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Clinicopathological and pedigree investigation of a novel spinocerebellar neurological disease in juvenile Quarter Horses in North America

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Abstract

Background: In 2020, a novel neurologic disease was observed in juvenile Quarter Horses (QHs) in North America. It was unknown if this was an aberrant manifestation of another previously described neurological disorder in foals, such as equine neuroaxonal dystrophy/equine degenerative myeloencephalopathy (eNAD/EDM).

Abbreviations: EJSCA, equine juvenile spinocerebellar ataxia; eNAD/EDM, equine neuroaxonal dystrophy/degenerative myeloencephalopathy; GGT, gamma-glutamyl transferase; MRI, magnetic resonance imaging; pNfH, phosphorylated neurofilament heavy; PPM, parts per million; QHs, Quarter Horses; UCSC, University of California Santa Cruz.

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Hypothesis/Objectives: To describe the clinical findings, outcomes, and postmortem changes with Equine Juvenile Spinocerebellar Ataxia (EJSCA), differentiate the disease from other similar neurological disorders, and determine a mode of inheritance.

Animals: Twelve neurologically affected QH foals and the dams.

Methods: Genomic DNA was isolated and pedigrees were manually constructed.

Results: All foals ($n = 12/12$) had a history of acute onset of neurological deficits with no history of trauma. Neurological deficits were characterized by asymmetrical spinal ataxia, with pelvic limbs more severely affected than thoracic limbs. Clinicopathological abnormalities included high serum activity of gamma-glutamyl transferase and hyperglycemia. All foals became recumbent (median, 3 days: [0–18 days]), which necessitated humane euthanasia ($n = 11/12$, 92%; the remaining case was found dead). Histological evaluation at postmortem revealed dilated myelin sheaths and digestion chambers within the spinal cord, most prominently in the dorsal spinocerebellar tracts. Pedigree analysis revealed a likely autosomal recessive mode of inheritance.

Conclusions and Clinical Importance: EJSCA is a uniformly fatal, rapidly progressive, likely autosomal recessive neurological disease of QHs <1 month of age in North America that is etiologically distinct from other clinically similar neurological disorders. Once the causative variant for EJSCA is validated, carriers can be identified through genetic testing to inform breeding decisions.

KEYWORDS
ataxia, inherited, neurodegeneration, spinal cord

1 | INTRODUCTION

In March 2020, a novel neurologic disease was observed in juvenile Quarter Horses (QHs) in North America. Based on the early age of onset of clinical signs, these foals were initially suspected to be affected with equine neuroaxonal dystrophy/degenerative myeloencephalopathy (eNAD/EDM), spinal abscess or osteomyelitis, trauma, or congenital myelopathy. In QHs, a combination of genetic susceptibility and postnatal deficiency in vitamin E result in the development of eNAD/EDM.[1] Clinical signs of eNAD/EDM include symmetric generalized proprioceptive ataxia (≥ grade 2 of 5), wide-base stance at rest, and proprioceptive deficits.[2] Currently, the only way to conclusively diagnose eNAD/EDM is through postmortem histologic evaluation of the brainstem and spinal cord.[3,4] In young QHs with eNAD/EDM, decreased serum vitamin E, specifically α-tocopherol, concentrations can be identified.[1]

However, these foals were phenotypically different from classical eNAD/EDM and, with continued investigation into the clinicopathologic findings of these QH foals, it became apparent that eNAD/EDM was not the cause of disease. Since 2020, a total of 12 QH foals affected with this novel neurologic disease have been identified. Owing to the clinical phenotype and neuropathological findings, the authors currently propose the term, Equine Juvenile Spinocerebellar Ataxia (EJSCA), to identify this unique disease. This case series aims to report the clinical findings, outcomes, and postmortem changes identified in cases of EJSCA. Further, the authors propose a potential mode of inheritance for this spinocerebellar ataxia.

2 | MATERIALS AND METHODS

2.1 | DNA extraction for biobank storage

Genomic DNA was isolated from whole blood samples according to the WIZARD Blood DNA Extraction Kit protocol (Promega, Madison, WI; $n = 8/12$, 67%). If no blood sample was available, genomic DNA was isolated from available tissue ($n = 3/12$, 25%) using the Gentra Puregene Tissue kit (Qiagen, Germantown MD). For 1 sample, only paraffin-embedded tissue was available and DNA isolated using Puregene Formalin-fixed Paraffin-embedded tissue (Qiagen, Germantown MD).

2.2 | Pedigree analysis

Six-generation pedigrees were available for affected foals ($n = 12/12$, 100%) and constructed manually.

