TITLE: Laminitis in horses

AUTHORS: Nicola Menzies-Gow

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Laminitis in Horses

Introduction

Laminitis is a common and painful condition of the adult equine, often resulting in permanent lameness or euthanasia. Reported estimates of laminitis frequency to range from 1.5-34%,[1] depending on the population studied (general practice or referral institutions), proportion of ponies versus horses, presence of intercurrent diseases (particularly gastrointestinal disease) and the geographic location (generally USA, UK or Australia). It may occur as a single episode or, more commonly, as repeated bouts over a prolonged period (recurrent laminitis). The risk of all-cause mortality was increased nearly 6-fold by the presence of laminitis in a population of horses treated in first opinion practices in the UK (hazard ratio 5.94 vs. no chronic disease) indicating the importance of this disease.[1]

Forms of Laminitis

Laminitis is now considered to be a clinical syndrome associated with systemic disease (sepsis or systemic inflammatory response syndrome [SIRS] or endocrine disease) or altered weight bearing rather than being a discrete disease entity.[2] Thus, laminitis can be divided into three forms:

1. Sepsis-associated laminitis

Laminitis that occurs secondary to the SIRS and in particular sepsis is termed sepsis-associated laminitis. It occurs in association with severe gastrointestinal disease and endotoxemia. Two models have been used to investigate the pathogenesis of this form of laminitis.[3,4] In the carbohydrate-overload models, the excess starch that arrives in the large intestine is digested

by intestinal bacteria resulting in a severe drop in intestinal pH, death of Gram-negative bacteria and enterocolitis in which mucosal injury results in the systemic absorption of numerous substances. However, the exact identity of the laminitis trigger(s) remains elusive. The other experimental model that appears to mirror sepsis-related laminitis is the black walnut extract model. These models have produced evidence of evidence of systemic inflammation, endothelial activation, leucocyte adhesion and emigration, altered cytokine expression and oxidative injury. These result in failure of critical laminar basal epithelial cell functions and consequent failure of the epithelial adhesion molecules (hemidesmosomes), which attach the epidermal cells to the basement membrane. Laminar separation follows.

2. Endocrinopathic laminitis

Endocrinopathic laminitis is the commonest form of laminitis, accounting for 90% of cases of laminitis in two studies.[5,6] It encompasses laminitis linked with insulin dysregulation (ID), as occurs in association with equine metabolic syndrome (EMS), pituitary pars intermedia dysfunction (PPID) and glucocorticoid administration. The key feature of EMS is ID, which may manifest as hyperinsulinaemia, an excessive insulin response to oral carbohydrate consumption or tissue insulin resistance.[7] PPID is a progressive neurodegenerative disorder associated with loss of the inhibitory dopaminergic input to the pituitary pars intermedia (PI).[8] This results in increased production of the normal hormone products of the PI, some of which may antagonise the actions of insulin resulting in ID in a subset of animals. Exogenous corticosteroid administration is associated with an increased risk of laminitis in animals possessing other laminitis risk factors,[1] possibly due to antagonism of insulin by the corticosteroid.

Prolonged experimental hyperinsulinaemia induced laminitis in healthy ponies[9] and horses.[10] In contrast to sepsis-associated laminitis, lamellar inflammation was not a major histological feature[11-13] and evidence of systemic or gastrointestinal inflammation was not apparent. The lamellar histological changes were more consistent with stretching rather than separation of the basement membrane, accompanied by increased mitotic activity and cellular proliferation.[11-13] Various theories have been postulated to explain the potential relationship between hyperinsulinaemia/ID and laminitis since alterations in glucose uptake/metabolism have been discounted.[14] One possibility is that whilst at physiological concentrations insulin preferentially binds to the insulin receptor (InsR), at high concentrations insulin can bind and activate the insulin-like growth factor-1 receptor (IGF-1R). There are significant numbers of IGF-1R in equine lamellar tissue.[15] Thus, hyperinsulinaemia may directly overstimulate IGF-1R-mediated cell proliferation, which could potentially weaken the lamellar suspensory apparatus triggering the onset of clinical signs. Alternatively, it may lead to receptor down-regulation via negative feedback.[16] A significant proportion of endocrinopathic laminitis cases occur at pasture; thus, consumption of pasture carbohydrate may exacerbate hyperinsulinaemia, resulting in laminitis.

