Polyneuropathy Associated with Forage Sources in Norwegian Horses

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Background: Cases of hindlimb digital extensor weakness of unknown etiology have been observed in Norway since 1995.

Hypothesis: We hypothesized that the observed bilateral extensor weakness was attributable to neuropathy of the distal nerves and that this was related to environmental factors, possibly dietary.

Animals: Seventy-five horses with digital extensor weakness occurring from 1995 to 2004 are described.

Methods: Eleven horses were examined at The Norwegian School of Veterinary Science, and the medical records of 64 horses seen in ambulatory practice were reviewed.

Results: There was no apparent sex, age, or breed predilection, but the majority were horses kept for pleasure or breeding purposes. Clinical signs varied from intermittent knuckling of the hindlimbs to paraplegia. Some horses showed no or only slow progression of signs, whereas others developed severe signs within hours. No other neurologic deficits were detected in any of the horses. Epidemiologic data and laboratory results were not supportive of an infectious etiology. The only common factor for all affected horses seemed to be feeding big bale silage or, occasionally, hay of poor microbiologic quality. Forty of the 75 horses were euthanized. Histopathologic examination of peripheral nervous tissue was performed in 22 horses, all of which had neuronal fiber degeneration. The majority of horses with mild signs recovered after 5–6 months of rest.

Conclusions and Clinical Importance: Clinical signs correlated with polyneuropathy involving sciatic nerves.

Key words: Equine; Knuckling; Mycotoxins; Neuronal fiber degeneration; Silage.

The pathophysiology of most neuropathies, other than those of traumatic origin, is poorly understood, but axonal degeneration is the main histopathologic finding regardless of etiology. There are few reports describing symmetrical digital extensor weakness as a singular sign of peripheral axonal degeneration in the horse. Furutaka et al. described 3 cases of bilateral peripheral axonal degeneration in horses with knuckling. In addition, axonal degeneration was reported in 2 horses with extensor weakness in Sweden. Since 1995, a number of horses and ponies exhibiting signs of bilateral digital extensor weakness, mainly in the hindlimbs, have been observed in Norway. The severity of neurologic deficits varied from subtle gait abnormalities, such as knuckling of the fetlocks of the pelvic limbs, to paraplegia. To our knowledge, no previously described syndrome fits the clustering of polyneuropathy cases observed. In this report, we describe the clinical findings, necropsy findings, and some epidemiological observations in 75 horses in Norway with bilateral extensor weakness.

Material and Methods

From June 1995 to August 2004, 11 horses with bilateral digital extensor weakness were referred to The Norwegian School of Veterinary Science (NSVS). Eight of these horses were euthanized and necropsy was performed. In addition, medical records from ambulatory veterinarians of 64 horses with clinical signs of bilateral digital extensor weakness were reviewed. Thirty-two of these horses were euthanized, 4 of which were necropsied at the NSVS. In another 10 horses, the examination was restricted to nervous system tissue submitted to the NSVS by ambulatory or abattoir veterinarians.

The age, breed, and sex distribution of the horses is presented in Table 1. Follow-up clinical observations of the survivors by owners or ambulatory veterinarians were obtained on one or more occasions in each case, ranging from 4 months to 9 years after the syndrome was first observed.

Case Selection and Classification of Clinical Signs

The horses included in this study had knuckling of the fetlocks of the pelvic limbs, with no apparent ataxia or flexor weakness. Weight bearing was possible while the digits were extended, but with knuckling, weight was supported on the dorsal surface of the foot (Fig 1). The more severely affected horses became paraplegic and recumbent. The syndrome was consistent with sciatic or peroneal nerve disease. The paraplegic horses may also have had a component of femoral nerve involvement.