3 | RESULTS

3.1 | Animals

Cases diagnosed with EJSCA were a median of 16 days of age (range 11–28 days of age). All ($n = 12/12$) foals were QHs. Fillies ($n = 10/12$; 83%) were overrepresented with only 2 of the affected foals being colts ($n = 2/12$; 17%). Foals all appeared healthy at birth, with the onset on neurological disease occurring within the first month of life. Foals were presented to the respective attending clinicians from varying locations of the United States (Oregon, California, New Mexico, and Texas), as well as in Alberta, Canada. All foals ($n = 12/12$) had a history of acute onset of neurological deficits with no history of observed trauma. All foals ($n = 12/12$) had physiological variables within reference ranges and no clinically notable abnormalities, other than the neurologic deficits, were found on physical examination. No foals presented with any evidence of trauma or muscle atrophy.

All foals ($n = 12/12$) had similar neurologic examination findings on admission. Foals had normal behavior and state of consciousness (bright, alert, and responsive). Cranial nerves and segmental reflexes were intact and appropriate bilaterally, except for 1 3-week old filly that had absent cutaneous trunci reflex caudal to T18 bilaterally. Asymmetrical general proprioceptive (spinal) ataxia was appreciated, with a pronounced sidedness (e.g., right worse than left, or vice versa). The pelvic limbs were more severely affected than the thoracic limbs by 2 or more grades. Most foals ($n = 11/12$; 92%) were graded 4–5 of 5 spinal ataxia on the pelvic limbs and grade 1–3 of 5 spinal ataxia on the thoracic limbs on admission (Video 1). Most foals showed an apparent abnormal compensatory stance (wide based or limbs under the thorax) and gait of the thoracic limbs owing to severity of pelvic limbs. Upon physical support, these foals spun the pelvic limbs sideways with the thoracic limbs planted to the ground and walked at times sideways like sidewinders.[5] The grading scale for ataxia was based on the modified Mayhew grading system.[6] Based on neurological examination, a multifocal progressive myelopathy (pelvic limbs more severely affected than thoracic limbs by more than 1 grade) was diagnosed, causing spinal ataxia. In some cases, a mild asymmetric paraparesis was also observed.

3.2 | Clinicopathological data

Five foals ($n = 5/12$, 42%) had complete hematology and biochemistry panels performed. No clinically significant findings were observed on either the erythrogram or leukogram. However, 4 ($n = 4/5$, 80%) of these foals had high gamma-glutamyl transferase (GGT) activity on biochemical profiles (59 ± 104 U/L; reference range <54 U/L). Additionally, all foals that had a minimum database performed were hyperglycemic (168 ± 7 mg/dL; reference range 50–107 mg/dL). Cerebrospinal fluid (CSF) centesis was performed in 5 foals ($n = 5/12$, 42%) and analysis revealed no cytological abnormalities. A biochemical profile including glucose, creatine kinase, electrolytes, and L-lactate in CSF performed in 2 filles was normal. Alpha-tocopherol concentrations were obtained in 3 foals ($n = 3/12$, 25%). Two foals had high serum alpha-tocopherol concentrations (21.8 and 33.0 μg/mL;

VIDEO 1 Video footage of the phenotypic characteristics of Quarter horse foals diagnosed with Equine Juvenile Spinocerebellar Ataxia (EJSCA). Note the general proprioceptive ataxia of all four limbs, which is most severe in the pelvic limbs and more pronounced when turning. Hypermetria is observed in the forelimbs. This foal progressed to recumbency within 3 days.

reference range >4 μg/mL), while the remaining foal for which alpha-tocopherol was available had above adequate hepatic concentrations obtained at necropsy (200 μg/mL; reference range >4 μg/mL). These 3 foals for which alpha-tocopherol concentrations were available had been supplemented antemortem. Phosphorylated neurofilament (pNfH) was quantified on CSF samples from 2 foals ($n = 2/12$, 16%) and was high in both cases (14.4 ng/μL and 17.5 ng/μL; reference range <3 ng/μL). One filly had a serum pNfH measured, which was within normal limits (0.60 ng/μL; reference range <1 ng/μL).

3.3 | Diagnostic imaging

Radiographs of the vertebral column were performed in 6 foals ($n = 6/12$, 50%) and revealed no abnormalities. Magnetic resonance imaging was performed in 2 foals ($n = 2/12$, 17%) and computed tomography myelography was performed in a single foal ($n = 1/12$, 8%) with no evidence of vertebral or spinal cord abnormalities.

