An update on equine laminitis

Atualização sobre laminite equina

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– REVIEW –

ABSTRACT

     Laminitis is a severe podal affection, which pathophysiology remains partially renowned. Ischemic, enzymatic, metabolic and inflammatory mechanisms are connected to the development of laminar lesions. However, few therapeutic measures are effective to prevent or control the severity of acute laminitis and its prodromal stage, which often determines serious complications such as rotation and/or sinking of the distal phalanx and even the loss of hoof. The purpose of this study is to compile the actual knowledge in respect to the pathophysiology and treatment of equine laminitis.

Key words: *horse, pathophysiology, treatment, podal disease.*

RESUMO

     A laminite é uma grave afecção podal, que permanece com fisiopatogenia parcialmente conhecida. Sabe-se que mecanismos isquêmicos, enzimáticos, metabólicos e inflamatórios estão envolvidos no desenvolvimento das lesões laminares. No entanto, poucas medidas terapêuticas são eficazes para prevenir ou controlar a gravidade da laminite nas fases prodrômica e aguda, o que frequentemente determina sérias complicações como rotação ou afundamento da falange distal e até mesmo perda do estojo córneo. O objetivo deste trabalho é compilar os mais atuais conhecimentos sobre a fisiopatologia e tratamento da laminite em equinos.

Palavras-chave: *equino, fisiopatogenia, tratamento, doença podal.*

INTRODUCTION

     Laminitis is a severe condition observed commonly in equine, generating intense painful discomfort and hoof alterations, often compromising the return to physical activities and reproduction. Treatment failure is responsible for euthanasia of numerous cases of horses with laminitis.

     Effective therapies for different stages of laminitis are scarce, due to lack of knowledge of the exact mechanism of development of the disease. For many years the disease has been associated with the ischemia tissue, nevertheless, recent studies have indicated different mechanisms. Thus, this review focuses on the updated knowledge regarding laminitis based on the latest research findings, mainly the pathogenesis of the disease.

Experimental models of laminitis induction

     The study of inflammatory laminitis, in association with systemic diseases, is being performed by cornstarch induction, black walnut extract and oligofructose administration (WEISS et al., 1997; FAGLIARI et al., 1998; FALEIROS et al., 2009a; LIMA et al., 2013). The disease can also be induced in healthy horses via insulin administration (DE LAAT et al., 2010), in an experimental model related to secondary laminitis to endocrine changes. BELKNAP et al. (2011) induced endochrinopathy laminitis into ponies by a diet rich in carbohydrates for seven days.

     Furthermore, other studies have shown that experimental models of gastrointestinal obstruction/

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ischemia can also promote lesions in the laminar tissue (RIO TINTO et al., 2004; LASKOSKI et al., 2010), which is supported by severe changes in laminar tissue reported in horses with natural colic syndrome not yet evidencing clinical signs of foot disease (LASKOSKI et al., 2009).

Morphological changes of laminar tissue can be even observed in the prodromal phase of laminitis (POLLITT, 1996; LASKOSKI et al., 2009). The main feature is the evidence of modifications involving the interdigitations between dermal and epidermal tissues of the hoof laminar tissue, which are joined by the basal membrane. These structures are responsible by the union of the distal phalanx to the hoof wall (POLLITT, 1996). Classification of severity changes in laminar tissue is surrounded by alterations in the nuclei of basal cells, shape of the secondary epidermal laminar and the outline of the basal membrane. The most severe cases of laminar injury includes total destruction of the interdigitations, with consequent weakness of the tissue, which turns not to be able to maintain the adherence of the distal phalanx to the hoof wall (POLLITT, 1996; LASKOSKI et al., 2010). Laminitis secondary to metabolic abnormalities differs in respect to histopathology of laminar tissue of the hoof, appearing subtle injury of the laminar structures (KARIKOSKI et al., 2014), and being detected even without clinical signs of disease in horses with PPID - Pituitary Pars Intermedia Dysfunction (LASKOSKI et al., 2015).

Clinical Signs

The clinical signs of laminitis more frequently observed are intense podal discomfort, lameness and difficulty in stay in the quadrupedal position, with changes in corneal apparatus of the hoof. On the other hand, the signals may vary according with the stage where the disease is located. The prodromal phase includes the development of lesions in laminar tissue of the hoof, displaying subtle clinical signs, such as increased digital pulse and changes associated with sepsis as congested mucous membranes, tachycardia, increased capillary refill time, anorexia, hyperthermia and intestinal motility reduction (POLLITT, 1999; PARSONS et al., 2007).