A semiquantitative grading system was established in order to rate the severity of clinical signs:

- Grade I: Intermittent knuckling of 1 or both hindlimb fetlocks when exercised or stressed that was corrected immediately.
- Grade II: Knuckling of 1 or both hindlimbs when exercised or stressed that remained in the abnormal position > 3 seconds.
- Grade III: Knuckling of both hindlimbs when stressed, unable to run, or collapse of the pelvic limbs while attempting to run.
- Grade IV: Paraplegia and recumbency.

Clinical Examination of Referred Cases

Neurologic examination was performed in addition to a full general physical examination on all 11 horses. The neurologic examination included assessment of mental attitude and posture,
cranial nerve function and cervical and cervicofacial reflexes, sensory perception to pricking of the skin, and proprioception of the limbs. Gait evaluation was performed in all but the 4 recumbent horses, at walking and trotting in a straight line as well as on a lunge, stopping from a trot, and during backing up. In the 64 horses not referred to the NSVS, medical records were reviewed.

**Laboratory Analysis**

CBC and serum biochemistry findings, including proteins, fibrinogen, aspartate aminotransferase (AST), creatine kinase (CK), urea, creatinine, glucose, and calcium (Ca$^{2+}$), were assessed in all 11 horses referred to the hospital and in 16 of the horses seen by ambulatory veterinarians. Plasma vitamin E ($\alpha$-tocopherol) concentrations were assessed by high-pressure liquid chromatography (HPLC) and blood selenium by hydride generation atomic absorption spectrometry with sodium borohydride in 23 cases. Equine herpes virus 1 (EHV-1) antibody titers were determined by complement fixation in 15 cases. Cerebrospinal fluid (CSF) was collected from the atlanto-occipital site in 1 and from the lumbosacral site in 3 of the referred horses. The fluid was analyzed using an automated chemistry analyzer for protein and glucose concentrations as well as cytological examination.

Mouse inoculation was used for detection of Clostridium botulinum toxin in serum from 1 horse.

**Mycologic Examination of Roughage**

Four samples of hay and 5 samples of silage from 9 affected stables were submitted for mycological examination. The methods used were those described previously by Skaar and Stenwig. Briefly, dilutions of the samples were inoculated on the surface of duplicates of Malt/Yeast Extract Sucrose Agar, and incubated in plastic bags for 7 days at 25°C in a normal atmosphere before inspection and counting. The mold counts are referred to as colony-forming units (CFU) per gram sample wet weight calculated as weighted average from the plate counts.

**Pathologic Examination**

Necropsy was performed at the NSVS on 12 of the horses. Peripheral nerve tissues were available for histopathologic examination from another 10 horses. This material was fixed in 10% phosphate-buffered formalin immediately after collection. Sections of nervous tissue were examined from both the lumbar intumescence of the spinal cord and branches of the sciatic nerves in 19 horses. In 1 horse, material was available only from the spinal cord and in 2 horses only from the sciatic nerve. The number of specimens collected from the sciatic branches was /C2$^2$/4 in 12 horses. The histologic examination also included the brain in 7 horses and the brachial plexus in 5. For control purposes, samples from the spinal cord and peripheral nerves were collected from 5 horses without gait deficits.

The formalin-fixed specimens were embedded in paraffin and 3µm sections were stained with hematoxylin and eosin (HE). Selected sections from the spinal cord and peripheral nerves were also stained with van Gieson, Luxol fast blue, and the Bodian method.

**Statistical Methods**

In 1 affected stable, a univariate statistical analysis to detect any association among the continuous variable age (t-test), the categorical variable sex (chi-square test), and disease was performed. Statistical evaluation was not possible on the other premises because information on the nondiseased horses was too scant.

**Results**

**Clinical and Laboratory Findings**

All animals were bright, alert, and responsive, with normal appetite. Heart rate and temperature were within normal limits. Grading of the clinical signs was carried out retrospectively on the basis of the medical records. The severity of hindlimb digital extensor weakness varied from grade I to grade IV, some horses never deteriorating beyond the lower grades. Four horses developed grade IV signs within hours of onset whereas others progressed from grade I to grade IV slowly over weeks. Diffuse muscle atrophy of the hindquarters was observed in 1 horse with prolonged grade 1 clinical signs. Signs of cranial nerve dysfunction were not observed in any of the horses.

