

Age over 25 years, but not plasma adrenocorticotrophic hormone concentration above the seasonally adjusted reference range is predictive for radiographically assessed changes of chronic laminitis in elderly horses

G. Christen¹, C. Precht², J.H. van der Kolk¹, N. Fouché^{1§}, V. Gerber^{1§}

¹Swiss Institute of Equine Medicine, University of Bern, and Agroscope; ²Department of Clinical Veterinary Medicine, Clinical Radiology, Vetsuisse Faculty, University of Bern

Höheres Alter (über 25 Jahre), nicht jedoch eine Adrenocorticotropin-Konzentration oberhalb des saisonalen Referenzbereichs ist prädiktiv für röntgenologisch diagnostizierte chronische Hufrehe bei älteren Pferden

Endokrinologische Veränderungen in Folge eines equinen Cushing Syndroms (ECS, PPID) sind die häufigste Ursache für Hufrehe bei älteren Pferden. Ziel dieser Studie war es, das Vorkommen röntgenologisch diagnostizierter, chronischer Hufrehe bei Pferden einer älteren Population zu ermitteln. Insgesamt wurden 51 Pferde untersucht. Innerhalb dieses Projektes sollte herausgefunden werden, ob Pferde einer höheren Altersgruppe, einer Gruppe mit Anzeichen von Adipositas (anhand des «body condition score», «cresty neck score») oder einer ACTH Konzentration oberhalb des saisonalen Referenzwertes ein höheres Risiko für chronische Hufrehe haben (Resultate werden als Odds-Ratio (OR) und Konfidenzintervall (KI) angegeben). Nach Einteilung der Pferde in zwei Gruppen aufgrund des Alters stellte sich ein signifikanter Zusammenhang heraus, wobei die Tiere der älteren Gruppe (26–32 Jahre) ein erhöhtes Risiko für radiologische Anzeichen chronischer Hufrehe hatten im Vergleich zur jüngeren Gruppe (15–25 Jahre) (OR 3.33; KI 1.05–10.59). Die anderen Parameter (Ernährungszustand, ACTH-Konzentration) hatten keinen Einfluss auf das Risiko für chronische Hufrehe in dieser Population.

Schlüsselwörter: Equiden, geriatrisch, Equines Cushing Syndrom, Hormone, Hufbeinrotation

Abstract

Endocrinopathic laminitis occurs as a consequence of hormonal derangements like pituitary pars intermedia dysfunction (PPID). The objective of the present study was to assess the occurrence of radiographic changes associated with chronic laminitis in elderly, clinically sound horses. Fifty-one horses were included in the study. Horses were assigned to different age groups, in groups according to their BCS and CNS as well as to groups with different ACTH concentrations in order to assess their risk of chronic laminitis (reported as odds ratios (OR) and confidence intervals (CI)). Horses assigned to an older age group (26–32 years) were significantly more likely to have radiographically assessed changes of chronic laminitis than horses in a younger age group (15–25 years) (OR 3.33; CI 1.05–10.59). The other variables (body condition score, cresty neck score, ACTH concentration) were not associated with an increased risk of having laminitic changes in these horses.

Key words: Equine, geriatric, pituitary pars intermedia dysfunction, hormone, rotation of the distal phalanx

<https://doi.org/10.17236/sat00283>

Eingereicht: 17.01.2020
Angenommen: 29.09.2020

§Shared senior authorship

Age over 25 years, but not plasma adrenocorticotrophic hormone concentration above the seasonally adjusted reference range is predictive for radiographically assessed changes of chronic laminitis in elderly horses

G. Christen et al.

Equine laminitis is one of the most common causes of severe lameness in horses and an important reason for euthanasia in older animals. Endocrinopathic laminitis occurs as a consequence of hormonal derangements like pituitary pars intermedia dysfunction (PPID) and equine metabolic syndrome (EMS)^{3; 8} and early identification of individuals with increased risk of laminitis is of great importance. Repeated episodes of subclinical laminitis have been speculated to precede acute clinical laminitis^{9; 10; 13; 17} and Wylie et al.¹⁸ showed that horses with a history of laminitis are more prone to have further laminitic episodes. Since by definition, subclinical laminitis is not apparent to the observer, such episode often remain unrecognized by the owners.¹⁷ Non-invasive in-vivo diagnosis of subclinical or chronic laminitis in the absence of clinical signs such as abnormal hoof morphology, lameness, short stride, turning pain and increased digital pulses is currently only possible with the use of radiography. Based on the radiographically assessed laminitic changes preference is given to the term chronic over subclinical. Identification of specific clinical signs or laboratory markers (such as age, body condition score (BCS), cresty neck score (CNS) or ACTH concentrations) indicating the likelihood of clinically not apparent, chronic laminitis in aged horses would therefore allow early recognition of at-risk individuals. The objective of the present study was therefore to assess if horses belonging to an older vs. younger age group, to a higher vs. lower body condition and cresty neck score group or having ACTH concentrations above the reference range vs. within the reference range were more likely to be diagnosed with chronic laminitis based on radiographic changes. Single odds ratio analysis was

