Recurrent Bilateral Forelimb Contracture in an Arabian Filly with Suspect Marfan's Syndrome

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Class of 2019

Clinicopathological Conference

Presented on June 15th, 2018

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Introduction:

A 17-month-old, 313 kg chestnut Egyptian Arabian filly originally presented for an approximate 6-month history of bilateral flexural forelimb deformities despite having a bilateral distal digital check ligament desmotomy performed at 13 months of age. The filly would present again at 23, 24, 28, 30, and 32 months of age for recurrent bilateral forelimb contracture. After each successive hospital visit, she demonstrated resolution of clinical signs, however, it was not sustained. The chronicity of contracture in this filly is likely due to the connective tissue disorder known as Marfan's Syndrome.

History and Presentation:

Upon presentation the filly exhibited a grade V/V lameness in the right forelimb and a grade IV/V lameness in the left forelimb. There was significant contracture observed bilaterally at the level of the distal interphalangeal joint and consequently, a bilateral club foot conformation. The contracture was so severe that the filly was walking on the dorsal hoof capsule of the right forelimb. The filly's physical exam parameters were within normal limits with exception given to her bilateral club foot conformation. Her distal limbs were thoroughly evaluated to rule out abnormalities that may have been contributing to her lameness. No external wounds, palpable joint effusion or swellings were noted on the examination of the distal limbs. The filly was sedated to facilitate radiographs using 10 mg butorphanol (0.05 mg/kg IV) and 10 mg detomidine (0.08 mg/kg IV) administered intravenously. Bilateral radiographs of the scapulohumeral joints and distal interphalangeal joints were performed. Radiographic findings of the right and left scapulohumeral joints were normal with no evidence of osteochondrosis desicans lesions. Radiographic findings of the right and left distal interphalangeal joints revealed pathological flexion of the distal interphalangeal joints consistent with contracture of the deep

digital flexor tendon and the subsequent tension which was being placed on the dorsal joint capsule. Widened vascular channels with undulating margination of the right and left third phalanx were also present. These radiographic changes were likely due to pedal osteitis secondary to severe contracture. The filly was diagnosed with bilateral stage II flexural deformities of the distal interphalangeal joint with the dorsal hoof wall measuring greater than 90 degrees. As a consequence of the filly's severe acquired bilateral flexural limb deformities, a deep digital flexor tenotomy was performed. The filly was anesthetized routinely, and the deep digital flexor tendon was transected at mid metacarpal three in both forelimbs. Prior to recovery both forelimbs were placed in half limb bandage casts to provide additional support to her limbs while the soft tissue structures acclimated to the significant change following each tenotomy. The filly recovered uneventfully in the half-limb casts. Post-operatively, she received flunixin meglumine 1.1 mg/kg orally every 12 hours and ranitidine 7 mg/kg orally every 8 hours for approximately 14 days. The casts were removed after 14 days and replaced with a Robert Jones bandage which provided less rigid support to allow more weight bearing and strengthening of these soft tissue structures. Acrylic toe extensions were applied to both front hooves to offer stability and limit knuckling over at the fetlock. Dietary changes were prescribed as her deformities were likely a result of her rapid growth rate as well as mineral supplementation with copper sulfate to top dress her food. A pelleted diet and increased forage consumption were recommended over grains as the pellets have decreased levels of simple carbohydrates. The filly was discharged with instructions for 30 days of stall rest following surgery with 10 minutes of hand walking daily.

At the 4, 10 and 16-week recheck appointments following her bilateral deep digital flexor tenotomy, the filly displayed remarkable improvement with maintained resolution of the deep

digital contracture. Adequan, a polysulfated glycosaminoglycan therapy, was initiated at her 4-week recheck, with an initial intramuscular injection. It was administered once a day for four days, and then once monthly thereafter. Shorter acrylic toe extensions were placed at each successive visit. At the 16-week recheck, she was discharged with instructions to be turned out in a small pasture or paddock.

