary Specialty Center where she would be reassessed for any signs of improvement or worsening and to have the skin sutures removed from the incision site on her right hip. Twinkle

Star's owners were also instructed to keep her in areas with carpet or flooring with good traction to prevent any slipping or falling episodes.

Case Outcome

Since being discharged on July 26, 2019, Twinkle Star has shown mild improvements in her gait when compared to prior to surgery. Though she continues to show signs of mild to moderate proprioceptive deficits in her right thoracic and pelvic limbs, she has experienced fewer episodes of falling over. The owners also state that she has experienced no signs of pain and all pain medication have been discontinued. She is currently now only receiving omeprazole to keep her CSF production under control. The owners are aware that Twinkle Star's neurological status may not improve much more but that the goal of surgery was to hopefully prevent any progression of disease. Overall, the owners are very pleased with Twinkle Star's improvement and happy they pursued surgical treatment.

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