performed to determine whether changes were significantly more likely to be present in these horses.

For this prospective study, horses owned by a foundation for retired equids were examined. The study was approved by the Animal Experimentation Committee of the Cantons of Jura and Berne, Switzerland (authorization number JU EXPE01/14+). The foundation «Stiftung für das Pferd» in les Breuleux, Switzerland, owned all horses and gave informed consent for study participation. Horses were kept in three different locations, but under similar management conditions. Animals over 15 years of age without clinical signs of acute laminitis such as lameness, weight shifting, reluctance to move, turning pain and/or increased digital arterial pulses were included in the study. A clinical examination was performed in every horse and body condition was assessed by a single experienced observer (GC) using a 9-point body condition score (BCS)⁶ and a 5-point cresty neck score (CNS).¹ Blood was collected into glass EDTA tubes with aprotinin (BD Vacutainer®, Fa. Becton Dickinson, New Jersey, USA), centrifuged and the plasma was frozen immediately. ACTH analyses were performed using a chemoluminescence immunoassay (Immulite 2000 Xpi, Siemens AG, Erlangen, Germany) previously validated for use in horses.¹⁴ Endocrine testing was performed in the first week of July. Radiographs were taken on both front feet during the first week of August. Prior to radiography, the horses' feet were cleaned using a hoof pick. If present, shoes were not removed. Horses were placed on a 10,5 cm high wooden plank and a metal wire of 6 cm in length was attached to the dorsal hoof wall from the hairline of the coronary band pointing distally. Lateromedial radiographic views were obtained. Radiographs were taken using a portable X-ray machine (GIERTH HF 300, Gierrth X-Ray International GmbH, Riesa, Germany) with the following settings: 50 mA, 56 kV and 0,06 s, the film focus distance was 80 cm. The beam was centered on the sole and between the dorsal and palmar aspect of the hoof. Measurements were made by a board certified radiologist (CP) using eFilm (Merge Healthcare Incorporated, Illinois, USA). The distal phalanx rotation relative to the dorsal hoof wall (angle H), coronary extensor distance (CED) and soft tissue thickness dorsal to the middle aspect of the distal phalanx (STTM) were measured and graded as described.^{2; 16} Figure 1 shows a radiograph with the angles S and T from which angle H is calculated as described by Cribbs and Eustache.² In order to classify STTM as normal or not, the following reference values were used: Hanoverian horses (17,0–19,1 mm) were used as reference for Warmbloods, Thoroughbreds (13,9–19,7 mm) for Thoroughbred horses, Freiburger horses and Haflingers.² The occurrence of gas lines, dropped sole, distal phalanx remodeling and a sinking coronet were evaluated subjectively according to Pollitt¹⁵

Figure 1: A radiograph showing the measurements of the angles S and T that were used to calculate angle H (Angle H = Angle T minus Angle S). The angle H in the presented case was measured as 4°.



Tabelle 3: Risk of subclinical laminitis and effect estimates of categorical variables

Categorical variables	P-value	Odds Ratio	95% CI
AGE (1–2)	0,04	3,33	1,05–10,59
BCS (1–2)	1	1	0,31–3,21
CNS (1–2)	0,32	1,75	0,58–5,32
ACTH>43 – ACTH=≤43	0,34	1,72	0,57–5,22

and categorized as present or absent. The angle of the distal phalanx rotation relative to the dorsal hoof wall (angle H) was recorded and laminitic changes were defined as an angle $H \geq 2^\circ$.² None of the horses had radiological signs of laminitis other than rotation of the distal phalanx and only angle $H \geq 2^\circ$ was used to define chronic laminitic changes in this cohort of horses. The foot with the higher grade was taken into statistical account.

