Long-term follow-up of Norwegian horses affected with acquired equine polyneuropathy.

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Ethical animal research

Owners gave informed consent for their horses' inclusion in the study.

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Summary

Background: Acquired equine polyneuropathy, a neurologic disease clinically characterised by knuckling of metatarsophalangeal joints, has been described in numerous Nordic horses during the last 20 years. Although clinical recovery has been reported, large-scale data on long-term follow-up of survivors has been lacking.

Objectives: To describe long-term survival of acquired equine polyneuropathy affected horses registered in Norway, with a focus on athletic performance and possible residual clinical signs connected to the disease.

Study design: A retrospective cohort study.

Methods: The study includes 143 horses recorded with acquired equine polyneuropathy in Norway from 2000-2012, with the follow-up period continuing until 2015. Participating owners of survivors completed a standardized questionnaire, providing information on disease and convalescence, management, performance-level and possible residual clinical signs. To investigate the follow-up of survivors, we performed 2 multivariable linear regression models.

Results: The follow-up time of survivors was of 1.0 to 14.5 years (median 5.3, IQR 2.5-7.2). Fifty-seven horses survived and all but 3 horses returned to previous or higher level of performance. However, possible disease-related residual clinical signs were reported in 14/57 horses. Forty-nine of the survivors were in athletic use at time of contact. The majority of survivors were categorized with low severity-grades at time of diagnosis and the initial grade was significantly associated with time to resumed training. Only 3 horses had experienced relapse/new attack during the follow-up period.

Main limitation: Athletic performance was judged by owners, which renders a possible source of bias.

Conclusions: Although acquired equine polyneuropathy is a potential fatal disease, most survivors will recover and return to minimum previous level of athletic performance. Some horses display residual clinical signs, but often without negative effect on performance and relapse of disease is rare.

Introduction

Acquired equine polyneuropathy (AEP), formerly also known as Scandinavian knuckling syndrome, is a neurological disease seen in Norway, Sweden and Finland [1-3]. The first observations of this clinically uniform neuromuscular syndrome were made in Norway in 1995 [1]. Since then, more than 400 new cases have been identified in Scandinavia. Clinical signs are characteristic, with knuckling in the fetlock joints, mainly of the pelvic limbs (Fig 1). The horses are otherwise bright, alert and responsive. No predilection of breed, age, sex or use has been reported [3]. Extensive studies have so far failed to identify the aetiology of the disease [1; 3; 4]. However, there is a seasonal pattern as most cases appear during winter and spring [5]. Moreover, most affected horses have been fed wrapped forage, suggesting an environmental, possibly feed-related trigger. Although previous studies have concluded that there is no indication of an infectious aetiology, AEP often affects more than only one horse at the farm [1; 3].

The severity of clinical signs varies from intermittent knuckling, often worsened by stress, to recumbency. The disease course is unpredictable. Many horses recover after months of rest, some however become recumbent and a few continue to knuckle over time. Most recumbent cases are euthanized and fatality rates have varied from 29-53% [1; 3]. Although horses that remain able to rise up and stand with or without support, seem to recover, one study reported intermittent knuckling up to 17 months after onset of disease [3]. Histopathological examination of peripheral nerves from horses euthanized due to AEP has revealed large fibre predominant neuropathy with conspicuous inclusion body schwannopathy and demyelinating inflammation [2; 6] supporting ubiquitous histopathological features.

Although previous reports indicate that many AEP affected horses recover [1; 3], there is a lack of large scale follow-up studies of survivors and objective long-term survival data. The only treatment recommendation is to rest for months or even years, and the lack of knowledge of the disease`s time-course and outcome is frustrating for owners. There is a need for more information on the prognosis and athletic expectations of horses affected with this relatively new disease. The objectives of this study were to describe long-term survival of AEP affected horses in Norway, primarily focusing on athletic performance and possible residual clinical signs connected to the disease.

Materials and methods.