3. Supporting limb laminitis

Supporting limb laminitis (SLL) is uncommon; a UK study revealed a practice prevalence of just 0.02%.[17] However, it is a major contributor to treatment failure in painful limb conditions such as fractures and refractory cases of synovial sepsis. Although the severity and duration of lameness are considered risk factors,[18] the development of supporting limb laminitis (SLL) remains unpredictable.[19] There has been little research on the pathophysiology of SLL, but

studies utilising tissue microdialysis suggest that cyclic loading of the feet plays an essential role in digital homeostasis at rest and that decreased frequency of unloading of a limb, combined with increased mean load bearing on that limb, can result in lamellar ischaemia. [20] Thus, SLL may be a consequence of lamellar ischaemia.

Stages of Laminitis

Acute laminitis can be divided into three stages. Firstly, there is a developmental or prodromal phase that begins with contact with the pathophysiological trigger and ends with the onset of lameness up to 72 hours later. This is followed by the acute phase during which the clinical signs are seen. Thus, the clinical signs only become apparent once the lamellar tissues have already been subjected to significant metabolic and degenerative changes and treatment should be initiated as soon as possible. The acute phase is followed by either resolution of the disease or entry into the chronic phase.

Risk factors for laminitis

A systematic literature review identified those risk factors with the most reliable evidence.[21] These included being a pony,[22,23] the spring and summer months,[24] being female,[22,24] increasing age,[22] regional or generalised obesity,[22] and endotoxemia.[25] However, that this review did not separate the three forms of laminitis. In a case-control study that included only endocrinopathic laminitis, factors which increased the laminitis risk included weight gain in the previous three months, the summer and winter months, new access to grass in the previous four weeks, box rest in the previous week, owner-reported history of laminitis, lameness or foot-soreness after shoeing/trimming, pre-existing endocrinopathic (PPID and

EMS) disease and increasing time since the last anthelmintic treatment.[26] Factors associated with a decreased laminitis risk were increasing height, feeding of additional supplements in the previous week and transportation in the previous week.[26] Similarly, cases of endocrinopathic laminitis were significantly older and more likely to be pony breeds compared to the general hospital population.[5]

Diagnosis

The diagnosis of laminitis is usually based on the clinical signs (Table 1; Figure 1).[27] The lameness can vary in severity from that which is only perceptible at the trot, through to spending prolonged periods recumbent.

Further diagnostic tests are performed in those cases where an underlying endocrinological abnormality is suspected. A diagnosis of EMS is based on a history of recurrent laminitis in an animal often described by the owners as a good doer or easy keeper. However, generalised or regional obesity are not a prerequisite of EMS (Figure 2). It develops in animals <15 years old and there may be a genetic link with certain breeds being over-represented. The gold standard test to identify ID is yet to be determined; however, there are tests designed to detect the specific manifestations (Table 2).

PPID is more common in older animals and in ponies compared to horses. Clinical signs can be divided into early and advanced (Table 3; Figure 3). Currently recommended further diagnostic tests include resting ACTH concentrations (using seasonally adjusted laboratory reference ranges) and the ACTH response to a TRH stimulation test. In addition, tests for

insulin dysregulation should be performed to identify the subset of animals with PPID that have ID.

Lateromedial foot radiographs are taken in those cases where movement of the pedal bone is suspected or in those cases which fail to respond to the initial treatment (Figure 4).

Treatment of acute laminitis

Treatment should be initiated as soon as possible and should be aimed at providing analgesia and foot support. Additionally, cryotherapy is indicated in certain circumstances.

Analgesia

Laminitis is an extremely painful condition and non-steroidal anti-inflammatory drugs (NSAIDs) are the first choice for analgesia (Figure 5). However, there is no evidence to suggest that any one specific NSAID is superior to the next.[28]

If NSAIDs do not provide sufficient pain relief, then opiates can be used in addition, including butorphanol, pethidine and morphine (Figure 6). Transdermal fentanyl was reported to be effective in horses with pain refractory to NSAID analgesia, especially in animals of lower body weight in one small clinical report.[29] However, uptake of fentanyl from a transdermal patch is highly variable in adult horses.[30] Tramadol has been advocated, however it has a low oral bioavailability (~9%), a short half-life (~2 hours)[31] and did not alter hoof withdrawal or skin-twitch latency to a thermal stimulus.[32] Thus, current evidence does not support its use alone.

