Neuroaxonal Dystrophy of the Accessory Cuneate Nucleus in Horses

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Abstract. Data were collected from 37 horses with a neurologic disability and compared to a group of 34 normal horses. Affected horses had neuroaxonal dystrophy, gliosis, vacuoles, and sometimes pigment localized to the accessory cuneate nuclei with minimal or no changes in the spinal cord and no changes in the proximal peripheral nerves. The focal nature of the change and usual absence of significant light microscopic spinal cord or peripheral nerve changes are different than previously described equine neuropathologic conditions.

Neuroaxonal dystrophy has been associated with various neurologic diseases in man,1,8,11 a familial neurologic disease in Suffolk sheep,5 in cats29 and dogs,6 vitamin E deficiency in rats,9,17,21,24 biliary atresia in infants and cystic fibrosis in children and young adults,27 ataxia in red deer,2 alcoholism, giant axonal neuropathy in dogs,12 certain intoxications (hexanes, organophosphates, diethylthiocarbamate, iminodipropionitrile and p-bromophenylacetylurea in some species),4,7,15 malignancies, chronic chemotheraphy, chronic diseases and debilitation and as a natural aging change in dogs and in man.10,22,23 It may accompany more diffuse lesions in the nervous system of horses as seen in equine degenerative myeloencephalopathy.18 Its clinical and pathological manifestations vary among species and with the underlying condition or experimental method of induction. Although evidence suggests metabolic derangement of nerve cells and axons, the etiology and pathogenesis in the natural disease states are unknown. A natural disease condition of neuroaxonal dystrophy without the diffuse changes seen in equine degenerative myeloencephalopathy is associated with a neurologic disorder which may be familial in horses. The condition has been seen most commonly in the Morgan breed. Frequently, affected horses have been related.

The objectives of this study were: to define the character of the lesions; to compare changes within groups with clinical signs of varying severity; to compare affected horses with normal horses; to evaluate any age-related changes; and, to determine if there was an association between lesions in the medulla and spinal cord and the presence of gross vertebral changes.

Materials and Methods

Clinical signs and lesions from 28 normal Morgan horses, six normal horses of other breeds, 21 Morgan and three non-Morgan horses with similar severe neurologic signs, and 13 mildly affected Morgan horses were analyzed and compared (table I). The normal population (group N) consisted of 12 horses less than ten years old (two less than two years old), ten between 11 and 20 years, and 12 older than 20. A group of 13 horses less then two years old with other unrelated neurologic deficits (myelitis or cervical cord compression, group X) also was included for comparison. The abnormal population was subdivided into 24 severely affected horses (21 Morgans, three non-Morgans, group S) and 13 mildly affected horses (group M). Lesions were compared among groups. The relationship of lesions with age at necropsy and age at onset of neurologic deficit were compared in the abnormal horses (table I).

Each horse had at least one complete physical, musculoskeletal, and neurological examination prior to euthanasia. The examination consisted of evaluation of skin sensation; tail tone; cranial nerve function; balance, limb movement and position when standing, walking, trotting, cantering, circling tightly and pivoting on the forelegs, stopping from all three gaits, in response to being swayed to each side during lateral, ventral and dorsal neck flexion, and when possible, at a walk and trot up and down an incline.25 Sometimes incoordination was too severe to permit safe evaluation of all the above movements. Complete blood counts were done on 49 horses. Gross necropsy examinations were done immediately following euthanasia with barbiturate, and the brain, spinal cord, sciatic nerve and muscle were fixed in 10% formalin.