![Fig 1. Horse with bilateral digital extensor weakness.](image-url)
Proprioception of the hindlimbs varied, but in most horses tolerance of unusual hind-limb positions, circum-
duption, or divergence from normal limb movements
while backing or stopping was observed. Sensory perception
of skin pricking was assessed as decreased distal to
the hock in some horses.

CBC and biochemical test results were within normal
limits, with the exception of increased activity
of AST and CK in the recumbent horses. Plasma vitamin E concentrations were within the reference range
(>1.0 μg/mL). Two of 23 horses had selenium concentrations below the reference range (<0.05 μg/g)
and another 8 had borderline low concentrations
(0.05–1.0 μg/g). Antibody titers for EHV-1 were deter-
mained in 15 horses, 14 of which were negative.

Glucose and protein concentrations as well as cytolog-
ical evaluation were within normal limits in all 4 samples
of CSF. No C. botulinum toxin was detected in serum
from the 1 horse tested. Mycological examination of the
feed samples revealed that 7 of 9 samples contained
counts regarded as high (>1.6 × 10⁵ CFU/g), varying
between 1.6 × 10⁵ and 2.4 × 10⁶ CFU/g, and dominated
by toxigenic storage fungi in the genera Aspergillus and
Penicillium.

**Outcome**

Forty of the 75 horses were euthanized because of
hindlimb digital extensor weakness. Thirty-three of these
horses were recumbent (grade IV), whereas 5 were
classified as grade III. In addition, 1 horse with grade I
and another with grade II signs were subjected to euthanasia.
Both had exhibited clinical signs for more than 2 months
without improvement. The period from 1st observation of
clinical signs to euthanasia varied from 1 day to 3
months. Follow-up information was available in all 35
surviving horses. Four horses were classified as grade III,
16 were grade I, and 15 were grade II. Two of the grade
III horses had improved to grade I after 4 months, but
then were lost to follow-up. The remaining horses all re-
gained normal gait after 5–6 months of rest. A full
neurologic examination was not performed in any of the
horses.

**Pathologic Findings**

Pathologic abnormalities were restricted to the ner-
vous system. All histologic examinations of sciatic nerve
branches indicated areas of thick, irregular swollen axons
in the longitudinal sections of the nerve bundles. The
myelin sheath contained large vacuoles and occasionally myelin figures or granular material were observed. In
some areas, the nerve bundles were infiltrated by occasional
numbers of macrophages (Fig 2). In 8 horses, a moderate
increase of fibrous tissue was observed within these bun-
dles (Fig 3). All of these horses had displayed clinical
signs for >1 month. Swollen axons and large vacuoles
could also be observed in longitudinal sections of the
lumbar intumescence of the spinal cord, although the
lesions were more moderate than those seen in the
peripheral nerves of the hindlimbs. In the limited materi-

![Fig 2. Myelin sheath containing numerous macrophages (vertical arrow) and some large vacuoles with myelin bodies and other debris (horizontal arrows). HE, × 20.](image)

Epidemiologic Aspects

The horses were located in 27 different premises and
distributed all over Norway. No obvious climatic or re-
gional associations seemed to be present. New cases
occurred every year during the study period. Initial clin-
ical signs occurred during late winter and spring in all but
2 cases.

Twenty-five of the 27 stables fed silage. A total of 10
cases were recorded in the 2 stables where only hay was
used as roughage. In both places, the hay was of poor
microbiologic quality.

Digital extensor weakness tended to occur in several,
but not all, horses at each location. The uniformity of
clinical signs and histopathologic findings was compat-
ible with a disease in the peripheral nervous system. No

![Fig 3. Numerous fibrocyte nuclei and diffuse occurrence of collagenous fibrils (horizontal arrow). Remnants of myelin sheaths containing macrophage and remnants of axon material (arrow heads). Van Gieson, × 20.](image)
association was detected between disease and age and disease and sex.