If single drugs do not provide adequate analgesia, then multimodal therapy can be used in the hospital setting. Possible combinations typically involve NSAID administration in

combination with a constant-rate infusion of lidocaine, ketamine, butorphanol, α_2 agonists or combinations thereof.

A neuropathic component to the pain associated with laminitis has been demonstrated[33] making ketamine and gabapentin potentially suitable drugs. In one study, oral tramadol alone provided little pain relief, but the combination of tramadol and ketamine resulted in decreased blood pressure, decreased forelimb offloading frequency and increased forelimb loading in horses with naturally occurring laminitis.[34] Gabapentin improved hindlimb pain that was probably associated with femoral neuropathy in one horse[35] and has a relatively low bioavailability, but no apparent adverse effects following oral administration in horses.[36] Further work is needed to assess the clinical effect of gabapentin more objectively in horses with clinical pain. Newer therapies, such as soluble epoxide hydrolase inhibitors and vanilloid receptor antagonists may prove useful in the future, but again further work is needed.[37]

Foot Support

Supporting the foot is an essential part of the management of acute laminitis. The horse naturally adopts a stance that bears most of the weight over the caudal part of the foot rather than the painful toe region. Additional support should be applied to this region of the foot in order to provide pain relief and to minimise the mechanical forces on the laminae and hence pedal bone movement. The simplest method is to increase the depth of the bedding, ensuring that the bedding extends to the door where the horse will spend a significant proportion of its day standing using shavings, sand, peat or hemp based products as they pack beneath the feet best (Figure 7). Extra support can be applied directly to the caudal two thirds of the foot itself using methods that can be broadly divided into frog only supports and combined frog

and sole supports (Figure 8). Currently, there is no evidence to suggest that any one foot support method is superior.[28] The supports should be left in place whilst the horse remains acutely painful and can be replaced by more permanent alternatives once the horse is comfortable if required.

Vasodilator Therapy

Vasodilator therapy was historically used based on laminitis being a consequence of digital hypoperfusion. However, this pathogenesis concept is now outdated for two forms of the condition. Nevertheless, the sedative effect of acepromazine may have the additional beneficial effect of reducing movement or even resulting in increased periods of time spent recumbent with the weight taken off the feet. In a single study evaluating the outcome of equine pasture-associated laminitis managed in first opinion practice in the UK, there was a trend toward use of acepromazine being associated with survival.[28]

Cryotherapy

Prophylactic continuous cooling (cryotherapy) of the equine digit effectively limited the biochemical, histological and clinical abnormalities associated with experimentally-induced sepsis-associated; most probably through interruption of inflammatory signaling pathways as well local vascular and metabolic mechanisms.[40] In addition, prophylactic digital cryotherapy was associated with a decreased incidence of laminitis in horses with colitis[41] and prevented or limited lamellar failure in experimentally-induced sepsis-associated laminitis when initiated after the onset of clinical signs of laminitis.[42] Thus, there is evidence to support the use of cryotherapy both in the prevention and treatment of sepsis-associated laminitis. It has

been recommended that the hoof temperature should be maintained at <10°C for 72 hours, achieved by immersion of the foot and pastern region in ice and water.[43] There is currently no published evidence relating to the use of cryotherapy for the prevention or treatment of endocrinopathic or supporting limb laminitis.

Diet

Animals with acute endocrinopathic laminitis should be removed from pasture and box rested. A diet based on grass hay (or hay substitute) with low (<10%) non-structural carbohydrate (NSC) content should be fed and cereals avoided. Ideally, the forage should be analysed before it is fed. Some recommend soaking hay in water for 30 to 60 minutes before feeding to leach water soluble carbohydrates and so circumvent the need for analysis; however, this does not reliably decrease the NSC content to <10% in all cases.[44] Forage-only diets do not provide adequate protein, minerals, or vitamins; thus a low-calorie commercial ration balancer product that contains high-quality protein and a mixture of vitamins and minerals is recommended.