At 23 months of age, the filly presented again for bilateral forelimb contracture after she had experienced a growth spurt. This time the contracture was noted at the level of the metacarpophalangeal joint. Oxytetracycline (administered twice at 23 months) was initiated as a tendon laxity therapy. Her forelimbs were placed in stack wraps for additional support and to encourage stretching of the musculotendinous units. Moderate acrylic toe extensions were also applied to both front hooves at this visit as well. She received flunixin meglumine 1.1 mg/kg orally every 12 hours for 7 days to address any pain or discomfort associated with the farriery adjustments. Throughout her two-week stay at the hospital, she improved greatly as her metacarpophalangeal joints were in normal alignment. She displayed normal conformation at discharge and was again prescribed small pasture or paddock turnout with instructions to return for re-evaluation in 30 days.

The filly presented at 24 months of age for her 30-day recheck appointment. The acrylic toe extensions were removed to allow for proper examination of her gait and conformation. Upon evaluation of her forelimb conformation, the filly appeared to have maintained her deep digital flexor tendon release, showing no signs of knuckling at the distal interphalangeal joint. However, mild to moderate buckling was present at the level of the metacarpophalangeal joint, consistent with continued superficial digital flexor tendon contracture, with the left forelimb being more significantly affected than the right forelimb. A bilateral superior check ligament

desmotomy was performed, after which each limb was placed in sleeve casts, inclusive of each hoof, and the filly was maintained on stall rest for approximately six weeks. Post-operatively, she received flunixin meglumine 1.1 mg/kg orally every 12 hours and ranitidine 7 mg/kg orally every 8 hours for approximately 14 days. Oxytetracycline (administered twice at 23 months and again at 24 months) was also administered at this visit. The filly was discharged in her sleeve casts with instructions to maintain strict stall rest with 10 minutes of hand walking three times daily. Her casts were removed two weeks following discharge, and significant improvement was noted as she was no longer bilaterally upright and there was no perceivable lameness.

At 28 months of age the filly presented for worsening of her superficial digital flexor tendon contracture, specifically on her right forelimb. At this visit her right superficial digital flexor tendon was injected with 200 units of botulinum toxin type-A (administered once at 28 months). Following the botulism injections, her left forelimb was placed in a stacked leg wrap and her right forelimb was placed in a splint which was then replaced by a distal limb cast. She was prescribed strict stall rest for two weeks. At her 2-week recheck appointment, the cast was removed and replaced, and she was discharged with instructions to maintain stall rest for another three weeks. At her second cast removal visit, radiographs were obtained to further evaluate her right forelimb. A mild amount of degenerative osteoarthritis was present in the right forelimb distal interphalangeal joint. However, osteoarthritis was expected considering the amount of time the filly was in a cast and would likely resolve once she returned to unassisted weight bearing of her right forelimb.

At 30 months of age, the filly returned for a recheck examination. Ultrasound evaluation revealed a more normal architecture of the superficial digital flexor tendon muscle concurrent with normal conformation. The filly received her second 200 units of botulinum injection into

her right superficial digital flexor tendon at this visit (administered once previously at 28 months, and once at 30 months of age). At this point in time, the suspicion of a more complicated diagnosis was confirmed after pursuing additional diagnostics. Radiography of her right forelimb was performed to evaluate the length of her radius. The growth plate was noted to be almost completely closed (90%) and her radius was approximately 14 inches in length, quite extensive for her breed. An echocardiogram also was performed to evaluate her heart function. This exam revealed the presence of mild regurgitation at both the tricuspid and mitral valves, while no arrhythmias were observed, and her heart revealed normal fractional shortening.