Data was analysed using NCSS (NCSS Analytical Software version 12, East Kaysville, Utah, USA). P-values <0,05 were considered significant. Horses were assigned to different age groups (using the 50th percentile; AGE 1: 15–25 years of age; AGE 2: 26–32 years of age) and in groups according to their BCS and CNS (BCS 1 (normal and thin horses): poor to moderate [1–5]; BCS 2 (obese horses): moderately fleshy to fat [6–9]; CNS 1 (normal horses): no visual appearance of a crest to noticeable appearance of a crest [0–2]; CNS 2 (obese horses): crest enlarged and thickened to crest droops to one side [3–5]). Horses were furthermore assigned to group ACTH>43 if their plasma ACTH concentrations exceeded 43 pg/ml⁴ whereas the group ACTH=≤43 consisted of horses with ACTH concentrations = or <43 pg/ml. Logistic regression models were used calculate occurrence of chronic laminitis (yes/no – based on angle $H \geq 2^\circ$) in the different groups (AGE 1 vs. AGE 2; BCS 1 vs. BCS 2, CNS 1 vs. CNS 2, ACTH>43 vs. ACTH=≤43), reported as odds ratios (OD) and confidence intervals (CI). Results are displayed as means ± standard deviation (SD) for parametric results and as medians and ranges for non-parametric data.

A total of 51 horses were included in the study. Horses were aged between 15 and 32 years (25 ± 4 [mean ± SD]) and there were 26 mares and 25 geldings. The following breeds were represented: Warmblood horses (n=31), Freiburger (n=8), Arabian (n=4), Haflinger (n=2), Quarter horse (n=2), Belgian Draft horse (n=1), Criollo (n=1), Camargue horse (n=1) and Standardbred (n=1). The BCS ranged from 3 to 8 (6 ± 1 [mean ± SD]) and the CNS from 1 to 4 (3 ± 1 [mean ± SD]). None of the horses had hypertrichosis or abnormal hair coat shedding. ACTH values ranged from 7,4–235 pg/ml (41,3 [median]). Angle H ranged from –3 to 13° (1 [median]). It was increased in 24/51 horses (2–13°; 3 [medi-

an]) whereas 27/51 had no evidence of radiographic changes (–3–1°; 0 [median]).

Horses in group AGE 2 (n=22) were significantly more likely to have radiographically assessed laminitic changes than horses in group AGE 1 (n=29). There was no difference in occurrence of chronic laminitis between the groups BCS 1 (n=17) and BCS 2 (n=34) or CNS 1 (n=25) and CNS 2 (n=26). Horses assigned to group ACTH>43 (n=26) did not have an increased risk of having laminitic changes compared to horses with plasma ACTH concentrations below 42 pg/ml (ACTH=≤43; n=25). All effect sizes of categorical variables on the risk of having chronic laminitis changes are displayed in Table 1.

Horse owners experience an increased pleasure at keeping their horses in retirement, often well beyond the age of 25 years. Knowledge of age-related problems and the early recognition of diseases enable the implementation of better management and veterinary care to maintain the animal in a pain-free status. In this study, belonging to a higher age group was associated with an increased risk of chronic laminitis. Horses in the older age group between 26 and 32 years of age were more likely to have an abnormal rotation angle than horses in the lower age group between 15 and 25 years of age. Owners and veterinarians should therefore be aware of the increased probability of radiographically apparent laminitis in those animals, even in the absence of clinical signs of laminitis or PPID. A laboratory biomarker identifying horses at risk in the subclinical stages of laminitis would furthermore be of great value, but rotation angles did not differ between normal horses and horses with increased plasma ACTH concentrations. According to our results, ACTH therefore cannot be used as such a biomarker. Other biomarkers have previously been assessed in order to identify horses at risk for laminitis or in the early stages of the disease and include cartilage oligomerix matrix protein⁵ and plasma citrulline levels.⁷ However, these new potential biomarkers are currently not offered by commercial laboratories. Plasma adiponectin, serum basal insulin and post-dexamethasone insulin levels were identified as risk factors for the development of acute episodes of laminitis in ponies without PPID over a three year period¹² and laminitis occurrence was predicted with an oral glucose test in ponies

Age over 25 years, but not plasma adrenocorticotrophic hormone concentration above the seasonally adjusted reference range is predictive for radiographically assessed changes of chronic laminitis in elderly horses

G. Christen et al.

fed a diet high in nonstructural carbohydrates.¹¹ Insulin and adiponectin therefore seem to be of greater value for the prediction of laminitis but if this also applies to clinically not apparent laminitis remains unknown. The main limitation of our study is the lack of insulin measurement as a predictor of laminitis. This would have complemented a recent publication where hyperinsulinemia has been documented to correlate with laminitis severity (assessed radiographically), in horses with moderate and severe PPID,¹⁷ but not in animals with pre-clinical PPID. Further limitations of our study are the limited number of horses leading to low statistical power and the lack of a positive control group with clinical signs of laminitis.