Cross sections of the medulla, cerebellum, cervical, thoracic and lumbar spinal cord were examined (table I). In abnormal horses, samples of nerve and muscle were examined and samples of midbrain and cerebrum also were evaluated. Tissue was embedded in paraffin and 6 μm sections were cut. Sections were stained with hematoxylin and eosin (HE); Bodian's, luxol fast blue, periodic acid-Schiff (PAS), carbol-fuchsin, and...
### Table I. Lesions and ages of the clinical groups; numbers of horses

<table>
<thead>
<tr>
<th>Clinical group</th>
<th>Horses</th>
<th>Cervical vertebral lesions</th>
<th>Spinal cord histology</th>
<th>ACN change (overall mark)</th>
<th>Age of onset (years)</th>
<th>Age at necropsy (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>NE</td>
<td>N</td>
<td>MA</td>
<td>OA</td>
<td>SA</td>
</tr>
<tr>
<td>Normal (N)</td>
<td>34</td>
<td>7</td>
<td>18</td>
<td>5</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Mild (M)</td>
<td>13</td>
<td>1</td>
<td>8</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Severe (S)</td>
<td>24</td>
<td>0</td>
<td>10</td>
<td>12</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Other CNS</td>
<td>13</td>
<td>0</td>
<td>4</td>
<td>1</td>
<td>2</td>
<td>6</td>
</tr>
</tbody>
</table>

NE = not examined; N = normal; MA = mildly abnormal; OA = moderately abnormal; SA = severely abnormal; ACN = accessory cuneate nucleus; ND = not determined; CNS = central nervous system.

### Table II. Lesions of the accessory cuneate nucleus

<table>
<thead>
<tr>
<th>Clinical group</th>
<th>Horses</th>
<th>Mean age (years)</th>
<th>Moderately sized spheroids #/hpf</th>
<th>Small spheroids #/hpf</th>
<th>Gliosis #/hpf</th>
<th>Vacuoles #/hpf</th>
<th>Overall assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>N</td>
</tr>
<tr>
<td>Normal (N)</td>
<td>34</td>
<td>15.58</td>
<td>8.54</td>
<td>13.31</td>
<td>210</td>
<td>3.16</td>
<td>14</td>
</tr>
<tr>
<td>Mild (M)</td>
<td>13</td>
<td>4.99</td>
<td>18.08</td>
<td>20.87</td>
<td>298</td>
<td>9.98</td>
<td>0</td>
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<tr>
<td>Severe (S)</td>
<td>24</td>
<td>2.30</td>
<td>21.58</td>
<td>19.63</td>
<td>322</td>
<td>16.76</td>
<td>0</td>
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<tr>
<td>Other CNS</td>
<td>13</td>
<td>4.4</td>
<td>9.95</td>
<td>11.92</td>
<td>265</td>
<td>3.12</td>
<td>8</td>
</tr>
</tbody>
</table>

Lesions of the accessory cuneate nucleus using a numerical ranking system

<table>
<thead>
<tr>
<th>Clinical group</th>
<th>R₁ (Small spheroids)</th>
<th>R₂ (Moderately sized spheroids)</th>
<th>R₃ (Large spheroids)</th>
<th>R₄ (Vacuoles)</th>
<th>R₅ (Gliosis)</th>
<th>R₆ (Pigment)</th>
<th>Total rank</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal (N)</td>
<td>0.56</td>
<td>2.50</td>
<td>2.24</td>
<td>1.47</td>
<td>1.04</td>
<td>0.78</td>
<td>8.68</td>
</tr>
<tr>
<td>Mild (M)</td>
<td>1.62</td>
<td>4.19</td>
<td>3.48</td>
<td>2.85</td>
<td>3.51</td>
<td>1.22</td>
<td>17.64</td>
</tr>
<tr>
<td>Severe (S)</td>
<td>1.50</td>
<td>4.40</td>
<td>2.91</td>
<td>4.02</td>
<td>3.94</td>
<td>1.78</td>
<td>18.90</td>
</tr>
<tr>
<td>Other CNS</td>
<td>.808</td>
<td>2.54</td>
<td>2.18</td>
<td>1.31</td>
<td>2.58</td>
<td>0.49</td>
<td>9.89</td>
</tr>
</tbody>
</table>

* All horses were ≥14 years of age.
** Horse was 26 years of age.