At 32 months of age, the filly presented for right forelimb lameness. Upon examination, the right forelimb showed significant contracture despite normal conformation on presentation at 30 months. When her right forelimb bandage was removed, right forelimb varus was observed. She exhibited a grade V/V lameness of the right forelimb at the walk and trot and showed no deviation from midline on carpal or shoulder flexion. A right forelimb abaxial nerve block (50% mepivicaine and 50% bupivacaine) was performed, but there was no improvement in gait. Radiography of the filly's proximal and distal interphalangeal joints revealed normal alignment. The filly was then anesthetized and underwent a right forelimb superficial flexor tenotomy and a deep digital flexor tenotomy. Originally, only a superficial digital flexor tenotomy was planned, but there was minimal release following its transection. Fibrosis of the deep digital flexor tendon to the superficial digital flexor tendon was diagnosed intraoperatively, thus requiring transection of both the deep digital flexor tendon and the superficial digital flexor tendon. The fibrosis of the two tendons was likely due to the prior deep digital flexor tendon tenotomy. Post-operatively, she received flunixin meglumine 1.1 mg/kg orally every 12 hours and ranitidine 7 mg/kg orally

every 8 hours for approximately 14 days. A cast was placed on her right forelimb, and a support bandage was placed on her left forelimb. The casts would remain in place for one month.

Discussion:

Flexural limb deformities are a common condition in the equine patient in which a joint is held in an abnormally flexed or extended position in the sagittal plane[1]. Classification of flexural limb deformities include: congenital flexural limb deformities, those which are present at birth up to one month of age, and acquired flexural limb deformities, those which develop during the growing period. Congenital deformities are likely a result of a multitude of factors, such as genetic predisposition, intrauterine mispositioning, teratogenic agents, neuromuscular disorders, poor dam nutrition, and dam hypothyroidism [2, 3, 4, 14]. Acquired deformities may be the result of trauma or a component of the developmental orthopedic disease (DOD) complex, which includes angular limb deformities, osteochondrosis dissecans, subchondral cystic lesions, physitis, and cervical vertebral misarticulations or malformations[5]. It likely that pain, a sequela to the aforementioned DOD complex conditions or acute trauma, stimulates contraction of the musculotendinous unit through the *flexion withdraw reflex*. In addition to pain, inconsistent bone and tendon/ligament development, which may be a result of rapid growth in individuals with renowned genetic potential or those maintained on a high plane of nutrition, also contributes to acquired flexural limb deformities. With acquired flexural deformities, hyperflexion is seen more often than hyperextension, though severe continuous overload of the forelimbs has the potential to induce hyperextension deformities.

The focus of this discussion is congenital and acquired hyperflexion management. Congenital flexural limb deformities most commonly involve the carpus, metacarpophalangeal,

or metatarsophalangeal joints, while acquired flexural limb deformities most commonly occur in the distal interphalangeal joint of the forelimbs or the metacarpophalangeal joints[14, 15].

It is imperative to treat flexural limb deformities timely and appropriately as complications can progress quickly; however, in congenital cases where the foal can stand without assistance, resolution of clinical signs may occur without treatment[1]. The mainstays of treatment are essentially the same for both congenital and acquired hyperflexion deformities, though there are subtle differences for both classifications and the specific joint involved. Medical management is an appropriate and reliable treatment for all cases, excluding severe cases of flexural limb deformities. Nutrition may aid in the control of the growth rate, though genetic disposition is ultimately the determining factor of growth potential. In weaned animals, the concentrate in the diet should be decreased and balanced with mineral supplements, paying specific attention to the calcium and phosphorus ratio. In nursing animals, dietary changes can be addressed at the level of the mare, or the foal can be weaned early. Controlled exercise, such as hand walking for thirty minutes, three times daily, is also beneficial when medically managing cases of hyperflexion as it lengthens and strengthens the musculotendinous unit. Together, the inciting cause and treatment of flexural limb deformities (both congenital and acquired) can be painful, therefore it is imperative to manage pain where possible. However, this can be a difficult task as non-steroidal anti-inflammatory drugs (NSAIDs) should be used judiciously in the equine patient because of their potentially detrimental side effects[6]. Farriery is also a common treatment option for this condition, though changes must be made gradually, or stimulation of the *flexion withdraw reflex* can occur. In congenital hyperflexion cases, a gradual lowering of the heels is beneficial. Additionally, in congenital and acquired hyperflexion cases, glue on shoes may be warranted; toe extensions will prolong breakover and stretch the flexor tendons and suspensory