Treatment of Underlying Endocrinopathies

Additional therapies are indicated if an underlying endocrinopathy is confirmed.

Pituitary pars intermedia dysfunction (PPID)

The first choice treatment for PPID is the dopamine agonist pergolide, which replaces the lost dopaminergic inhibition to the PI and so reduces hormone production. It is licensed for the treatment of PPID in the horse in the UK (Prascend, Boehringer Ingleheim; Figure 9). The initial dose is 2μg/kg p.o. SID for 4-6 weeks. The dose is increased in increments of 1μg/kg/day with reassessment every 4-6 weeks to a maximum of 6μg/kg/day if there is not adequate clinical

or laboratory response; or decreased slowly at 4-6 week intervals to the lowest apparently effective dose. Within the first month of treatment there should be an improvement in attitude, lethargy and control of hyperglycaemia and a decrease in PU/PD; improvement in the other clinical signs will occur within one to twelve months. Reported side effects include diarrhoea, depression, anorexia and colic; however only anorexia and depression are reported with any frequency. Monotherapy with the serotonin antagonist cyproheptadine (Periactin, Merk Sharp & Dohme Ltd) is not advocated; however, it can be used in conjunction with pergolide if pergolide alone is not effective.

Equine metabolic syndrome (EMS)

Treatment of EMS should focus on management changes aimed at weight reduction, if the animal has regional or generalised adiposity, and exercise, which additionally improves ID. Weight reduction is achieved through feeding a diet high in fibre and low in NSC. Grain and other concentrated sources of calories should be removed from the diet. Hay or hay substitute should initially be provided at 1.5% of current body weight per day, with subsequent further reductions in feed amount depending on the extent of weight loss. This should be decreased to <1.0% of target body weight, as this may increase the risk for hindgut dysfunction, stereotypical behaviours, ingestion of bedding, or coprophagy. The ration should be divided into three to four feeds per day and strategies to prolong feed intake time should be considered, such as use of multiple hay nets with small holes. The optimal amount of exercise required has yet to be determined, but daily light exercise is probably best once the laminitis has resolved.

If management changes are unsuccessful alone, then pharmacologic interventions can be additionally used in the short term (3-6 months). Metformin was initially advocated to improve insulin sensitivity; however, the bioavailability is very low (7%)[45] and it does not have insulin sensitising effects[46] in the horse. Instead metformin reduces the glycaemic and insulinaemic responses to oral carbohydrate ingestion;[47] thus it may be more useful in preventing post prandial hyperinsulinaemia associated with turn out to pasture or feed consumption. Levothyroxine is advocated in animals with generalised or regional adiposity. Weight loss is promoted through an increase in the metabolic rate; however, the diet has to be strictly controlled because polyphagia may be a consequence of medication.

Prevention

Sepsis-associated laminitis

Prevention of sepsis-associated involves early and effective treatment of the cause of the sepsis or SIRS, the use of appropriate anti-endotoxic therapy and the prophylactic use of digital cryotherapy.

Supporting limb laminitis (SLL)

More research is necessary before specific recommendations for prevention of SLL can be made. Some authors suggest that as limb cycling is an essential component of the circulation, it would be prudent to institute, whenever practicable, measures to improve foot circulation in horses at risk of SLL via either controlled exercise (walking) or physical therapy.[19] However, the ideal frequency and duration remains unknown.[19]

Endocrinopathic laminitis

Prevention of endocrinopathic laminitis centres on appropriately treating the underlying endocrinopathy, maintaining an optimum body condition and limiting intake of pasture NSC that may exacerbate ID.

A diet based on grass hay (or hay substitute) with low (<10%) NSC content should be fed and cereals avoided. The NSC content of pasture fluctuates widely; thus, zero grazing should be considered. However, if an animal is to be turned out, steps should be taken to minimise NSC intake (Table 4). Forage-only diets do not provide adequate protein, minerals, or vitamins and so a low-calorie commercial ration balancer product that contains high-quality protein and a mixture of vitamins and minerals is recommended.

If weight gain is required or the animal is undertaking a large amount of exercise, then caloric intake can be increased by adding unmolassed soaked sugar beet pulp to the diet (0.2-0.7kg/day) or by feeding vegetable oil (100-225ml SID or BID up to a maximum of 100 ml/100 kg of body weight).