Study population

Since the recognition of a new neuromuscular disease in Norway in the end of the1990`s, information on the disease has been channelled through different media. This has been directed towards veterinarians and horse-owners, and has encouraged them to report AEP cases to Equine Clinic, Norwegian University of Life Science (NMBU). From year 2000 to 2012, a total of 254 clinically confirmed cases of AEP were recorded in Norway. Of these, 88 (35%) were euthanized within 6 months due to severe and/or persistent disease signs. From the initial 254 registered horses, the current retrospective cohort study involved a subpopulation of 143 affected horses where detailed information was available, a thorough work-up had been performed and owners were available and willing to participate (Fig 2, Supplementary Item 1). Although long-term follow-up of survivors was the main aim of the study, data on non-survivors were included when this served as useful background information. The follow-up period was from January 2000 to July 2015. Eighty of the present cases (80/143) have been included in previous reports on the disease [1; 3; 6]. The majority of the included cases had been examined by at least one of the authors (SHO, CFI, KHJ). In the remaining cases, data were collected from veterinary medical records and through interviews with owners and/or veterinarians performed by e-mail or telephone on at least one occasion. Videos were reviewed when available.

Collection of data

Inclusion criteria for AEP cases have previously been described [1; 3]. In short, these were a history of repeated bilateral pelvic limb fetlock knuckling with otherwise normal behaviour, appetite and clinical parameters. Inclusion criteria for plausible cases, were acute recumbency with no obvious other cause, and identification during or up to 2 months prior to the first definitive case in an outbreak. Horses with ataxia, signs of brain disease or general systemic illness were excluded from the study. A previously established semi-quantitative grading system [1] was used to rate the severity of clinical signs (Table 1). Horses which were not euthanized because of the disease were categorized as survivors and retrospectively graded by one of the authors (SHO) based on clinical signs at time of

diagnosis. Non-survivors were graded retrospectively at the time of diagnosis and then again at time of euthanasia.

Follow-up data collection

The follow-up time was calculated from the time of diagnosis until the last time-point of contact with owner. For non-survivors, this coincided with the time of death. In the time period of 2014-2015, survivors were followed via standardized questionnaires that the owners completed, and then reported either by e-mail or through telephone interviews (see supplementary information for translated version). Ten of the survivors visited the Equine Clinic NMBU for reasons unrelated to AEP on one or more occasions after diagnosis of AEP and neurological examinations were repeated by one of the authors. Background information obtained from records from time of diagnosis included age, sex, breed, use, type of forage fed, other affected horses at farm, severity grade and time from diagnosis to last observed knuckling (disease duration). This information was compared to current data collection that also included: management during the first 6 months after diagnosis, when and how training was resumed, athletic performance-level compared to before the illness and comments on possible residual clinical signs connected to the disease. The questionnaires requested exact dates on several of the events. When the owners responded with imprecise information, they were asked to identify the month of event. Young horses not yet in training and broodmares were defined as non-athletes.

Data analysis

Data handling and statistical analyses were performed in Stata (Stata SE/11, Stata Corp., College Station, TX, USA), and characteristics of survivors and non-survivors were compared by using simple logistic regression. Two continuous outcomes were used to study the follow-up of horses that survived AEP; a) disease duration (squared) and b) time from diagnosis until resumed training (log transformed). Transformations were performed to fit the assumptions of normality. Potential explanatory variables tested in the multivariable linear regression models were age, breed, use, type of forage fed and severity-grade at time of diagnosis. Descriptive statistics of these variables and their associations between outcome and explanatory variables were performed using both scatterplots and smoothed line

plots in STATA. When building the models, a forward stepwise technique was used according to the methods described by Dohoo et al [7]. Explanatory variables with a univariable Wald P-value <0.20 were considered in the regression models. Distortion and confounding could then be observed as each variable was included and confounding variables were tested by running the model with and without that variable. When distortions were detected, 2-way interactions were tested. Correlation between explanatory variables was tested by using the variance inflation factor (VIF) and dealt with if present. Influential data-points were evaluated and data was only excluded and reported on when the observation reduced the models` validity. Normality probability plots for the standardized residuals were evaluated for each model. In all analyses, statistical significance was considered with a P-value $\leq$0.05. The final model had the highest R^2 and thereby minimizing the mean square error. When only one explanatory variable was found to be significantly associated with the outcome, model results were reported in box-plots rather than tables. A Kaplan-Meier plot was used to show the graphical association between severity-grade at time of diagnosis and time to death due to AEP.