3.4 | Outcomes

All foals rapidly progressed and followed a similar pattern. Following the presenting signs of acute pelvic limb ataxia, the thoracic limbs subsequently developed moderate to marked hypermetria. In some foals ($n = 3/12$, 25%), intention tremors developed in the head and neck, particularly during nursing. Soon thereafter, all foals became recumbent (median, 3 days: [0–18 days]) and unable to rise without assistance owing to pelvic limb incoordination and paraparesis, which necessitated humane euthanasia ($n = 11/12$, 92%; the remaining case was found dead).

3.5 | Postmortem evaluation

Necropsies were performed on 10 of 12 foals. Examined tissues included the middle gluteal muscle, semitendinosus muscle, epaxial lumbar, epaxial thoracic, kidney, intestine, spleen, liver, lung, heart, vertebral column, cerebrum, brainstem, and cerebellum. When evaluating the spinal cord, 2-3 sections were evaluated within the cervical region, 2-4 sections within the thoracic region, and 1-3 sections with thin the lumbar region of each case. There were no notable gross necropsy findings observed within. Histologic evaluation revealed dilated myelin sheaths with digestion chambers throughout the entire spinal cord that was most severe in the cervicothoracic region. Lesions were most prominent in the dorsal spinocerebellar tract (Figure 1), but also noted within the fasciculus cuneatus and ventromedial tracts. Affected animals also exhibited rare increases in glial cells (Figure 1C). There were no lesions identified in the brainstem, including the medial and lateral cuneate nuclei and gracilis nucleus, or cerebellum. These findings are most consistent with a degenerative axonopathy distinct from eNAD/EDM.

3.6 | Pedigree analysis

The pedigrees of the 12 affected foals were obtained and a pedigree analysis was conducted manually. Six of the affected foals ($n = 6/12$, 50%) shared a sire and all foals were related on the sires' side within

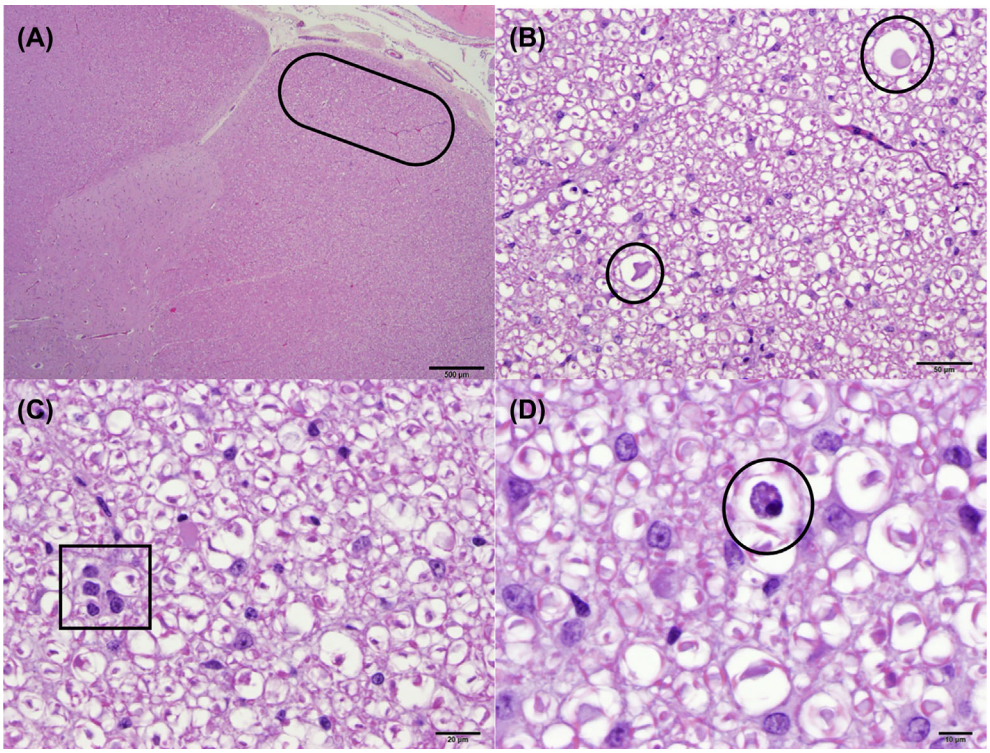

FIGURE 1 Histology of affected spinal cord from an equine juvenile spinocerebellar ataxia foal at the level of C7. (A) Lesions were largely confined to the dorsal spinocerebellar tract, highlighted in the oval. (B) Lesions consisted of dilated myelin sheaths and axonal spheroids (circles). (C) Affected animals also exhibited rare increases in glial cells (box). (D) Digestion chambers were also observed (circle) implying Wallerian-type degeneration of axons.