Several supplements containing magnesium, chromium or cinnamon and a variety of herbs are marketed with claims for improved insulin sensitivity but scientific evidence of their efficacy is lacking. A recent study demonstrated that a supplement containing chromium, magnesium and other nutraceuticals had no effect on insulin sensitivity in laminitic obese horses.[48]

Exercise is also essential in the prevention of laminitis as it has been shown to improve insulin sensitivity and decrease food intake. Light exercise is sufficient to improve insulin sensitivity,

but that this probably needs to be maintained on a regular and possibly even daily basis for the improvement to persist.

Conclusion

In conclusion, laminitis is a common and painful condition of the horse that is now considered to be a clinical syndrome associated with systemic disease (sepsis-associated or endocrinopathic laminitis) or altered weight bearing (supporting limb laminitis) rather than being a discrete disease entity. Various risk factors have been identified for endocrinopathic laminitis. Diagnosis is based on the history and clinical signs. Further diagnostic tests are undertaken in cases where an underlying endocrinopathy is suspected and radiographs are taken if pedal bone movement is suspected or the animal is not responding to appropriate therapy. Analgesia and foot support are the mainstay of therapy. Digital cryotherapy is useful in the treatment of sepsis-associated laminitis. Prevention involves prompt treatment of any underlying disease (all forms of the disease), use of digital cryotherapy (sepsis-associated laminitis), and maintaining an optimum body condition and limiting carbohydrate intake to minimise exacerbation of ID (endocrinopathic laminitis).

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Tables

Table 1: Clinical signs of laminitis

Clinical signs associated with laminitis
Lameness affecting two or more limbs
Characteristic stance of leaning back on the heels and taking weight off toes
Bounding digital pulses
Increased hoof wall temperature
Pain on hoof tester pressure at the region of the point of the frog
Palpable depression at the coronary band

Table 2: Further diagnostic tests use to identify insulin dysregulation in clinical practice

Manifestation of ID	**Appropriate Test**
Hyperinsulinaemia	Basal insulin concentration
Excessive insulin response to oral carbohydrate	Oral sugar test (OST) Oral glucose test (OGT)
Tissue insulin resistance	Insulin tolerance test (ITT) Combined glucose insulin test (CGIT)

Table 3: Clinical signs associated with pituitary pars intermedia dysfunction

Early clinical signs	**Advanced clinical signs**
Delayed haircoat shedding Regional hypertrichosis Lethargy Regional adiposity Change in body conformation Laminitis	Generalised hypertrichosis Loss of seasonal haircoat shedding Skeletal muscle atrophy Hyperhidrosis Absent reproductive cycling/infertility Laminitis Polyuria/polydipsia (PU/PD) Secondary infections Neurologic deficits/blindness

Table 4: Methods to minimise NSC ingestion from pasture

Methods to minimise NSC content of pasture	Methods to minimise amount of pasture consumed
• Manage pasture to encourage growth, but regularly top to minimise amount available for ingestion • Turn out from late night to early morning when the NSC content of the pasture is lowest • Avoid turn out if there has been a frost with bright sunshine or a drought as this restricts growth but photosynthesis continues allowing the NSC to accumulate	• Limit grazing especially in spring and autumn when the grass is growing • Rotate paddocks to keep them at the ideal height • Limit grazing through limited time at pasture • Limit grazing geographically e.g. strip grazing • Limit grazing through use of grazing muzzle

Figure Headings

Figure 1: A New Forest gelding with the characteristic stance of leaning back on the heels

Figure 2: A Welsh mare with generalised obesity

Figure 3: A New Forest pony gelding with hypertrichosis and recurrent laminitis consistent with a diagnosis of PPID

Figure 4: A) Lateromedial radiograph of the foot showing pedal bone rotation and B) Gross appearance of the same foot post mortem

Figure 5: Various non-steroidal anti-inflammatory drugs are available to provide analgesia

Figure 6: Opiates and Ketamine can be used to provide additional analgesia

Figure 7: Foot support can be provided in the form of a deep bed which extends all the way to the stable door

Figure 8: Various foot supports are commercially available

Figure 9: Pergolide (Prascend; Boehringer Ingleheim) is licensed for the treatment of PPID