#/#hpf = number per high power field (400X); N = normal; MA = mildly abnormal; OA = moderately abnormal; SA = severely abnormal; ND = not done; CNS = central nervous system.
Gomori's reticulin stains were done on selected sections. In order to eliminate possible bias in interpretation of changes, sections were evaluated with no accompanying information on the horse's identity, age or signs. Two to five sections were taken through the medulla at the level of the obex where the accessory cuneate nucleus is well defined and prominent to assess neuroaxonal dystrophy within the nucleus; it was graded as normal, mildly abnormal, moderately abnormal, and severely abnormal based on numbers and sizes of spheroids, vacuoles, glial cells and presence of pigment. Similar sections were compared from each horse. Sections with little accessory cuneate nucleus area were examined but not included for analysis and comparative purposes. A numerical ranking system using numbers for each parameter also was used and the two different grading systems compared (table II). Numerical scores were assigned arbitrarily for the different characteristics to aid comparison of the various criteria and the different groups. The method used for the scoring in the ranking system is outlined in table III. Each horse's score for individual parameters, as well as the overall score, could be assessed, and the mean for each clinical group determined. Changes were compared between the two abnormal populations and with a normal but older population of Morgan horses as well as with other breeds without these neurologic signs. Data were analyzed and significant differences (P < 0.01) were subjected to age-adjusted analysis to eliminate possible influence of age. Statistical methods used were two-way tables, chi-square and Stuart's Tau-C test, least squares and Duncan's multiple range test.

Results

History

The age when signs first were seen varied with the severity of the horse's deficits, with the astuteness of the owners or trainers, and the horse's use. Thirteen horses within group S had signs by approximately six months of age, four when approximately one year, three at approximately two years, two when older than three years, and two at undetermined ages. Within group M, three were abnormal at about six months, four between one and two years of age, one when older than three years, and five at undetermined ages. There never was any history of illness or unusual medication during the dam's pregnancy. Diet was adequate to excellent and consisted of commercial grain mixtures and hay and often vitamin and mineral supplementation. Anthelmintic medication varied from infrequent to routine at two-month intervals. Initial reported signs varied from merely a rather stiff, stilted hind-leg gait to frank hind-limb incoordination, inability to stop well, and falling. Signs usually were reported to be mildly but not rapidly progressive.

Clinical signs

Within the clinically abnormal population (groups M and S), 13 half siblings were distributed in three family groups, 12 full siblings were distributed in five family groups, and others were related less closely. Physical examinations revealed no systemic diseases. One horse had mild scoliosis. Body condition usually was good but several horses were slightly thin and had ascarid infestation. Some affected horses had poorly muscled necks but none had frank muscle atrophy. Ophthalmologic examinations were unremarkable. When complete blood counts were done they were normal.

The neurologic dysfunction was restricted to gait abnormalities, although the severely affected horses, when stationary, also sometimes stood with their hind feet placed too far anteriorly under their trunks. When walking or trotting, severely affected horses had a markedly dysmetric hind-limb gait. As the horses became more incoordinated, the hindquarters sometimes developed a lateral swaying motion and the hind foot

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Large spheroids/nucleus</th>
<th>Moderately sized spheroids/nucleus</th>
<th>Small spheroids/nucleus</th>
<th>Pigment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Numbers:</td>
<td>&gt;5 1-5 21-30 41-20 6-10</td>
<td>Some Few &gt;30 21-30 11-20 5-10</td>
<td>Few &gt;30 21-30 11-20 5-10</td>
<td>Absent</td>
</tr>
<tr>
<td>Assigned score</td>
<td>4 3 6 5 4 3 2</td>
<td>2 5 4 3 2</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Vacuoles/nucleus</th>
<th>Glial cells/hpf*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Numbers:</td>
<td>&gt;30 21-30 11-20 5-10</td>
<td>&gt;350 300-350 250-300 201-249</td>
</tr>
<tr>
<td>Assigned score</td>
<td>6 5 4 3 2</td>
<td>5 4 2</td>
</tr>
</tbody>
</table>

*#/hpf = number per high power field (400x).
movement became more shuffling with scuffing of the hind toes on the ground and some interference of each foot on the opposite leg. Foreleg movement was normal except in the most severely affected horses when it was slightly less precise than normal (somewhat flinging and more basewise); however, it was difficult to tell if this was secondary to the severely abnormal hind-limb movement or a primary foreleg gait deficit. The mildly affected horses' hind-limb movement was dysmetric and stiff without impulsion.