**Case Example 1.** A stable in western Norway kept 18 Icelandic horses on big bale silage. On March 1, 2001, a 5-year-old mare was found recumbent with hindlimb paraparesis. The severity of clinical signs fluctuated unpredictably between grade I and grade IV, until the horse finally was unable to stand even with the help of slings and was euthanized on April 23. On March 9, a 2nd horse showed signs of digital extensor weakness in the hindlimbs. Fifteen of the 18 horses became affected over the next 2 months, 6 of the 15 becoming recumbent and necessitating euthanasia. The time from first clinical signs until euthanasia ranged from 1 to 54 days. The age range of the affected animals was 1–13 years (median 3 years). There were 7 males and 8 females, 2 of which were pregnant.

Samples from the lumbar intumescence of the spinal cord and branches of the sciatic nerve from 2 of the euthanized horses were submitted for histopathology. Neuronal fiber degeneration was confirmed in both cases. Mild changes were also observed in the submitted spinal cord. All survivors recovered completely after approximately 5 months of rest. Vitamin E and selenium supplements were administered PO once a week from March 10. Most of the affected horses were treated initially with nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and B vitamins, but nothing seemed to influence the course of the disease. The silage was removed and all horses were turned out on pasture from the beginning of May. One horse on the farm received hay instead of silage. This horse exhibited none of the described clinical signs.

**Case Example 2.** Two farms in northern Norway housed 7 horses each. Stable 1 fed only hay whereas Stable 2 fed both silage and hay from the same hay producer as Stable 1. In March 2002, 5 horses were moved from Stable 2; 3 were moved to Stable 1 and 2 were moved to Stable 3 more than 1000 km away (Fig 4). One month later, digital hindlimb weakness grade I was observed in 2 of the horses from Stable 1. During May and June, 9 of the 14 horses developed clinical signs of digital extensor weakness in the hindlimbs; 5 of these horses deteriorated from grade I to grade IV, necessitating euthanasia. In Stable 1, 6 of the horses became affected, 1 of which was initially from Stable 2. One of the 2 remaining horses in Stable 2 became affected. Both of the horses that were moved to Stable 3 developed grade I clinical signs, but none of the other horses in the new stable showed any signs of disease. Some of the affected horses initially received acupuncture and NSAIDs, and neither treatment improved the condition. A new lot of hay and pasture was provided during the summer. All horses with only mild hindlimb weakness recovered after 5–6 months of rest.

Samples from the lumbar intumescence of the spinal cord and the branches of the sciatic nerve from 3 of the euthanized horses showed evidence of neuronal fiber degeneration. Microbiological examination of the hay revealed high mold counts dominated by toxigenic storage fungi, especially *Aspergillus*, and the hay was characterized as not suitable as horse feed.

### Discussion

The clinical signs of the horses of the present report are consistent with symmetrical digital extensor weakness.
The results of the study indicate that a polyneuropathy was the cause of the syndrome and the etiology seemed to be related to environmental factors, possibly dietary. The branches of the sciatic nerves showed neuronal fiber degeneration in all the horses examined, and it is reasonable to assume that the pathologic changes were related to the clinical signs.

Symmetrical distal neuropathy in horses is uncommon and there are few reports on the condition. Gustafsson and Roneus\(^2\) reported 20 cases of horses in Sweden with clinical signs similar to those described in the current study, but were not able to draw any conclusions from the histopathologic examination. Furuoka et al\(^3\) described 3 cases of peripheral neuropathy associated with neurogenic muscular atrophy. All were light breed horses < 14 months of age. The clinical signs, described as knuckling, were most prominent in the forelimbs. The cause of the disease was not determined, but similarities to neurotoxic lesions as well as genetic factors were discussed.