When a painful laminitis occurs in the acute phase, the intensity can be assessed by grades of OBEL. At this stage it may occurs stabilization without rotation or sinking of the distal phalanx, and the condition enters into the sub-acute phase, until full tissue repair. However, there may be progression to the chronical phase, mainly if the appropriate therapeutic measures are not carried out in time (HOOD, 1999).

Radiographic modifications showing rotation or sinking of the distal phalanx may supplement the diagnosis of chronical phase of laminitis (MORRISON, 2010). Severity of radiographic changes is commonly associated with pain intensity displayed by the animal, in exception mainly to cases of endochrinopathy laminitis, in which clinical evidence may usually appear in a milder way (JOHNSON, 2002a). In addition it is valuable to note signs of hoof deformation, perforation of the sole, rings formation in the wall of the hoof, stretching of the gripper bead and groove formation in the coronary bald, and it can occur loss of corneal apparatus (HOOD, 1999; MORRISON, 2010).

Laminitis pathogenesis

Laminitis occurs by loss of integrity of the laminar tissue. The rotation and/or sinking of the distal phalanx may occur, secondarily, as a result of the weight down force of the animal and the pull exerted by the deep digital flexor tendon (POLLITT, 1996). Equine with severe trauma in hind or fore limbs, such as fractures that preclude the support of weight on this member, often develop laminitis in the contralateral limb, possibly by reduction of the perfusion of the laminar tissue of the hoof caused by excessive weight (BAXTER & MORRISON, 2008). In fact, only few studies are performed on laminitis in this case.

Experimental results have indicated a correlation of various mechanisms involved in the pathogenesis of the disease, resulting in loss of interdigitations, weakening of the laminar tissue hoof and rotation or sinking of the distal phalanx (POLLITT, 1996; RIO TINTO et al., 2004; LASKOSKI et al., 2009; KARIKOSKI et al., 2014). The main appointed mechanisms are ischemic, enzymatic, endocrine (metabolic) and inflammatory injuries.

Ischemic mechanisms

Ischemia as a cause of laminitis gave rise to the vascular theory, which enlightens the laminar tissue lesions to be initially caused by vasoconstriction digital and/or openings of arteriovenous shunts in laminar tissue, triggering blood stasis and, consequently, tissue edema and necrosis (PERONI et al., 2005; NOSCHKA et al., 2009). Evidence of systemic inflammatory indicates that inflammatory mediators such as cytokines may cause digital vasoconstriction (NOSCHKA et al., 2009).

In addition, thrombogenic events, such as aggregation and platelet adhesion to the endothelium

integrity, commonly in cases of acute abdomen conditions, may result in reduction or lack of blood flow to the laminar tissue of the hoof. MARTINS FILHO (2008) and WEISS (1994) have observed the presence of micro thrombi in laminar vessels, however these findings are not appointed by most histopathological studies.

Experimental results demonstrate the absence of xanthine oxidase, an enzyme released during tissue ischemia (LOFTUS et al., 2007), challenging vasoconstriction as the primary event in the development of laminitis. There are studies demonstrating that sub-laminar vasodilation occurs early in the development of the disease, which is associated to the temperature increase and blood flow in laminar tissue (POLLITT& DAVIES, 1998) proven by scintigraph (TROUT et al., 1990), suggesting that increase of irrigation in laminar tissue might contribute to the failure of interdigitations. The study of VAN EPS & POLLITT (2004) demonstrated that cryotherapy prevents injury of the laminar tissue after laminitis induced experimentally. However, it is known that reduced blood flow detected by venography,   occur in chronical laminitis phase (BALDWIN & POLLITT, 2010).

Enzyme mechanisms

The laminitis could occur by the degradation of basal membrane components such as collagen, for enzymes activated in the hoof or arising from bloodstream (POLLITT, 1996). The enzymes initially implicated in this process were matrix metalloproteinase (MMPs) 2 and 9 (POLLITT, 1996; 1999). The activation of these enzymes it is still little known, suggesting the involvement of bacterial toxins absorbed from the gastrointestinal tract, and inflammatory cytokines triggered by systemic inflammatory response, such as tumor necrosis factor (TNF-α). Among the bacterial toxins that activate MMPs, exotoxins of Streptococcus species, particularly **Streptococcus bovis** assume great importance (POLLITT, 1999). Nonetheless, the increase of the substance may occur as a result of the morphological alteration of the laminar tissue, and not to be the cause of the disease (LASKOSKI et al., 2013).