Mildly affected horses had stiff hind-leg movement when cantered and kept their hind legs moving together—not separated as in a normal “3-beat” canter. The gait became stiffer and more bouncy with increasing severity. Afflicted horses could not stop smoothly from any gait. When stopping, severely affected horses often had increased bounce and stiffness in their hind-leg movement; mildly affected horses had stiff upward movement of the hind feet followed by hesitant jerking of the foot in mid-flight and excessive downward force during foot placement.

Mildly affected horses backed up normally and could be pushed sideways normally. Severely affected horses kept their hind feet on the ground excessively long when being pushed backwards, but they would move their forefeet backwards, thus developing a steeper croup slope and appearing ready to sit down. Swaying the horses sideways elicited hind-limb dysmetria. Circling the horse tightly, with its forelegs making a small arc in the center of the circle while the hind legs moved circumferentially, elicited either stiff abduction or circumduction of the hind leg on the outside of the described circle—or the horse preferentially kept its hind feet immobile and placed abnormally far anteriorly under its body and would pivot around them. When the afflicted horses were walked down an incline, the hind leg dysmetria, incoordination, and interference increased.

Some mildly affected horses were observed over two to five years; their abnormal hind-limb gait and equivocal foreleg gait deficits worsened and there was no development of other neurologic or systemic disabilities. No horses improved, although there was slight daily variability in the severity of their signs. Electromyography revealed no evidence of denervation or myopathy, and nerve conduction velocity was normal in the one chronically diseased horse in which it was evaluated. In general, the progression was slow over months or years and the horses never became recumbent, even in the advanced stages of disease.

Gross necropsy results and vertebral abnormalities

Gross necropsy examination of the abnormal horses (groups S and M) showed no significant abnormalities in muscles, hind-limb joints, or viscera. Disarticulation of the cervical vertebrae revealed a grossly normal vertebral canal in 14 horses. The caudal articular processes of the third and fourth cervical vertebrae had developed lateral peripheral cartilage ridges or rims extending ventrolaterally in 14 horses, and there was mild asymmetry of some articular processes but the latter was considered insignificant. In a few horses, caudal articular processes of the third and fourth cervical vertebrae angled outwards as if they had been worn abnormally but not sufficiently to develop a rim. Vertebrae were graded normal in 18 of 34 normal horses, 8 of 13 mildly affected and 10 of 24 severely affected horses; mildly abnormal in 5 of the normal, 2 of the mildly affected and 12 of the severely affected horses; and moderately abnormal in 4 normal horses, 2 mildly affected and 2 severely affected horses (table I).

The effect of age of onset, duration of signs and age at necropsy on the degree of cervical vertebral change was analyzed statistically using Duncan's multiple range tests. Age of onset of neurologic signs in groups S and M did not correlate with whether the cervical vertebral changes were evaluated as normal or mildly or moderately abnormal. Horses with severely abnormal vertebrae in group X were significantly younger at necropsy than horses with the other grades of vertebral changes, and they had a shorter duration of neurologic signs because they frequently were killed soon after signs were noticed. Their severely abnormal vertebrae often caused extreme cervical cord compression and marked clinical neurologic deficits which resulted in early euthanasia. The four horses within group N with vertebrae classified as moderately abnormal were old. The duration of signs was the same regardless of whether vertebrae were graded as mildly abnormal or normal. There was no significant correlation between the cervical vertebral changes and any changes in the accessory cuneate nuclei except that the horses in group X with severely abnormal vertebrae had significantly fewer spheroids than horses with normal or mildly abnormal vertebrae.

Microscopic changes

Multiple sections of the cervical, thoracic, and lumbar spinal cord revealed no significant lesions in 28 of the 37 abnormal horses (table I). There were very rare
single degenerated axons or small clusters of two to six glial cells in the ventral and lateral fasciculi in one normal and six abnormal horses. Nerve roots were normal. Gray matter was unremarkable; a spheroid rarely was found in the ventral horn or in Clarke’s nucleus areas. Two horses had significant spinal cord lesions. One four-month-old male, severely affected clinically since several weeks of age, had diffuse degenerated axons in the spinal cord and was classified as having a moderate myelopathy. The other horse which was included in the mild category was a female with an odd gait of unknown duration that had been difficult to interpret and classify because of a frequent shuffling pace; she had wallerian degeneration of the ventral and ventrolateral white matter of the lumbar spinal cord—unrelated and in addition to changes in the accessory cuneate nuclei. Proximal peripheral nerves were normal except in one horse where homogeneous torpedo-like structures were found in one small area.