ligament. In acquired hyperflexion cases, it is occasionally beneficial to raise the heels to remove tension from the deep digital flexor tendon and load the superficial digital flexor tendon and the suspensory ligament. Furthermore, application of acrylics to reconstruct the toe provides protection to the toe and also decreases the *flexion withdraw reflex.* Acrylics create leverage at the toe and with concurrent exercise, the flexor muscles become more relaxed. Intravenous oxytetracycline administration has become a popular treatment modality for congenital flexural limb deformities, specifically hyperflexion of the metacarpophalangeal joint as it has not been reported to have significant effects on the distal interphalangeal joint[7]. Oxytetracycline induces a decrease in matrix metalloproteinase 1 (MMP-1) mRNA expression which promotes elongation and relaxation of tendons and ligaments when weight bearing[7]. The most common dose used is 2-3 grams administered slowly once daily. Recently, botulinum toxin type-A has been used in both human and experimental animal models to encourage tendon laxity by inhibiting the action of the motor neurons in the muscle belly injected[23]. Splints and casts can be used to stretch the musculotendinous units, though there is risk of bandage and cast sores[8, 9, 10]. The degree of the limb that is incorporated within the cast is dependent upon the severity of the deformity. Lastly, *hopping* has been reported to correct of a flexural limb deformity of the metacarpophalangeal region[8]. This procedure requires two handlers, one to hold the non-affected limb and the other to lead the horse at a walk. The horse is forced to bear all of its weight on the affected limb while it hops. With repetition, stretching of the musculotendinous unit occurs.

Surgical intervention is seldom necessary in congenital flexural limb deformity cases: however with acquired flexural limb deformities, surgical management is necessary when medical treatments have failed and in cases where the patient is severely affected. The surgery performed will depend on the joint affected by the flexural limb deformity. Desmotomy of the

accessory ligament of the deep digital flexor tendon is the treatment of choice for stage I (hoof-ground angle of 90 degrees or less) flexural deformities of the distal interphalangeal joint[8, 13, 15]. Normally, passive elongation of the tendon is limited because the accessory ligament is unyielding. Transecting this ligament increases the functional length of the musculotendinous unit and allows the heel to drop. Flexural deformity of this joint commonly occurs between 1 and 10 months of age in rapidly growing foals. This condition if often bilateral with one side more severely affected than the other[16]. Tenotomy of the deep digital flexor tendon is the treatment of choice for stage II (hoof -ground angle 115 degrees or greater) flexural deformities of the distal interphalangeal joint, though the deformity has been reported to recur within months after surgery[11]. For flexural limb deformities at the level of the metacarpophalangeal joint, the severity of the deformity may also be classified into grades. During forced extension, if the fetlock angle is less than or equal to 180 degrees, desmotomy of the accessory ligament of the deep digital flexor tendon or desmotomy of the accessory check ligament of the superficial digital flexor tendon may be performed[21]. If the angle of the fetlock is greater than 180 degrees, then a desmotomy of the accessory ligament of the deep digital flexor tendon and desmotomy of the accessory check ligament of the superficial digital flexor tendon may be performed. However, a tenotomy of the superficial digital flexor tendon may be performed in severely affected cases[1]. Lastly, with flexural deformities at the level of the carpal joint, palmar carpal joint transection or tenotomy of the ulnaris lateralis and flexor carpi ulnaris tendons can be performed with optimism[12]. This condition is most commonly present at birth but can develop anywhere from 1-4 months of age.