The field data relied on information from owners. Horses with missing data were excluded when these explanatory variables were tested in regression analyses. However, the final models did not exclude any horses.

Results

The included cases comprised of a number of different breeds and uses, with no sex predilection, (Supplementary Item 1). Median age for both survivors and non-survivors were 6.0 years. For survivors, IQR was 3-8.5 (range 1-22, one missing), for non-survivors IQR was 3-9 (range 1-19, 16 missing). None of the affected horses were stabled alone. Forty-eight (84.2 %) of the survivors and 65 (75.6 %) of non-survivors were stabled with other AEP affected horses.

Survivors

Fifty-seven horses (40%) were classified as survivors. Ten of these were euthanized due to unrelated reasons during the follow-up period. The survivors were followed from 1.0 to 14.5 years (median 5.3, IQR 2.5-7.2) (Fig 3).

Disease period

Median disease duration was 4.9 months (IQR 2.9-6.0), but varied greatly on a range from 1 day until 2.4 years (Fig 3). Severity grades of clinical signs at the time of diagnosis were low in most surviving cases, and only 7.0% (n=4) and 3.5% (n=2) were grade III and IV, respectively (Fig 4). Being grade II at the time of diagnosis was associated with a significantly longer disease duration than grade I ($P<0.01$) (Fig 5). No significant association was observed between disease duration and explanatory variables such as sex, breed, age or use.

Most horses were box rested or kept in small paddocks for weeks or months until the knuckling ceased. Forty-four (77.2 %) horses were turned out on pasture or restricted grass areas when the clinical signs subsided. While most owners reported improvements, particularly in behaviour, one horse experienced worsening clinical signs. The owners frequently reported stressors such as being left alone and running on pasture or trailer rides, as provoking knuckling in the convalescence period. Most owners began training with short sessions of walking, lunging or long-reining before riding/driving.

Athletic performance after disease

All but one of the 57 survivors (Supplementary Item 2, No 11) were used in the discipline that their owners intended after disease. Forty of the survivors (70%) were in some kind of athletic training before disease. Of these, all 40 recovered and returned to training again, and all but 3 (Supplementary Item 2 No 12-14) returned to previous or higher performance-level. The median time from diagnosis until training resumed was 6.7 months (IQR 5.0-10.0) ranging from 2 to 20 months. Horses with grade II at time of diagnosis resumed training later than those with grade I ($P<0.002$) (Fig 5). The explanatory variables sex, age, breed and use were not significantly associated with time until training was resumed.

Seventeen horses (30%) were not in training when disease occurred, and 9 of these were young horses not yet in training. Two young horses were severely affected, where one was initially grade IV (Supplementary Item 2, No 11) and the other was grade III. The latter recovered after 5 months of rest and was broken to ride as planned, 2 years later. The remaining young horses were all low grades (I-

II). Six of them were broken to ride/drive, while one went into breeding, as planned. The performance of all was judged satisfactorily by their owners. Eight of the horses that were not in training prior to disease were used for breeding, one of which was a grade IV pregnant Shetland pony that was recumbent and periodically held up by slings for 2 months. She gave birth to a healthy foal 3.5 months after diagnosis and returned to breeding and light training without remaining clinical signs. One other broodmare was broken to ride after surviving the disease, while 6 continued as breeding horses. All were considered fully recovered.