4-5 generations. The foals were also related on the dams' side within 4-6 generations. With both sexes affected and 2 healthy parents producing affected foals, an autosomal recessive mode of inheritance for the disease is likely (Figure 2).

4 | DISCUSSION

The purpose of this case series was to describe the clinicopathologic findings and a proposed mode of inheritance for EJSCA in QH foals. These foals consistently presented with an acute onset of ataxia, affecting the pelvic limbs more severely within the first month of life, with the majority of foals exhibiting clinical signs 1–2 days before presentation. Clinicopathologic findings demonstrated increased GGT in most foals, which may be associated with an underlying oxidative stress. Clinical disease progressed to inability to stand, even with assistance, resulting in death or euthanasia. The single foal that was found dead was found in the field and no necropsy was performed. At necropsy of the other foals, no gross lesions of the nervous system were identified across all samples. However, histologic assessment identified spheroids and dilated myelin sheaths with digestion chambers throughout the entire spinal cord, but most severe in the cervicothoracic region, with prominent involvement of the dorsal spinocerebellar tract. As the dorsal spinocerebellar tracts receive proprioceptive input from the pelvic limbs, the pelvic limb deficits observed are likely owing to the damage in these tracts. With less severe lesions in the cuneate tracts of the spinal cord, milder deficits would be observed in the forelimbs. Damage to the ventromedial tracts may have led to paraparesis of the pelvic limbs that was eventually observed in most foals. No lesions were identified in the cerebrum, brainstem, or cerebellum. This histologic diagnosis is consistent with a degenerative axonopathy.

Degenerative axonopathies are characterized by progressive spinal ataxia and paraparesis in other species, including cattle and sheep.[7–12] This ultimately leads to permanent recumbency in a responsive animal. Progressive spinal ataxia, affecting the pelvic limbs, and paraparesis indicate a lesion from T3 to caudal spinal cord segments.[13] In cattle, progressive limb ataxia and paraparesis can result from trauma, vertebral/extradural abscessation, degenerative myelopathies owing to organophosphate toxicity, or inherited defects.[14–18] In horses, trauma and infection result in similar clinical signs[19,20]; however, there are no reports to date of inherited defects leading to an early onset progressive limb ataxia and paraparesis.

Of the early onset degenerative axonopathies, only degenerative axonopathy (Demetz syndrome) in Tyrolean Grey cattle and bovine spinal dysmyelination in Brown Swiss have lesions confined to the brainstem and spinal cord.[7,21] In Tyrolean Grey cattle, degenerative axonopathy is clinically characterized by progressive ataxia most prominent in the pelvic limbs starting at 1 to 1 and a half months of age.[7] Affected calves eventually become recumbent.[7] This is similar to EJSCA in QH foals, where the pelvic limbs are more severely affected, progressing to recumbency. However, EJSCA occurs slightly earlier in life (within the first month) in foals than in cattle with degenerative axonopathy.

Other comparable diseases in ruminants include bovine spinal dysmyelination in Brown Swiss, but these calves are unable to stand from birth.[21] In contrast, EJSCA foals typically appear healthy at first then progress to being unable to stand. The other inherited axonopathies (central and peripheral axonopathy of Maine-Anjou cattle and neuroaxonal dystrophy of sheep) have lesions extending into the cerebrum and/or cerebellum.[22,23] Central and peripheral axonopathy of Rouge-des-Pres cattle presents as a progressive ataxia most prominently affecting the pelvic limbs, and affected calves consistently have a swaying motion of the hindquarters that leads to loss of balance.[10] Signs begin between 5 and 16 weeks and end in recumbency within