Chronic laminitic changes can be present in the absence of clinical disease, especially if the horses' age exceeds 25 years. We think that radiographic changes are related to early or pre-clinical PPID in this cohort of horses

because this remains the best explanation for the higher incidence of laminitis in the old age group but only ACTH concentrations above the reference range were not predictive of chronic laminitis. This highlights the need for other diagnostic markers to predict the risk of laminitis in aged horses. Radiographic assessment of aged horses with suspicion of pre-clinical PPID remains important as no other diagnostic option for laminitis is currently available in the absence of clinical signs.

Acknowledgments

The authors thank «Die Stiftung für das Pferd» for access to the study population and good collaboration and Synlab for performing all the analyses at a research fee. The presented study was funded by the Swiss Institute of Equine Medicine Research funds (ismequine.ch) (33–890).

L'âge supérieur à 25 ans est prédictif des modifications de fourbure chronique constatées radiographiquement chez les chevaux âgés, mais pas la concentration plasmatique d'hormone adrénocorticotrope ajustée aux variations saisonnières

La fourbure endocrinopathique survient à la suite de troubles hormonaux tels que le dysfonctionnement de la pars intermedia de l'hypophyse (DPIH). L'objectif de la présente étude était d'évaluer les changements radiographiques associés à la fourbure subclinique chez les chevaux âgés cliniquement sains. Cinquante et un chevaux ont été inclus dans l'étude. Les chevaux ont été assignés à différents groupes d'âge, en groupes en fonction de leur Body Condition Score (BCS) et de leur Cresty Neck Score (CNS) ainsi que des groupes avec différentes concentrations d'ACTH afin d'évaluer leur risque de fourbure chronique (rapportés sous forme de rapports de cotes (Odds-Ratio, OR) et d'intervalles de confiance (IC)). Les chevaux faisant partie d'un groupe d'âge plus avancé (26 à 32 ans) étaient significativement plus susceptibles de présenter des signes radiographiques de fourbure chronique que les chevaux d'un groupe d'âge plus jeune (15 à 25 ans) (OR 3,33; IC 1,05–10,59). Les autres variables (BCS, CNS, concentration d'ACTH) n'étaient pas associées à un risque accru de modifications de type fourbure chez ces chevaux.

Mots clés: équin, gériatrie, dysfonction de la pars intermedia de l'hypophyse, fourbure subclinique, rotation de la phalange distale

L'età superiore ai 25 anni, ma non la concentrazione dell'ormone adreno-corticotroppo plasmatico superiore all'intervallo di riferimento stagionale, è indicativa nei cavalli anziani di una laminite cronica diagnosticata per radiografia.

La laminite endocrinopatica insorge in quanto conseguenza di squilibri ormonali come la disfunzione della pars intermedia ipofisaria (PPID). L'obiettivo dello studio qui di seguito era di valutare l'incidenza dei cambiamenti radiografici associati alla laminite cronica nei cavalli anziani, clinicamente sani. Per lo studio sono stati esaminati 51 cavalli. I cavalli sono stati assegnati a differenti gruppi di età, al loro body condition score (BCS), al loro cresty neck score (CNS) e a gruppi con concentrazioni di ACTH differenti, in modo da valutare il rischio di sviluppo di una laminite cronica (i risultati sono riportati come odds ratio (OR) e intervallo di confidenza (CI)). I cavalli appartenenti a un gruppo di età più anziano (26–32 anni) sviluppavano una maggiore probabilità di mostrare dei cambiamenti radiografici associati alla laminite cronica che il gruppo di cavalli più giovani (12–25 anni) (OR 3,33; CI 1,05–10,59). Le altre variabili (body condition score, cresty neck score e concentrazione di ACTH) non sono state correlate a un aumento del rischio di laminite cronica in questa popolazione.

