Laminitis
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Introduction

There is a tendency to think of laminitis as a single disease entity, when in fact it is more accurately a common endpoint with a variety of etiologies, including sepsis, endocrinopathies, and excessive weightbearing. Increasingly, research suggests that the mechanisms by which laminitis develops differ among these situations and that therefore, there is a need to develop different diagnostic and therapeutic approaches for each. Recent advances in our understanding of the pathophysiology of laminitis are rooted in several established in vivo experimental models. Most widely used are the black walnut and carbohydrate overload/oligofructose models, which most closely mimic sepsis-induced laminitis. Hyperinsulinemia models have been introduced more recently in an effort to recapitulate laminitis resulting from endocrinopathies, but results from these studies are more mixed, and there is some question as to how similar the pathology resulting from this model is to naturally-occurring disease. Support limb (overload) laminitis is more difficult to model accurately, not least because of humane concerns, but there have been attempts to study the effects of uneven weightbearing on the laminae over a more compressed time period than would typically be seen in naturally-occurring disease.

Laminitis has been described as occurring in stages, although these are relatively poorly defined. During the development (prodromal) stage, histological changes are present in the foot although clinical signs have not yet appeared. The acute phase of disease is marked by the onset of clinical signs, including reluctance to bear weight and an abnormal stance. With the abatement of severe clinical signs, and in the absence of radiographic changes, a horse is considered to be in the subacute phase. The subacute phase may precede full recovery, may relapse into acute laminitis, or may progress to chronic laminitis in which radiographic changes are present (e.g. rotation of P3 within the hoof capsule). Chronic laminitis may also be called founder. Recurrent laminitis episodes are not uncommon, particularly in horses with predisposing risk factors such as equine metabolic syndrome (EMS).

Diagnosis of laminitis is typically made based on the presence of one or more classic clinical signs. In one large epidemiologic study, clinical signs that were most discriminating of laminitis versus other causes of lameness included 1) reluctance to walk; 2) short, stilted gait at the walk; 3) difficulty turning; 4) shifting weight; and 5) increased digital pulses. Additionally, 92% of horses with bilateral forelimb lameness in this study population had laminitis. Interestingly, the classic "laminitis stance" with the affected forelimb(s) placed in front of the body was not found in the majority of laminitic horses, suggesting that this may not be as useful as anecdotal reports would indicate.

While laminitis is considered by both veterinarians and owners to be among the most important causes of lameness, information regarding its prevalence in the general population is limited. A recent retrospective study found that 1 in 200 veterinary visits (0.5%) in the UK were related to active cases of laminitis. In contrast, a recent prospective study of ponies reported a cumulative laminitis incidence of 10% over three years. Previous reports of disease frequency have ranged from 1.5% to 34%, but direct comparison between these studies is difficult because of differences in populations and case definition. Proposed risk factors for laminitis
include signalment (age, sex, breed), height/bodyweight, obesity, pre-existing endocrinopathy (EMS, pars pituitary intermedia dysfunction [PPID], insulin resistance [IR]), endotoxemia, exercise, season, hoof/shoeing effects, and genetics. However, the evidence for many of these is mixed, or not of high quality. A recent large case-control study identified eight factors associated with an increased risk of an acute episode of laminitis: 1) recent weight gain; 2) summer/winter months; 3) recent introduction to grass; 4) recent stall rest; 5) history of previous laminitis episode; 6) lameness or foot soreness after shoeing/trimming; 7) EMS or PPID; 8) increasing time since anthelminthic treatment. It should be emphasized that these links between risk factors and disease reflect correlation, not necessarily causation. It is almost certain that laminitis is a multifactorial disease with many interacting risk factors determining which members of a susceptible population are actually affected. Risk of support limb laminitis has been reported at 12% in one hospitalized population. Risk factors identified in that same study were type of cast (full-limb and transfixation pin casts had higher risk than half-limb casts), length of time spent in a cast and increasing body weight.

Proposed Etiologies

Three major etiologies have been suggested to underlie the development of laminitis: inflammation and degradation of the extracellular matrix/basement membrane, metabolic abnormalities (primarily related to glucose/insulin metabolism), and vascular abnormalities. Mechanical forces are likely to play an important contributing role, particularly in cases of support limb laminitis. Most of the information supporting each of these hypotheses has been derived from experimental models of laminitis.

In models of sepsis-associated laminitis (carbohydrate overload and oligofructose models), the intestinal epithelium breaks down rapidly, releasing toxins into the circulation and stimulating a profound inflammatory response. Interestingly, administration of endotoxin alone has not been shown to be sufficient to induce laminitis in otherwise healthy horses. The black walnut model is also thought to initiate a systemic inflammatory response, but the specific toxin responsible for this is unknown. Large numbers of leukocytes have been found to infiltrate the lamellae at the time of onset of clinical signs in each of these models, but their exact role in the breakdown of the basement membrane is unknown. Similarly, many inflammatory cytokines are upregulated in the acute phase of laminitis, but there is still some uncertainty as to which are the factors that induce tissue changes and which are increased in response to these changes. For example, matrix metalloproteinases (MMPs) were initially thought to play an important role in separating epithelial cells from the basement membrane via enzymatic digestion of the extracellular matrix. However, more recent work has demonstrated that MMP activation occurs relatively late in the course of disease and is therefore unlikely to be an initiating factor for laminitic changes.

