11ème Congrès
de médecine et chirurgie équine
Genève, du 15 au 17 décembre 2009

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11. Kongress für Pferdemedizin und -chirurgie
Genf 15. bis 17. Dezember 2009

11th Congress on Equine Medicine and Surgery
Geneva 15th to 17th December 2009

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HEAVES IN HORSES : ALLERGY OR NON-SPECIFIC RESPONSE TO ENVIRONMENTAL ANTIGENS?

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INTRODUCTION

It has been known since antiquity that stabled horses have an increased risk of developing a chronic, recurrent, and debilitating respiratory syndrome. This condition is now called “Heaves” or Recurrent Airway Obstruction (RAO, and previously COPD, small airway disease, emphysema …). The finding that only a subset of horses developed heaves when exposed to moldy hay was the basis for the proposed “allergy” theory, in which predisposed individuals mount an antigen-specific inflammatory response (hypersensitivity reaction) to components of environmental dust. However, it has recently been suggested that RAO may result from a non-specific inflammatory response to inhaled pro-inflammatory agents including molds, endotoxin, particulates, and noxious gases, which are present in the breathing zone of, stabled horses.

HYPERSENSITIVITY REACTIONS

Type I : hypersensitivity reaction (Allergy)

Because exacerbation of clinical signs can be provoked by the inhalation of moldy hay, it has been postulated that heaves is an allergic reaction to specific inhaled molds and fungi. Investigations have been directed toward the possible roles of specific molds that are abundant in poor quality hay that, when inhaled, cause airway obstruction in animals with heaves, but not in control horses. The report of genetic predisposition to the disease also supports an immune-specific component to the disease.

Studies of atopic human asthmaics and various animal models of allergic pulmonary diseases have highlighted a 2-phase response when sensitized subjects are exposed to inhaled allergens. The early phase response occurs within minutes after susceptible subjects have inhaled an allergen. It is initiated by the activation of cells bearing allergen-specific IgE, primarily mast cells leading to liberation of numerous pro-inflammatory mediators, which induce mucus secretion, vasodilation, microvascular leakage, and airway smooth muscle contraction. Together, these changes result in a narrowing of the airway lumen and airflow obstruction that typically lasts less than 45 minutes to 1 hour (Figure 1). While elevated levels of IgE in bronchoalveolar lavage fluid and serum have been observed, an early phase response is not clinically apparent in horses with heaves, as hours or days of stabling are usually required before airway obstruction ensues. This suggests that IgE mediated mast cell response is not central to the airway obstruction present in heaves.

The second stage, the late phase response, occurs hours after allergen provocation and is reminiscent of the time course of recruitment of neutrophils and development of airway obstruction in heaves. While it was previously believed that the late response resulted primarily from the release of mediators by sensitized mast cells, it is now recognized that T cells, particularly the CD4+ T cells, play a key role in coordinating the asthmatic late phase response. The underlying mechanisms by which a selected T cell population initiates and propagates the inflammatory response include the elaboration of Th2-type cytokines, chemokines, and the interaction with pulmonary leukocytes. Recent reports suggest involvement of Th2-type cytokines in heaves alone or mixed Th1-type/Th2 responses. Interestingly, Th2-type cytokines are capable of contributing to airway inflammation through direct and indirect effects on neutrophils, monocytes, and pulmonary macrophages and endothelial cells.
Type III: hypersensitivity (Arthus) reaction
A type III hypersensitivity reaction to inhaled allergens results from the local pulmonary deposition of immune complexes and the resultant activation of the complement system. This reaction requires pre-sensitization, which is demonstrable by the presence of precipitating antibodies against the offending antigen in the serum of affected individuals. Farmer’s lung in man, a condition associated with a type III hypersensitivity reaction to F. rectivirgula and other thermophilic actinomycetes, shares many epidemiological similarities with heaves. As in heaves, it affects middle age farmers and the disease peaks when farmers feed stored hay to farm animals. Similar to heaves, there is a neutrophilic inflammation in the airway secretions of affected patients. However, the lung pathology in Farmer's lung disease and heaves is strikingly different, with the former being a bronchiolitis and alveolitis with granuloma formation and extensive fibrosis leading to a restrictive respiratory pattern. Also, fever, a characteristic finding in Farmer's lung disease, is not a feature of heaves. For these and other reasons, a Type III hypersensitivity reaction is not considered part of the pathogenesis of heaves.

NON-ANTIGEN SPECIFIC INFLAMMATORY RESPONSES

Typical stabling conditions expose horses to a mixture of gas and airborne dusts, both organic and inorganic, that have been shown to cause airway inflammation in humans. Similarly, stabling induces airway inflammation even in otherwise, young and healthy horses. The contribution of endotoxins, molds and particulates to heaves, as they are abundant in hay, has been recently investigated.

Endotoxins
Poorly cured hay is rich in bacterial components, including endotoxins. Inhalation of endotoxin by humans and animals induces inflammatory lung disease that has many similarities to heaves. However, the concentration of endotoxins required to cause airway obstruction in heaves is much greater that exposure occurring during natural hay and straw challenges. Furthermore, there are high endotoxin levels in Australian hay, where heaves does not occur. These findings suggest that although endotoxins may contribute to airway inflammation in horses, other components of stabled dust are more important in the etiopathogenesis of heaves.

Molds
The contribution of mold components, including allergens, glucans, proteases, and mycotoxins, to allergic airway inflammation is well known in both animals and humans. It has been demonstrated that β-D-glucan, a component of the cell wall of molds, yeast and certain bacteria and plants, can induce inflammation of the airways by non-immune medicated mechanisms. In horses, hay dust suspensions with a higher content of β-glucan are more likely to induce airway inflammation, supporting the concept that molds are involved in the pathogenesis of heaves.

Noxious gases
Stabled animals are exposed to various noxious gases, including ammonia, hydrogen sulfide, methane and
carbon dioxide that can induce airway inflammation. While the levels of these gases in stables are generally lower than those of environments used for food animals, these gases may exacerbate airway obstruction in horses with airway hyperreactivity, as seen in heaves.

**BACTERIAL AND VIRAL INFECTION**

There is currently no evidence indicating that heaves is a septic process. Bacteria often present in the tracheal secretions of heaves affected horses likely represent colonization of the airways due to impaired mucociliary clearance, as histological and cytological findings are not suggestive of infection. It had been suggested, based on circumstantial evidence that severe bouts of influenza and other respiratory infections may predispose horses to develop heaves. This association has yet to be confirmed.

**SUMMARY**

Taken together, heaves likely results from complex interactions between innate and acquired immune responses, environment and genetic susceptibility. While some findings appear conflicting at first glance, they may represent divergent pathways possibly leading to a common heaves' phenotype. Numerous inflammatory pathways are activated in both healthy and heaves susceptible horses when exposed to the strong pro-inflammatory agents present in horses' stables. Whether heaves results from an abnormal response to these antigen, a lack of normal feedback response to down regulate inflammation, or a combination of both, remains unknown. A better understanding of these responses is a prerequisite for the development of novel therapy for targeting selected pathways.

**REFERENCES**