By the time the questionnaire was presented to the owners, 11 of the 57 survivors (19%) were competing at low to moderate level in dressage or show-jumping. Seven competed at a higher level, 2 at the same and 2 at a lower level (Supplementary Item 2, No 12, 13). All 4 endurance-horses were competing at 80-160 km level. One of these was grade III initially, recovered within 5 months and returned to competition within a year. Three horses were trotters in active training, participating in 43 to 80 races over 3 or more years after the disease. All 3 were winning races and performed as expected or better according to owners/trainers.

Residual clinical signs

Fourteen of the surviving horses (24.6%) had either permanent, temporary and/or intermittent residual clinical signs that their owners associated with the disease (Supplementary Item 2). Although performances were judged to be satisfactorily, intermittent knuckling, stumbling or hindquarter weakness were present in 4 horses (Supplementary Item 2, No 2, 5, 6,10). One horse (No 7) appeared weak the first year after resumed training and another horse (No 1) had developed stringhalt after knuckling had ceased. Two horses (No 8, 9) had recovered fully after the initial illness and performed at the expected athletic level for 2 and 4 years respectively, before they started knuckling again. Both recovered after a period of rest and performed satisfactorily until euthanasia due to lameness (No 8) or end of follow-up period (No 9), which was 3 years after relapse for both. One case (No 9) was the only horse at the farm during the first round of disease, but part of a larger outbreak the second time. The other horse (No 8) was part of an outbreak the first time, but the only affected horse the second time.

In 3 horses (No 12-14), the owners reported residual clinical signs that had a negative impact on performance. While 2 of the horses were used for dressage, the third was used for pleasure. All 3 were affected with AEP in 2012. Another young quarterhorse (No 11), which was 1 of 2 surviving grade IV horses, appeared still weak in the hindquarters and short strided in all 4 limbs with moderate contracted tendons at the end of study-period, and had not been broken to ride. One horse (No 12) had been back in normal dressage training for 1 year before she started to knuckle again after an intense training-session. After a month on pasture, training was resumed, but at a lower level. This horse was the only affected horse at the farm both times.

Four owners reported that their horses had started knuckling again when training was resumed 2 to 3 months after the last observation of clinical signs. All recovered after extended rest, but 2 of them relapsed or suffered from a new attack (No 9, 12).

Non-survivors

Eighty-six (60%) of the horses from the study-population of 143 were euthanized during the follow-up period due to severe or non-resolving clinical signs of AEP. None of these horses were able to resume training because of knuckling. The median time from diagnosis to euthanasia was 24.5 days (IQR 6.5-61, n=84, 2 missing), on a range from 1 day to 22 months. Within 6 months, 96.4% (n=81) were euthanized (Fig 6). Simple logistic regression showed that severity grades at the time of diagnosis were significantly ($P<0.001$) higher in non-survivors compared to survivors (Fig 4). There was no significant difference in age, sex, breed or use when comparing survivors with non-survivors. In 13 non-survivors (15.1%) the initial grades were missing. At time of euthanasia, 82.1% (n=69) of the horses were recumbent, and pre-euthanasia grades were missing in 2 horses. Of the 9 lower-grades (I-II) non-survivors, 3 were euthanized due to additional problems with lameness or ill-thrift 2 to 3 months after diagnosed with AEP. Three grade II horses were euthanized after 2 to 5 months. The remaining 3 horses were euthanized 10, 12 and 22 months respectively after diagnosis. All 3 were low-grades initially and had periods without observed knuckling, but relapsed as soon as training was attempted.

Discussion

Among Norway`s approximately 125 000 horses [8], AEP is the most common equine polyneuropathy, although the 254 registered cases in a 12 years` period do not constitute a high number. Within 6 months from diagnosis, 35% of the diseased horses were euthanized, which illustrates the seriousness of the disease. On the other hand, in accordance with previous reports [1; 3], this study confirms that most horses that survive the disease will recover. In addition, we found that the majority of the horses return to athletic use and are able to perform at the same or higher level as prior to disease.