In the present study, there was no apparent age or sex predilection. Forty-two of the 75 horses were of Icelandic breed. Although they represented 56% of the cases, they were located in only 8 of the 27 different premises. The high number therefore may reflect the fact that Icelandic horses are often kept in larger herds, unlike riding stables, where different breeds are kept. With few exceptions, all of the affected horses were kept for pleasure or breeding purposes, and often group feeding of big bale silage was practiced. These horses are more likely to receive a variable-quality diet compared with sporting or performance horses, which may support our hypothesis of a possible dietary factor in the pathogenesis.

The cause of the clinical signs and nerve fiber degeneration described in the present report is currently unknown. Vitamin E and selenium deficiency was initially suspected, as some horses had low plasma selenium concentrations. Forage of Norwegian origin can be extremely low in selenium\(^8\) and 1 survey indicated that vitamin E concentrations in big bale silage are significantly lower than in silage from silotanks.\(^9\) However, the clinical signs and pathological findings in the present cases differ from conditions associated with vitamin E and selenium deficiency. Clinical signs of EHV-1 myeloencephalopathy may include hindlimb weakness and ataxia.\(^10,11\) All but 1 of the 15 horses tested for EHV-1 were sero-negative.

CBC, histopathologic, and CSF examinations were not indicative of ongoing infectious disease. Case example 2 depicts horses that developed clinical signs after moving to new premises, but none of their new stablemates became affected. Epidemiologically, infectious disease does not seem to be a probable cause of this syndrome.

The histopathologic examinations of the horses have shortcomings in that only the sciatic nerves and the proximal parts of the tibial and peroneal nerves were examined. In the future, it will be necessary to sample the distal parts of these nerves as well as other hindlimb nerves to evaluate the extent of peripheral nerve involvement. Nerve conduction studies and needle electromyography may also provide additional useful information. More sophisticated histological examinations, for example, nerve fiber teasing and electron microscopy on plastic-embedded 1 μm thick sections, would be valuable to distinguish between primary myelin or axonal involvement. Regardless of origin, whether a primary myelinopathy, axonopathy, or mixed polyneuropathy, it is characteristic for clinical signs of neuropathy to appear first in the distal parts of the extremities in that the larger, longer myelinated fibers are more susceptible.\(^12,13\) Clinical signs in the present cases and histopathologic examination strongly indicate that the nerves of the hindlimbs were most severely affected. In our material, both myelin and axons were affected, although the lesions were more conspicuous in the axons. Myelinopathy occurs as a result of either pathologic insult to the Schwann cell or damage to the myelin itself and can be either inherited or acquired.\(^14,15\) Acquired changes may be induced by toxins, such as lead and diphtheria, or may be immune-mediated.\(^15\) Secondary axonal involvement may occur, possibly as a result of a severe inflammatory process.\(^14\) In horses, polyneuritis equi is thought to be an example of primary myelinopathy attributable to circulating antibodies to P2 myelin protein.\(^16\)

Distal axonopathy with axonal degeneration is the most common of the generalized axonal neuropathies.\(^14\) Secondary demyelination usually accompanies these findings.\(^17\) Exposure to a variety of agricultural, industrial, and pharmaceutical chemicals may result in nerve lesions classified as a distal axonopathy.\(^14,18\) Experiments with acrylamide, considered to be prototypical among chemicals that produce distal axonopathy, have shown that the severity of clinical signs is both dosage- and timedependent.\(^19,20\) The work of LoPachin et al\(^18\) suggests that classically defined axonopathy is expressed only during subchronic, low-dose exposure. It is characteristic for clinical signs of toxic neuropathies to diminish and resolve when the toxin is removed.\(^12\) The variety of clinical presentations in the present cases, from mild knuckling to recumbency, could therefore be explained by a dose-dependent toxic insult. All grade IV and 5 of the grade III horses were euthanized, because of either animal welfare considerations or the owner’s unwillingness to continue with treatment. Both the 2 euthanized horses with low-grade signs had clinical signs for more than 2 months without improvement and euthanasia was performed at the owner’s request. Some of the affected horses potentially could have improved given more time. All the remaining grade I and II horses appeared to have recovered, which might be because of nerve fiber regeneration after removal of the toxin. All these horses stayed on the same premises during the 1st months of recovery. It has not been possible to identify changes in management in the recovery period other than change of roughage. No explanation for why some horses deteriorated whereas others stabilized or improved was found, but 2 owners reported that the horses that were more selective in their feed preference had fewer or no clinical signs of disease. There was no history of recent drug administration connecting the various cases.
Geographically, the cases were spread over 2000 km, which makes a common environmental toxin less likely. The only common factor identified was feeding of silage or hay of poor microbiologic quality. Consequently, botulism was considered, but the clinical histories and histopathologic findings made this diagnosis unlikely.