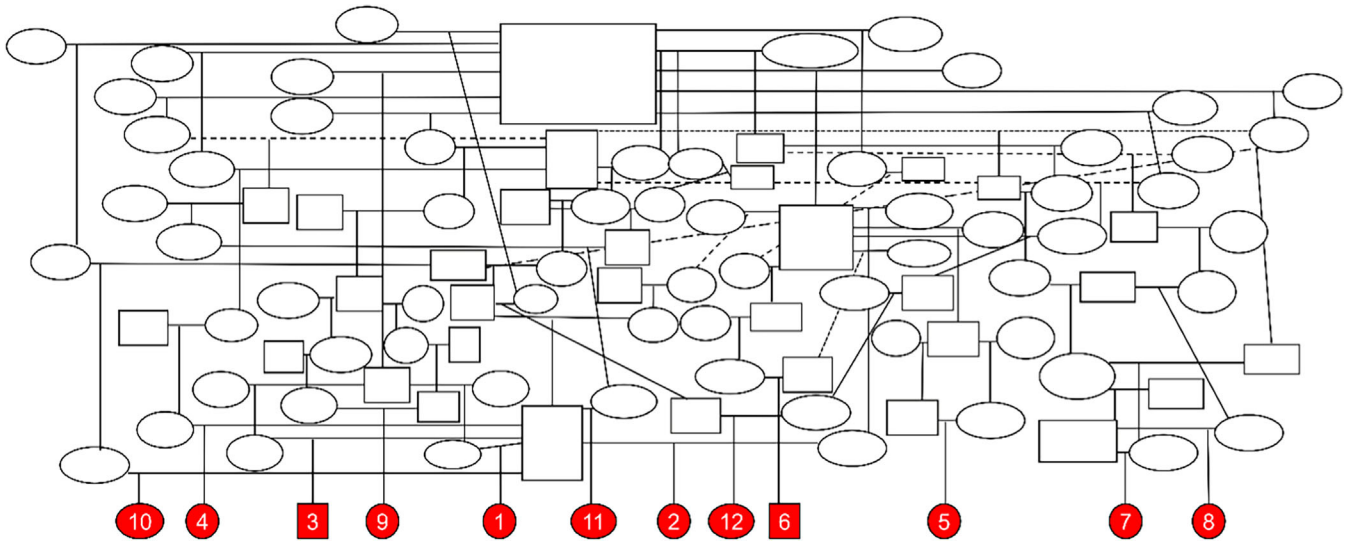

FIGURE 2 Pedigrees of affected horses as indicated by red shapes. Number corresponds to case number. Squares indicate males and circles are females.

1–3 weeks following onset of signs.[10] Neuroaxonal dystrophy in sheep has an age of onset of around 6 weeks, later than that of EJSCA affected foals.[23] The affected lambs were ataxic with a stiff gait that increased in severity over several days to recumbency.[23] Two genetic variants in phospholipase A2 group VI (*PLA2G6*) were identified in Swaledale sheep with neuroaxonal dystrophy. The associated variants frequently occur together in affected sheep and clinically affected animals are considered compound heterozygotes.[23] Compared with the aforementioned ruminant inherited axonopathies, QHs affected by EJSCA have similarities in clinical signs, but with earlier disease onset and a more rapid progression to recumbency. Most degenerative axonopathies across species have an autosomal recessive modes of inheritance.[7–12,21–26] Similarly, pedigree analysis of EJSCA affected foals also supports an autosomal recessive mode of inheritance.

A recent retrospective study of the causes of spinal ataxia of horses in California from 2005 to 2017 found that of the 2861 horses necropsied during the time period, 316 of them were ataxic.[27] The most common causes of ataxia were cervical vertebral compressive myelopathy, eNAD/EDM, and trauma.[27] In QHs specifically, eNAD/EDM was the most common diagnosis. Thus, eNAD/EDM was a strong differential diagnosis for this early onset ataxia in Quarter Horse foals. However, the defining lesions for eNAD—spheroids in the lateral accessory cuneate, medial cuneate, and gracile nuclei of the brainstem and nucleus thoracicus of the spinal cord—were not identified in these foals.[3] Although degeneration of the dorsal spinocerebellar tracts can be identified in horses with EDM, the absence of spheroids in the gray matter tracts precludes a diagnosis of eNAD/EDM.[3] Additionally, alpha-tocopherol concentrations were normal or high in all QH foals that had concentrations measured ($n = 3/12$, 25%) due to supplementation at birth. Therefore, eNAD/EDM was excluded as a diagnosis in these foals. Further, phenotypically, EJSCA foals present with asymmetrical paraparesis with a rapid progression, in conjunction with the disparity between the grades of ataxia between thoracic and pelvic limbs, which contrast with the phenotypical appearance to those foals with eNAD/EDM.

In summary, the newly identified neurodegenerative disease in QHs in North America during the first month of life was determined to be a degenerative axonopathy based on histological lesions that were most severe in the cervicothoracic spinal cord. Additionally, EJSCA has a suspected autosomal recessive mode of inheritance and further genetic investigation is warranted to identify an underlying causative variant(s). Once the causative variant(s) for EJSCA is validated, carriers can be identified through genetic testing to inform breeding decisions.

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CONFLICTS OF INTEREST DECLARATION

Authors declare no conflict of interest.

OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION

Approved by the University of California, Davis IACUC, protocol #20751, and carried out in accordance with guidelines and regulations. Written owner consent was obtained for all sample collections.

HUMAN ETHICS APPROVAL DECLARATION

Authors declare human ethics approval was not needed for this study.

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