The horses` athletic performance was judged by the owners, an important limitation of the study. Many of the included surviving horses were categorized as pleasure horses and athletic level of exercise might be too low to pick up mild remaining clinical signs of disease. However, 11 (19%) of the surviving horses were competing in dressage and/or show-jumping, indicating that they are under regular physical training. It is unlikely that a knuckling horse would go unnoticed by trainers or at competitions. The surviving group included 4 endurance-horses competing at national or international level and 3 trotters in active training, disciplines involving the most strenuous exercise. All of these horses performed at or above the owners' expected levels, without any remarks on residual neuromuscular signs from their owners.

Although almost one quarter of the respondents reported residual clinical signs that were possibly connected to the disease, only the minority believed that it affected the horses` performance-level. The most common comments were remaining weakness of the hindquarters and stumbling or infrequent knuckling. Most of the horses with such comments suffered from AEP in 2012, and therefore had the shortest follow-up time and could theoretically still be in recovery. Many owners of horses documented with AEP earlier in the study period commented on similar observations "for a long time" before the residual clinical signs eventually disappeared.

Interestingly, 2 of the horses developed stringhalt after the clinical signs of AEP had ceased. Australian stringhalt has previously been discussed in association with AEP [1; 2]. The disease has epidemiological similarities to AEP as it appears in clusters, and it has a seasonal pattern with strong association to feed and most horses will get better with time [9-11]. However, in spite of the similarities, the characteristic clinical signs in the diseases are strikingly different. The

pathophysiology of stringhalt is poorly understood, and it is unclear why the profound distal axonopathy found in Australian stringhalt cases [12; 13] results in hyperflexion rather than paresis. Stringhalt has not been observed during the knuckling-phase of AEP and it is possible that the current 2 cases represent sporadic stringhalt unconnected to AEP.

Almost 90% of the survivors were ranked at lower grades, which probably reflects stronger motivation for investing time and money in horses that are perceived as more likely to recover. However, all grade III horses recovered, and 2 did so within 5 months, the median disease duration for all survivors. Although the 2 other grade III horses had residual clinical signs (Supplementary Item 2, No 10, 14), only one of these preformed at a level which was lower than expected. Both of these cases suffered from AEP in 2012 and may therefore still be in recovery.

More than 80% of the non-survivors were grade IV by the time of euthanasia. Maintaining a recumbent horse for a long period is challenging, and requires both a cooperative horse and dedicated owner, as seen in the 2 surviving grade IV cases in the current study. Pregnancy have many physiological effects that may affect the disease course, yet the pregnant pony still gave birth to a healthy foal and recovered completely. The remaining clinical signs seen in the young quarterhorse may have been a result of immobility over a long period while still in growth and not necessary directly connected to AEP. However, these exceptional cases illustrate that even the most severely affected horses may recover. This is supported by reports from Sweden, where 2 grade IV ponies recovered and 1 of these returned to a career as show-jumper [3](G. Gröndahl personal communication). That the initial severity-grade does not always predict the outcome is also shown by 3 horses in the current study, which were euthanized due to non-resolving clinical signs 10 to 22 months from disease onset. All initially had low grades (I and II), and although they had periods without observed knuckling, all relapsed as soon as training was attempted. It remains unclear whether these horses had reached a plateau or if improvement might have occurred after further rest. Of the 9 non-survivors graded I or II at time of euthanasia, in 3 cases the decision was influenced by additional health issues. Grade I and II AEP is not necessarily an animal welfare problem, but most horses are intended for athletic use and consequently financial constrains is presumably part of the owners' decision-making in the longstanding cases.

Three horses (No 8, 9, 12) were affected a second time after having shown no signs of knuckling during daily exercise for 1 to 4 years. Whether these cases represent a relapse or new attack remains unclear, but it indicates that although rare, former clinically overt disease does not protect from future attacks. In depth histopathological examination, including semithin histology, nerve fibre teasing and transmission electron microscopy, of various peripheral nerves from AEP horses have indicated a uniform picture of large fibre, demyelinating polyneuropathy with conspicuous schwannopathic features [2; 6]. Whether or not survivors that apparently have recovered and are clinically unaffected, still display these characteristic histopathological changes, remains to be proven. However, since this only occurred in 3 horses, this study suggests that relapse of disease is rare.