Endocrine and metabolic mechanisms

Horses affected by Cushing's syndrome, obese animals or the ones receiving high and prolonged concentrations of glucocorticoids (RYU et al., 2004, DE LAAT et al., 2010) show endocrine disorders, such as hyperglycemia, hyperinsulinemia and insulin resistance (DE LAAT et al., 2010). The endochrinopathy laminitis is evidenced by milder clinical signs in comparison with laminitis secondary to inflammatory diseases, and in some animals it may occur rotation of the distal phalanx with hoof structural changes, with less intense painful discomfort which can be inconspicuous or absent (JOHNSON, 2002a).

Equine Cushing's syndrome commonly occur in animals with above 15 years of age and is evidenced by clinical signs of pelage increase, adipose tissue accumulation (especially in the orbital cavity), polyuria and polydipsia, and laminitis (JOHNSON et al., 2002b). The disease is best denominated for the PPID - Pituitary Pars Intermedia Dysfunction, since it occurs due to oxidative damage of the dopaminergic neurons, which fails to inhibit production of the melanocortins by pituitary pars intermedia, and the hypertrophy occur due to high production (MCFARLANE et al., 2005).

Researches indicated a positive correlation between obesity and radiographic measurements for laminitis in Creole and Mangalarga breeds (PAZ et al., 2013; MAGALHÃES et al., 2014). These results indicate that obesity triggers the weakening of the connection between the hoof and the distal phalanx with progressive separation of these structures. Regarding ponies, the overweight ones are the most affected animals (BELKNAP et al., 2011).

The ratio between laminitis and endocrine modifications was best observed after induction of laminitis by continuous insulin infusion in normal ponies (DELAAT et al., 2010). BELKNAP et al. (2011) demonstrated that developed laminitis in equine fed with high-carbohydrate diet is not connected to inflammatory events such as induction of other models. Thus, other causes of injury may be related to the metabolic laminitis.

Inflammatory mechanisms

The development phase of laminitis presents various inflammatory events such as elevated acute phase protein concentrations (FAGLIARI et al., 1998), inflammatory cytokines (LOFTUS et al., 2007), reactive oxygen species (HUURLEY et al., 2006) as well as leukocyte infiltration into tissue (HURLEY et al., 2006; FALEIROS et al., 2009a, LASKOSKI et al., 2013). Systemic inflammatory activation may be from infectious origin such as exposure to pathogen-associated molecular patterns (PAMPs), or even, due to extensive tissue damage associated with endogenous release of the damage associated molecular patterns (DAMPs). Endotoxin, one of the most common PAMPs was detected in the blood of horses after laminitis induced for carbohydrate administration (BAILEY et al., 2009).

There is evidence that laminitis may occur secondarily to systemic inflammatory response (FALEIROS et al., 2008). LASKOSKI et al. (2010) observed changes in the laminar tissue of horses after intestinal obstruction, probably due to systemic inflammatory activation triggered by ischemia-reperfusion injury that occurs in gastrointestinal disorders (RIO TINTO et al., 2004). FALEIROS et al. (2011a and 2009b) showed increase of chemokines in equine hoof with laminitis related to carbohydrate overload induction, which are linked to the activation and laminar leukocyte migration.

The black walnut extract induces leukocyte infiltration into the laminar tissue of the hoof in 1.5 hours, with a significant increase between 10 and 12 hours (FALEIROS et al., 2009a). In case of laminitis carbohydrates induction model, infiltration occurs later, increasing near to clinical signs time (FALEIROS et al., 2011b). Thus, it is supposed that changes in the laminar tissue, which are more severe in this induction model, are directly related to the presence of inflammatory cells. There is an increase of leukocytes in laminar tissue in the development phase laminitis in horses after experimental jejunal obstruction (LASKOSKI et al., 2012), and in horses with natural colic syndrome, especially if they showed leukopenia before death (LASKOSKI et al., 2015).

Apoptosis

The linkage of apoptosis with the pathogenesis of laminitis suggested the development of laminitis, since the laminar material does not display edema ornecrosis in the disease development. Apoptosis is a form of death of the cell which does not trigger a local inflammatory reaction, naturally existing in the laminar tissue of horses. There is an increased apoptosis in horses with laminitis naturally acquired until a week of evolution when compared to horses in the prodromal and chronical phase of the disease (FALEIROS et al., 2004). Increase of apoptotic cells was not observed in equines with experimental intestinal obstruction, which did not show clinical signs of laminitis, but laminar morphological changes (LASKOSKI et al., 2010). Thus, the occurrence of apoptosis may be associated with the severity of the lesions found in an attempt to cell renewal, after the prodromal phase of the disease, when clinical symptoms are manifested.

Treatment

There are several therapeutic treatments available for the treatment of laminitis. The main measures will be presented, highlighting the information based on the results of scientific research.