There was no correlation between spinal cord lesions and neuroaxonal dystrophy in the accessory cuneate nuclei, although there was a tendency for horses with mildly abnormal spinal cords to have more moderately sized spheroids and vacuoles than horses with normal or severely abnormal cords. Using Duncan’s multiple range test, there was no correlation between age of onset of signs, duration of disease, or age at necropsy and the extent of spinal cord lesions.

Examination of brain sections revealed lesions in the abnormal population that usually were restricted to the accessory or lateral cuneate nucleus; rarely there were sparsely scattered degenerated axons in the spinocerebellar tract, and in one horse, in the fasciculus cuneatus and medial cuneate nuclei. Neuroaxonal dystrophy varied in the nucleus with small (approximately 8 \( \mu \)m diameter), moderately sized (15–40 \( \mu \)m diameter) and very large (more than 45 \( \mu \)m diameter) spheroids or torpedo-shaped structures which usually stained homogeneously pink with hematoxylin and eosin (figs. 1, 2). Occasionally they had a slightly more irregular shape and they sometimes appeared granular or were vacuolated (fig. 3). There frequently were accompanying vacuoles of various sizes (25–120 \( \mu \)m diameter) which often were multicompartamental; no vacuoles due to status spongiosus were counted. Many vacuoles were suspected to be sites of spheroid drop out. There frequently was gliosis caused by an increase in small microglia, and to a lesser extent, astrocytes (fig. 1). Yellow-brown or pale yellow pigment, which stained positively as lipofuscin with periodic acid-Schiff and carbol-fuchsin stains, sometimes was found loose or phagocytosed and localized to the nuclei. Occasionally spheroids stained homogeneously pale blue instead of pink with hematoxylin and eosin; Buscaino’s bodies were found rarely. Spheroids stained pale pink with periodic acid-Schiff. Scattered large neurons in the reticular formation sometimes contained PAS-positive material near the axon hillock or paranuclear area. Results of the analysis of the various parameters within the different populations are given in table II.

Analysis of the extent of neuroaxonal dystrophy in the accessory cuneate nuclei in group S and group M horses compared to group N revealed a significant increase in moderately sized spheroids (p \( \leq \) 0.0001 for group S and p \( \leq \) 0.005 for group M), gliosis (p \( \leq \) 0.0001 for groups M and S) and vacuoles (p \( \leq \) 0.0001 for group S and p \( \leq \) 0.008 for group M). Group S but not group M had significantly more pigment (p \( \leq \) 0.0001) than group N. When compared to the group with different clinical neurologic conditions (group X), group S had
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The mean age of horses with pigment was 10.8 years, whereas the mean age of horses lacking pigment deposition was 3.7 years. Seventy-six percent of the severely affected horses and 70% of the normal horses had pigment, however, the mean age of the normal population was much higher (15.6 years vs 2.3 years for the severely abnormal group) and the difference may be age related. When 19 group S horses, 3 years of age or under, were compared to 25 other nonseverely affected Morgans of the same age from another study (J. Beech, unpublished observation), there was a significant difference; 74% of the group S horses had pigment compared to only 12% of the other group. Similarly, within group X only 12% of the horses three years of age or under had pigment.

Neuroaxonal dystrophy in the accessory cuneate nuclei was not related to the age of onset of clinical neurologic deficits but was correlated with the duration of signs and age at necropsy. Group N horses which were significantly older than the abnormal horses had significantly less neuroaxonal dystrophy. Group S horses usually had signs for a shorter duration prior to euthanasia than group M horses. When groups M and S were compared separately with group N, except for those horses less than one year of age in group M, total scores still were higher than in group N. Within group M, the severity of neuroaxonal dystrophy increased with age. This trend was not seen within group S. Horses less than one year old within group S had higher total scores than any other group and the scores decreased with age.