Medical and surgical management have both provided successful case outcomes in congenital and acquired deformity types; however to the author's knowledge, this is the first case

of an acquired flexural limb deformity to which has been unresponsive to both medical and surgical intervention. Patients whose flexural limb deformities fail to correct after both medical and surgical treatments have been pursued require a more in-depth evaluation of lameness. Careful evaluation of the affected limb is imperative, however, an in depth systemic physical evaluation may reveal additional evidence of a more extensive condition. Ehlers-Danlos Syndrome, Osteogenesis Imperfecta[19], Hereditary Equine Regional Dermal Asthenia, Hyperelastosis Cutis, Degenerative Suspensory Ligament Desmitis, and Marfan's Syndrome[18] are connective tissue disorders that have been described in domestic animals. In this filly's case, Marfan's syndrome was diagnosed through a series of phenotypic diagnoses after a more thorough physical exam of the patient's skeletal frame and cardiac function. We observed that the patient was exceptionally tall for her age and was growing taller at each recheck appointment. Eventually, the filly outgrew her dam, sire, and siblings and phenotypically no longer followed her breed predisposition. Though there is no single cause for the development of flexural limb deformities, in this case it is likely they developed due to the rapid increase in the length of the bone compared to the ligaments and tendons.

Marfan's Syndrome (MFS), where diagnosis in humans is obtained from the patients' family history and clinical examination, is an autosomal dominant hereditable connective tissue disorder. A person with Marfan's syndrome is born with this disorder even though they may not be diagnosed until later in life. Not every individual with this syndrome experiences the same degree of clinical characteristics. This syndrome is the result of the mutation of the gene that determines the structure of fibrillin-1 (FBN1), a protein important in the elastin composition within collagen of connective tissue[20]. The Ghent Nosology criteria for diagnosis emphasizes the cardiovascular and ocular manifestations of Marfan's syndrome; with aortic dilation and ectopia

lentis (dislocated lenses) being the cardinal features of diagnosis. In the absence of any family history, the presence of these two features is sufficient for the unequivocal diagnosis of Marfan's syndrome[22]. In the absence of one of these two cardinal features, the presence of an FBN1 mutation is sufficient for diagnosis. Similarly, a systemic score, which combines all major organ systems composed of connective tissue, greater than or equal to 7 is consistent with the diagnosis of Marfan's syndrome[24]. There is no cure for Marfan's syndrome. Instead, affected individuals must frequently be evaluated for skeletal abnormalities of the sternum and spine as abnormalities here could lead to heart and lung dysfunction. Additionally, eye examinations are important in order to detect any changes in vision. Lastly, annual echocardiograms help evaluate the function of the heart and allow monitoring of the size of the aorta. The skeletal abnormalities associated with Marfan's Syndrome differ in each affected individual but may include dolichostenomelia (long limbs), arachnodactyly (long and slender fingers and toes), scoliosis (curvature of the spine), chest wall deformity, tall stature, ligamentous laxity, abnormal joint mobility, and protrusion acetabulae (defect of acetabulum)[17]. A form of Marfan's Syndrome has been recognized in cattle where aortic dilation and aneurysm were described together with ocular abnormalities (microspherophakia, ectopic lenses, and lens opacities) and skeletal involvement (long thin limbs, joint and tendon laxity, and postural kyphosis)[26]. Unfortunately, there is not a *gold standard* method of diagnosis to this day. The nosology-based diagnosis is made in the absence of a reference standard and therefore its accuracy, specificity, and sensitivity cannot be determined. Likewise, analysis of the FBN1 mutation has its limitations as there is no distinct genotype that can be used to follow the disease over time[25, 26].

Conclusion:

The filly represented in this case report demonstrates the classic appearance of acquired bilateral flexural deformities (e.g. contracted tendons), though recurrent and unresponsive to medical and surgical management. Theses flexural deformities illustrate the clinical manifestation of a deeper connective tissue disorder, Marfan's Syndrome. This syndrome is not an uncommon condition in humans and has even been described in the bovine species but has yet to be described in the equine species. Presently, there is no treatment in humans or animals. Disease signs can be quite subtle in some patients, making diagnosis difficult. The filly currently oscillates between episodes of contraction with severe lameness and resolution of clinical signs with no perceivable lameness. We suspect that once her long bone growth is complete she will no longer present for contracture; however, she will likely experience lifelong osteoarthritis of her forelimbs. Similarly, the filly's associated cardiac anomalies will require lifelong monitoring and management.

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