Treatment of laminitis should be employed according to the clinical phase of the disease. The evidence of inflammation in the hoof laminar tissue during the prodromal phase of laminitis suggests that anti-inflammatory drugs may be useful at this point. LASKOSKI et al. (2012) found that hydrocortisone administration reduces neutrophil gelatinase associated to lipocalin (NGAL), indicating lower leukocyte infiltration into laminar equine tissue once submitted to experimental ischemia and reperfusion. LIMA et al. (2013) evidenced that administration of chemokine antagonists did not reduced painful discomfort in horses with induced laminitis, but prevented the increase of cytokines and epithelial cell degeneration indicators.

In regard to the use of heparin, there are controversial results. MARTINS FILHO et al. (2008) found no reduction in hoof injuries with heparin treatment in the start of lameness, when laminitis was induced for carbohydrate administration. However, the substance prevented laminitis in horses with proximal duodenum jejunitis (LA REBIERE et al., 2008). Additionally to the antithrombotic effect of heparin, it is suggested that the substance contain anti-inflammatory effects.

The most effective treatment prevention realized in the prodromal phase of inflammatory laminitis is the cryotherapy, which immerse equine hooves on ice while there is clinical signs of systemic inflammatory response, such as reddish mucous membranes, increased capillary refill time, tachycardia, tachypnea and depression (VAN EPS & POLLITT, 2004). Cryotherapy is more effective in the prodromal phase of laminitis; on the other hand, VAN EPS et al. (2013) had demonstrated reduction on the severity of acute laminitis, perhaps by reducing the edema resulting from the injury already established.

Equine movement restriction in acute laminitis and use of soft boots are utilized to reduce concussion of the hoof, which would trigger even more injury on the weakened tissue (MORRISON, 2010). The acepromazine may also be used to restrict movement of the horse by mild sedation, and there is a vasodilator effect (INGLE-FEHR & BAXTER, 1999), despite of the controversial use this stage.

In cases of secondary laminitis to metabolic abnormalities, it may be managed metformin, which increases sensitivity of cells to insulin, the dose of 15mgkg^{-1} twice a day. The medication evidenced a clinical improvement of 78% of poneys and horses with insulin resistance (DURHAM et al., 2008).

The analgesia in chronical phase is usually performed by administration of nonsteroidal anti-

inflammatory drugs. Regarding the improvement of laminar tissue circulation blood, which in the chronical phase happens to be compromised and often show larger areas of necrosis, INGLE-FEHR & BAXTER (1999) had observed that acepromazine increases digital blood flow, differently from the observation after pentoxifylline and isoxsuprine administration.

Corrective hoof treatment, in the chronical phase of laminitis, has a vast literature. The main treatments are the trimming and horseshoes application and similar appliances, and there are questionable effectiveness techniques, especially by individual response and different degrees of involvement hoof (PARKS & O'GRADY, 2003; MORRISON, 2010). The objectives of these practices are to stabilize the phalanx, reduce the pain and stimulate new hoof growth. The realignment of the distal phalanx and soil should be performed by removing the bead and the wall of the hoof, progressively. The application of traditional horseshoes heart-shaped, oval and inverted has been indicated. However, alternative materials and adhesives have been increasingly used, as fixing a wooden clog under the sole intent to recruit support from the frog and heels, and reduce surface contact with the ground, improving the "breakover", reducing the force to which the hoof let the soil (STEWART, 2010). Strategies to minimize the mechanical detachment, like application of fixing substances in the hoof sole, such as acrylic resin or epoxy in association with horseshoes (MORRISON, 2010) are useful in controlling the progression of the disease. In some cases, tenotomy is recommended, removing the pressure exerted by the tendon over the distal phalanx (HUNT et al., 1990). Resection of the hoof wall in the acute or chronical laminitis, allows the draining of liquids which contributes to the deterioration of the condition injury and edema. In certain cases, when irregular growth of the wall is noticed due to necrosis and committal of coronary band, removal of the wall allows the growth of tissue in realignment to the distal phalanx (RUCKER, 2010).

VAN EPS & POLLITT (2009) evidenced laminar tissue hoof to have high capacity to reorganize after the acute episode of laminitis. However, in some cases, the animal does not present positive response to treatment, and the condition worsens to the point of euthanasia as the last resort to relief suffering.

CONCLUSION

The development of research focused on the treatment of laminitis are fruitless without the knowledge about the pathophysiology of it. With the progress made in recent years, allowing new perspectives of investigations, it is believed that the development of lameness mechanism will be entirely clear and thus more accurate and effective therapies will be found to reduce the severity of this condition.

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