Evaluation of the extent of severity of the lesions by numerical scoring parallels the subjective impression and grading system, both revealing a significant difference between the groups. The degree of neuroaxonal dystrophy in the groups of abnormal horses also is greater than that reported in a control equine population.18

Discussion

The association between neuroaxonal dystrophy in the accessory cuneate nuclei and signs of neurologic disease is clear, but it is unclear why lesions at this site would result in the particular signs shown by these horses. This nucleus generally is thought to be associated with proprioception of the neck, but the signs of these horses were localized to the hind limbs. Despite the apparent association with cervical proprioception, there was no significant correlation between gross cervical vertebral changes and lesions in the nucleus. Mod-
Fig. 3: Vacuolated dystrophic axon. Large and small vacuoles within swollen axon.

crately abnormal vertebrae occasionally were seen in older horses and probably reflected wearing with age; it is possible that these changes when seen in younger horses reflected abnormal neck and limb movement. However, group S horses had no pattern of vertebral change; almost half were normal and half mildly abnormal and there were no significant differences in the classification of vertebral changes among the clinical groups. It is possible that abnormal neck proprioception could alter hind-leg gait. Functional abnormalities could exist in neural transmission without light microscopic morphologic abnormalities. The presence of spheroids confirmed by ultrastructural studies sometimes has not been apparent with light microscopy. It also is possible that undetected extensive axonal dystrophy and dying back affected distal peripheral nerves or muscle spindles, and our sections of nerve roots and sciatic nerves were too proximal to reveal lesions. Ultrastructural evaluation of terminal axons in conjunctival and skin biopsies had been used in man to identify affected infants, but its value in horses has yet to be assessed.

Several different nonfamilial and familial neuroaxonal dystrophies cause neurologic syndromes with various combinations of clinical signs and progression and various lesions in man.\textsuperscript{1,8,11,27} Clinical signs, age of onset and progression, sex distribution and family history of neurologic diseases vary in the groups. The dystrophic axons may be diffuse or mainly localized to the cuneate or cuneate, gracile, and medullary reticular nuclei.\textsuperscript{16} The early age of onset and familial incidence are characteristics shared with our horses, however, the lesions usually are more diffuse and the disease more rapidly progressive in the former.

Feline neuroaxonal dystrophy is characterized by dystrophic axons predominantly in the inferior olive and lateral cuneate and to a lesser extent in the midbrain, thalamus, and cerebellar vermis. Atrophy in the cerebellar vermis occurs with gliosis and neuronal loss in the inferior olive and parts of the thalamus.\textsuperscript{29}

In rottweiler dogs, neuroaxonal dystrophy is characterized by massive numbers of spheroids throughout the central nervous system, predominantly in the gracilis and cuneate nuclei and dorsal horn of the spinal cord, and there is mild atrophy of the cerebellar vermis. The spheroids resemble those seen in these horses, but there is no associated glial cell reaction or pigment deposition. Clinical signs differ from those shown by the horses. An autosomal recessive mode of inheritance was suggested.\textsuperscript{6}

In canine giant axonal neuropathy, spheroids are found mainly in the dorsal spinocerebellar tract in the high cervical cord, the lateral corticospinal tracts in the more caudal spinal cord, in the gracile and cuneate nuclei, in the cerebellar vermis and cerebral cortex with some associated wallerian degeneration and occasionally in the spinal cord intermediate and dorsal gray matter.\textsuperscript{12} Unlike in these horses, there was no associated microglial reaction. Clinical signs in the dog differed from those of our horses; the reported dog had progressive paraparesis and ataxia, with hypotony, areflexia and decreased proprioceptive function and pain perception—all in the hind limbs.\textsuperscript{9}

Suffolk sheep with suspected familial neuroaxonal dystrophy have lesions similar to those in the horse except spheroids are more diffuse and found in all levels of the spinal cord, medullary nuclei and in visual and proprioceptive pathways, while gliosis or pigment accumulation localized to sites of neuroaxonal dystrophy is absent.\textsuperscript{5} Although the authors suggested the absence of glial reaction could be due to the short course of the disease, it still represents a difference since affected horses of similar ages, and frequently with short duration of signs, had glial reactions.