The vascular anatomy of the dorsal laminae makes this region particularly susceptible to disruptions in blood supply. The blood flow moves from distal to proximal, and there is little collateral supply. Additionally, the digital veins do not have valves, and the “pumping” action achieved when the foot is cyclically loaded and unloaded seems to be necessary to promote healthy blood flow. Although the role of vasoconstriction and ischemia in sepsis-related and endocrinopathic laminitis is debated, there is a stronger argument for its role in support limb laminitis. Vascular dysfunction at the level of the endothelium is considered to play a key role in early inflammatory laminitis via increased infiltration of leukocytes and release of vasoconstrictive factors.
The mechanism by which hyperinsulinemia may cause laminitis is unclear. Initially thought
to have a direct role on glucose metabolism by the lamellae, studies have since demonstrated
that this is in fact an insulin-independent process in this tissue. Other proposed mechanisms
include effects on vascular perfusion, inflammation, and cytokine activation. Insulin resistance
(IR) does have an association with systemic inflammation, as well as with endothelial
dysfunction, but leukocyte infiltration is less in endocrinopathic laminitis than in sepsis-associated
disease. In fact, early histologic changes in the hyperinsulinemia model include
stretching/lengthening of the secondary epidermal laminae and abnormal keratinization rather
than breakdown of the basement membrane (although this does eventually occur to some
degree). Interestingly, histologic examination of the feet of ponies and horses with naturally-
occurring endocrinopathic laminitis did not find a correlation between severity of lesions and
duration of clinical signs, suggesting that subclinical disease must have been present for some
time prior to diagnosis.

The implication of exogenous steroid administration (particularly triamcinolone) as a cause
of laminitis has been widespread, but largely anecdotal. There is little direct scientific evidence
for this link, particularly at clinically-relevant doses, but it remains an area of concern,
particularly because of the risk of litigation. There is evidence to suggest that horses with other
predisposing factors for laminitis (i.e. EMS, PPID, etc.) may be more sensitive to exogenous
steroids, but normal horses seem to have very low risk. In one study, 3/2000 horses
administered 20-45mg triamcinolone or 80 mg methylprednisolone were thought to have drug-
related laminitis. In another, only 1 of 205 horses treated with up to 80mg triamcinolone
developed laminitis, and that horse had a previous history of the disease. Oral prednisolone
administration was also recently investigated and was not found to increase the risk of laminitis
when treated horses were compared to untreated controls.

Treatment and Prevention

It is perhaps obvious, but worth stating, that it is always preferable to initiate treatment
before the onset of clinical signs, so recognition of at-risk patients is crucial. As more is learned
about the particular mechanisms underlying tissue damage and failure in the various forms of
laminitis, the goal is to develop novel therapeutics that target these mechanisms. However, for
now, nonspecific therapies aimed at reducing inflammation (non-steroidal anti-inflammatory
drugs, local cryotherapy) and endotoxemia (polymixin B, plasma) remain the first line of defense
for acute laminitis, while horses prone to chronic disease are largely managed by
dietary/environmental modification and shoeing. Although relief of pain is an important goal and
often considered to be an indicator of treatment success, the importance of serial radiographs to
monitor progression of changes within the hoof capsule cannot be overemphasized.

The beneficial effects of local cryotherapy were highlighted in a recent study in which
treatment was initiated after the onset of lameness using the oligofructose model. Limbs that
were treated with cryotherapy had less severe damage on histologic exam compared to
untreated control limbs in the same horse, and crucially, did not have evidence of lamellar
separation. This suggests that this therapy could have real benefits in a clinical situation.
However, the method of cryotherapy determines its effectiveness. The same research team
evaluated the ability of seven different cooling methods to reduce hoof wall temperature and
found that hoof temperatures were lowest for methods that immersed the foot in ice/water and
extended to at least the pastern. Ice packs placed on the foot or coronary band, or ice boots that
did not include the foot, were least effective.
For horses with unilateral limb lameness, pain from the primary lesion may mask pain due to support limb laminitis, so periodic radiographs of the non-lame leg are recommended. Evidence suggests that development of laminitis in these cases may be due to cumulative tissue damage from repeated ischemic events, and that the longer the horse is lame the higher the risk is for laminitis; thus, achieving (and maintaining) comfort in the injured limb is of paramount importance. Studies looking at vascular perfusion suggest that even a small amount of motion (i.e. shifting weight) can beneficially impact circulation, so even imperfect pain control may reduce the risk of disease. It is important to remind clients that support limb laminitis can develop days to weeks after the primary injury.

**Future of Laminitis Research**

Laminitis remains an area of intensive research, particularly related to endocrinopathic and pasture-associated disease. Large projects in both the US and the UK (funded by the AAEP Foundation and Animal Health Trust/Royal Veterinary College, respectively) have reached out to equine practitioners and horse owners to enroll both affected and unaffected horses with the goal of standardizing case definitions, identifying risk factors, and developing evidence-based recommendations for prevention and treatment. Additionally, novel approaches such as protein delivery via adeno-associated viral vectors and stem cell transplantation are being developed that someday may have the ability not just to treat laminitis, but to reverse its effects.

**Selected references and recommendations for further reading**