Australian stringhalt is a poorly understood disease of horses classified as a distal axonopathy for which epidemiologic data strongly suggest a feed-related etiology. Similar to our cases, the disease appears in clusters, there is a seasonal pattern, and affected horses may recover spontaneously. The clinical presentation differs from the present cases, but less characteristic cases with knuckling of the forelimb or hindlimb fetlocks or both or hypermetria concurrent with hindlimb hyperflexion have been described and categorized as atypical stringhalt by Huntington et al. The pathophysiology of stringhalt is poorly understood, but normal movements of the hindlimbs depend on complex nerve-muscle arcs that theoretically could result in stringhalt movement if damaged. Damage to these reflex arcs could result in predominantly hypoflexion and paraparesis as seen in our horses. Mycotoxins or ingestion of toxic plants may induce Australian stringhalt, which typically appears in horses grazed on poor-quality pasture. Few of our horses had access to pasture and all had concurrently been fed roughage.

Poorly preserved silage may provide conditions favorable for the growth of storage fungi and production of mycotoxins. Ingestion of Penicillium mycotoxins may cause clinical signs similar to grass stagger in ruminants. With 2 exceptions, all cases occurred between January and June, with a peak in March and April. Consequently, the roughage used had been stored during the winter, but it was not possible to obtain adequate information regarding preparation and handling of the forage. Seven of 9 samples examined had high fungal counts. The molds most frequently isolated from grass silage in Norway are Penicillium roqueforti, Aspergillus fumigatus, Rhiizopus stolonifer, Mucor circinelloides, A. flavus, Geotrichum candidum, and Byssochlamys nivea. Some of these may produce neurotoxic mycotoxins such as penitrem, verruculogen, furinotremorines, cyclopiazonic acid, 3-nitropropionic acid, and roquefortin C. Several intoxications related to moldy feed are reported in animals. The neurologic signs induced by these mycotoxins mainly are shivering, tremors, or paralysis and do not correspond with the signs observed in our horses. However, because several nervous system disorders may be caused by unknown mycotoxins it cannot be ruled out. The understanding of the potentially additive or synergistic effects of multiple toxins in a matrix is poor and knowledge of mycotoxicoses in the horse remains scant.

The cause or causes of this syndrome remain unknown, but it is reasonable to assume that a neurotoxic insult may be involved in the etiology. Feeding roughage of poor microbiologic quality appeared to be the only common factor connecting the cases in the current study and a feed-related toxic insult is the most likely cause. Further investigation of this connection is warranted and will be an important challenge in the future in order to give horse owners advice as to the safety of feeding silage.

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Footnotes

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References


**Supplementary Material**

The following supplementary material is available for this article online:

**Video 1.** Horse with grade II distal limb extensor weakness apparent in forward and reverse motions as well as during standing. One episode of bilateral knuckling is shown. Mild hind-limb ataxia and circumduction is also evident during turning.

This material is available as part of the online article from: http://www.blackwell-synergy.com/doi/abs/10.1111/j.1939-1676.2007.0023 (This link will take you to the article abstract).

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