A limitation in the current study is the recruitment of cases, since the diagnosis is entirely based on clinical signs and reporting of possible cases depends on owners and/or veterinarians` cooperation and knowledge of the disease. Information on the disease was limited early in the study period and it is very likely that the number of cases was underreported. Diagnosis of mild cases can be challenging and therefore a strict selection was performed in this study to include only clinically definitive cases with a thorough history. Mild clinical signs in horses engaging in no or little athletic work can go unnoticed by owners, and was therefore probably underrepresented in this material. Although some misclassification of severity grades is unavoidable due to retrospective grading and subjective assessment, it is very unlikely that a low-grade horse will falsely be graded high grade or vice versa. This is supported by the results illustrated in Fig 5, showing an increase in disease duration and time to resumed training corresponding to severity-grade. The subpopulation of registered AEP horses in the current study is biased towards more non-survivors. Access to information is easier when the follow-up period is short and owners and veterinarians are more eager to establish contact in the most severe cases. This also reflects the relatively large amount of follow-up data that was lacking, which was mainly a result of an absence of updated owner contact information.

In conclusion, the majority of horses which survive AEP are able to perform at a satisfactory performance-level in the intended discipline after disease. Relapse is rare, but many horses show some clinical signs associated to the disease for prolonged periods. Convalescence time is lengthy in survivors and the fatality rate is high.

Figure legends:

Fig 1: Horse knuckling due to acquired equine polyneuropathy.

Fig 2. Flowchart of recorded clinically diagnosed acquired equine polyneuropathy (AEP) cases and study-population of a follow-up study in Norway 2000-2012. n=number of horses. * Includes 88 horses euthanized within 6 months from diagnosis due to severe and/or persistent clinical signs of AEP.

Fig 3: Follow-up until last time-point of contact with owners of 57 survivors of acquired equine polyneuropathy (AEP) in Norway. Three horses had clinical signs in 2 periods, and in 3 horses knuckling was only observed on one day. Arrows indicate Horses that were euthanized due to AEP unrelated reasons during study-period.

Fig 4: Severity grades (I-IV) at time of diagnosis of acquired equine polyneuropathy of survivors and non-survivors recorded in Norway 2000-2012. n=number of horses

Fig 5: Severity grades at time of diagnosis of survivors of acquired equine polyneuropathy recorded in Norway 2000-2012, compared to disease duration and median time (in months) to resumed training. In the figure to the right, only horses that were in training before disease are included, no grade IV horses were registered. Data are presented as median, 25^{th}-75^{th} percentiles (boxes) and min-max values (whiskers). Dots are individual outliers. n=number of horses

Fig 6: Kaplan-Meier plot showing the relationship between severity grade at time of diagnosis and survival time, in 70 horses with acquired equine polyneuropathy in Norway, 2000-2012. Only horses that were euthanized within 180 days and with initial severity grades recorded were included.

Table 1: Grading of the severity of clinical signs of acquired equine polyneuropathy.

Grade I:	Intermittent knuckling of one or both metatarsophalangeal joints when the horse was exercised or stressed, corrected immediately.
Grade II:	Knuckling of one or both metatarsophalangeal joints when exercised or stressed and remaining in that abnormal position >3 seconds.
Grade III:	Knuckling of both metatarsophalangeal joints when stressed, unable to run, or collapse of the pelvic limbs while attempting to run.
Grade IV:	Recumbency.

Supplementary Item 1: Demographics of acquired equine polyneuropathy (AEP) affected horses in Norway 2000-2012

Supplementary Item 2: Residual clinical signs recorded in 14 horses during follow up of acquired equine polyneuropathy affected horses in Norway 2000-2012

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