Parole chiave: equini, geriatrico, disfunzione della pars intermedia ipofisaria, ormone, rotazione della falange distale

References

- ¹ Carter RA, Geor RJ, Staniar WB, Cubitt TA, Harris PA: Apparent adiposity assessed by standardised scoring systems and morphometric measurements in horses and ponies. *The Veterinary Journal* 2009, 179: 204–210.
- ² Cripps P, Eustace R: Radiological measurements from the feet of normal horses with relevance to laminitis. *Equine veterinary journal* 1999, 31: 427–432.
- ³ Donaldson MT, Jorgensen AJ, Beech J: Evaluation of suspected pituitary pars intermedia dysfunction in horses with laminitis. *Journal of the American Veterinary Medical Association* 2004, 224: 1123–1127.
- ⁴ Durham AE, Clarke BR, Potier JF, Hammarstrand R, Malone GL: Clinically and temporally specific diagnostic thresholds for plasma ACTH in the horse. *Equine veterinary journal* 2020.
- ⁵ Galantino-Homer H, Linardi R, Engiles J, Deacon L, Modelski M, Pollitt C: Investigating serum biomarkers for equine laminitis. *Journal of Equine Veterinary Science* 2013, 33: 863–864.
- ⁶ Henneke D, Potter G, Kreider J, Yeates B: A scoring system for comparing body condition in horses. *Equine veterinary journal* 1983, 15: 371.
- ⁷ Jackson AL: Plasma Citrulline Levels in Horses at Risk of Acute Laminitis. In: 2013.
- ⁸ Karikoski N, Horn I, McGowan T, McGowan C: The prevalence of endocrinopathic laminitis among horses presented for laminitis at a first-opinion/referral equine hospital. *Domestic animal endocrinology* 2011, 41: 111–117.
- ⁹ Karikoski N, McGowan C, Singer E, Asplin K, Tulamo R-M, Patterson-Kane J: Pathology of natural cases of equine endocrinopathic laminitis associated with hyperinsulinemia. *Veterinary pathology* 2015, 52: 945–956.
- ¹⁰ Kawasako K, Higashi T, Nakaji Y, Komine M, Hirayama K, Matsuda K, Okamoto M, Hashimoto H, Tagami M, Tsunoda N: Histologic evaluation of the diversity of epidermal laminae in hooves of horses without clinical signs of laminitis. *American journal of veterinary research* 2009, 70: 186–193.
- ¹¹ Meier A, de Laat M, Reiche D, Pollitt C, Walsh D, McGree J, Sillence M: The oral glucose test predicts laminitis risk in ponies fed a diet high in nonstructural carbohydrates. *Domestic animal endocrinology* 2018, 63: 1–9.
- ¹² Menzies-Gow N, Harris P, Elliott J: Prospective cohort study evaluating risk factors for the development of pasture-associated laminitis in the United Kingdom. *Equine veterinary journal* 2017, 49: 300–306.
- ¹³ Morgan SJ, Hood DM, Wagner IP, Postl SP: Submural histopathologic changes attributable to peracute laminitis in horses. *American journal of veterinary research* 2003, 64: 829–834.
- ¹⁴ Perkins GA, Lamb S, Erb HN, Schanbacher B, Nydam DV, Divers TJ: Plasma adrenocorticotropin (ACTH) concentrations and clinical response in horses treated for equine Cushing's disease with cyproheptadine or pergolide. *Equine veterinary journal* 2002, 34: 679–685.
- ¹⁵ Pollitt CC: Equine laminitis. *Clinical Techniques in equine practice* 2004, 3: 34–44.
- ¹⁶ Stick J, Jann H, Scott E, Robinson N: Pedal bone rotation as a prognostic sign in laminitis of horses. *Journal of the American Veterinary Medical Association* 1982, 180: 251–253.
- ¹⁷ Tadros E, Fowlie J, Refsal K, Marteniuk J, Schott H: Association between hyperinsulinemia and laminitis severity

at the time of pituitary pars intermedia dysfunction diagnosis. *Equine veterinary journal* 2018.

- ¹⁸ Wylie CE, Collins SN, Verheyen KL, Newton JR: Risk factors for equine laminitis: a case-control study conducted in veterinary-registered horses and ponies in Great Britain between 2009 and 2011. *The Veterinary Journal* 2013, 198: 57–69.

Age over 25 years, but not plasma adrenocorticotrophic hormone concentration above the seasonally adjusted reference range is predictive for radiographically assessed changes of chronic laminitis in elderly horses

G. Christen et al.

Corresponding author

Garance Christen
Länggassstrasse 124
CH-3012 Bern
Telefon: +41 31 631 22 43
E-Mail: garance.christen@vetsuisse.unibe.ch