Experimentally, various chemicals have caused neuroaxonal dystrophy. In lambs, repeated chronic intraperitoneal administration of sodium diethyldithiocarbamate caused neuroaxonal dystrophy in the accessory
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cuneate nuclei, cuneate and gracilis nuclei, and in Clarke's column but there was no gliosis. Affected lambs did not have gait deficits but this apparently varies with the species. Triorthocresol phosphate administration to cats and p-bromophenylacetylurea and iminodiproprionitrile administration to rats causes spheroids as do some hexacarbons. There is, however, a difference in species susceptibility and the clinical signs and lesions vary. *Swainsona* spp poisoning has caused widespread neuroaxonal dystrophy in cattle and sheep and one foal. Neurons as well as visceral cells of other tissues are vacuolated and there are varying numbers of spheroids, especially in posterior brainstem nuclei and cerebellum, sometimes mild to moderate gliosis, demyelination, and varying pigment changes. Many affected cattle apparently recover if removed from infested pasture. In cattle, cycad palm poisoning also can cause neuroaxonal dystrophy as well as myelin degeneration in the spinal cord, medulla and dorsal root ganglia. None of the toxicities reported have sufficient clinical or pathological similarities to the neuroaxonal dystrophy reported here to conclusively implicate a toxic etiology in these horses.

Equine degenerative myeloencephalopathy shares some similarities as well as having important differences. Horses with equine degenerative myeloencephalopathy have similar clinical signs except foreleg involvement is common and hind-limb movement is more incoordinated relative to the degree of jerking, stamping, and dysmetria. Age of onset of signs generally is younger. The lesions are more diffuse and include diffuse fiber degeneration and demyelination and gliosis in the white matter tracts throughout the spinal cord and spheroids in medullary, cranial cervical, and thoracolumbar nuclei. Within the medulla, spheroids are largest and most numerous in the lateral cuneate nuclei. Astrogliosis and lipofuscin pigment accumulation has been described in areas of neuroaxonal dystrophy. There was no suggestion of a hereditary basis and a toxic etiology was suggested—unlike in this group of Morgan horses.

Neuroaxonal dystrophy due to vitamin E deficiency has been described in rats, but deficiency must be chronic and there also is a myopathy and demyelination. Spheroids are located mainly in the posterior gray horns, Clarke's column, gracile and cuneate nuclei, spinal trigeminal tract and tractus solitarius nuclei, and in the posterior columns. The peripheral nervous system is affected less severely, but axonal degeneration occurs in distal peripheral nerves in a pattern similar to the dying back process. Vitamin E deficiency in primates has been associated inconsistently with dystrophic axons. Different findings may reflect duration of deficiency. Ingestion must be chronic and in one study a significant decrease in serum vitamin E levels was not seen until 8 to 13 months after initiation of the diet, and clinical signs were delayed until the third year. Although monkeys, like rats, had axonal degeneration and lipopigment accumulation, unlike in rats, spheroid formation was limited and rarely involved caudal medulla nuclei.

People with intestinal malabsorption of fat-soluble vitamins develop extensive spheroid formation and posterior column degeneration and vitamin E deficiency has been suggested as a cause. Some patients have had low serum vitamin E levels. Further support for vitamin E deficiency as a cause is the reported improvement, or at least stabilization of usually progressive neurologic signs following vitamin E supplementation, however, others report negative results in treating patients and vitamin E deficient rats. Studies in monkeys showed repletion of their vitamin E status to normal serum levels did not alter the neurologic changes with the exception of certain peripheral nerve ultrastructural changes. There was no evidence to support vitamin E deficiency as a cause of canine neuroaxonal dystrophy and the serum levels were normal in the four affected dogs.

Since these horses often had neurologic signs at a very young age and had no clinical or pathologic evidence of myopathy, no evidence of malabsorption, and no history of deficient diet, it is difficult to implicate vitamin E deficiency strongly as a cause of the syndrome. Accurate analysis of serum vitamin E levels was not possible in the horses due to failure to add an antioxidant prior to storage, and interpretation of their significance might be difficult even under ideal conditions. In monkeys, for example, the severity and extent of the lesions in the nervous system did not correlate with the duration of markedly low serum vitamin E levels.

Analysis of lipofuscin has suggested that the accumulation during vitamin E deficient states has certain characteristics and analysis of pigment in neuroaxonal dystrophy might help resolve the question of a deficiency. It has been reported that in vitamin E deficient states the pigment tends to occur in clumps, does not stain uniformly, and is not extracted by lipid solvents. In several of our horses when pigment was stained, it was found in clumps but no further definitive studies were possible. Whether information from studies on mice can be directly applied to other species is specu-
In several horses scattered large neurons contained paraceous and/or polar clumps of lipofuscin; this distribution is common for late deposition of the pigment and not a characteristic of the vitamin E deficient state. Vitamin E protects membrane integrity by free radical scavenging and by stabilizing structure; a deficiency could allow membrane degeneration and it has been suggested that it may protect structures from premature aging.28

Neuroaxonal dystrophy has been described as a normal aging phenomenon in man and in dogs, but the spheroids characteristically are not associated with other changes such as gliosis or vacuoles.3,22,23 In man, spheroids are especially prominent in the gracile nucleus, and changes in the cuneate nucleus are rare and mild. Certain authors have found no clear association between neuroaxonal dystrophy in the gracile nuclei and a particular disease, whereas others have correlated it with various diseases.17,27

Granular bodies have been reported in dogs more than five years old; they were more prominent in the anterior cervical cord and gracile nucleus and were not associated with a cellular reaction or neuronal change.22 Cyst-like filamentous structures with no cellular reaction occur in widely separated areas, especially cerebral white matter, with no association with diet or age.23 A low frequency of spheroids has been reported in the lateral cuneate nuclei in 8 of 15 control horses; their ages ranged from 7 to 14 years and numbers were less than five per nucleus.18 In group N when horses over ten years of age were compared to younger horses, there was an increase in the overall numerical score for neuroaxonal dystrophy because of an increase in vacuoles, pigment, gliosis, and large and small spheroids. However, there was no difference between the 11 to 20 and over 20-year-old group, and despite the increase with age it was significantly less compared to the mildly abnormal spinal cord lesion group, but other changes (gliosis, small and large spheroids, and pigment in the accessory cuneate nuclei) were not significantly different among the four groups of horses. Although this report restricts itself almost entirely to Morgans, the author also has seen similar clinical syndromes and localized neuroaxonal dystrophy in several related Arabian horses.

The pathogenesis of neuroaxonal dystrophy still is unclear, but may involve defective oxidative metabolism. The oxidative effect of accumulated iron has been suggested as a cause and was supported by finding that 11 human patients with increased hemosiderin caused by previous hemorrhage had abundant spheroids only in the hemosiderin-containing areas. Heme iron can catalyze the peroxidation of lipids and this might result in deranged metabolism and spheroid formation.26 Such a hypothesis could explain the reported beneficial effects of vitamin E, a biological antioxidant, but it does not explain development of spheroids in areas without pigment accumulation. Other unrelated metabolic defects, induced or inborn and associated with inherited metabolic defects, could yield the same end result.

The etiology of the neuroaxonal dystrophy and the functional relationship of the lesion to the clinical signs of neurologic disease in these horses remain speculative. Future studies may reveal if the condition is familial or reflects a specific metabolic defect or toxicity.

Acknowledgements

The author thanks R. Carter for statistical analysis and F. Mallon, R. Harvie, and M. Gardiner for their contributions. The project primarily was made possible through the generous contributions of M. Gardiner.

Addendum

Since acceptance of this manuscript, there has been a report of myelopathy in Mongolian wild horses associating the condition with low plasma alpha tocopherol levels.


References


10 FUJISAWA, K.: A unique type of axonal alteration (so called axonal dystrophy) as seen in Goll’s nucleus of 277 cases of controls. A contribution to the pathology of aging process. Acta Neuropathol (Berl) 8:255–275, 1967


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