Immune Dysfunction in Aged Horses

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KEYWORDS

• Immunosenescence • Adaptive immunity • Proinflammatory • Geriatric horse

KEY POINTS

- Aging in horses, as in people, is associated with changes in both adaptive and innate immune responses.
- Age-related progressive impairment in the ability to respond to pathogen challenge and an increased inflammatory reactivity may predispose the geriatric horse to many diseases of old age.
- The high prevalence of pituitary pars intermedia dysfunction (combined with the difficulty in establishing an early diagnosis) means that all aged horses should be considered at high risk of poor immune function and treated accordingly.
- More work is needed to better understand the interactions of age on immunity, vaccine response, and disease risk in the horse.

IMMUNOSENESCENCE

Immunosenescence is the term that describes age-associated remodeling of the immune system that occurs in the elderly, resulting in poor immunity and an exaggerated inflammatory state. In people, immunosenescence is characterized by alterations in the composition of lymphocyte populations, blunted or dysregulated immune response to pathogens, pathogen-associated molecular patterns or vaccinations, and a generalized proinflammatory state.[1] Immunosenescence is considered an important risk factor for morbidity and mortality of the aged, contributing to development of many afflictions of the elderly, including neoplastic, inflammatory, and degenerative diseases. Furthermore, an increased susceptibility to infectious pathogens and a decreased response to vaccines designed to protect against infection are commonly observed in the aged. Albeit limited, current evidence suggests that horses likely undergo similar age-related changes in immune function as that observed in people.

Studies of age-associated changes to immune function are plagued by a unique set of confounders, and as a result, data among the studies are often contradictory.

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For example, the definition of what age constitutes "aged" is arbitrary, yet critical in study design. If horses are enrolled too young, age-associated changes may not yet have occurred. If enrollment is limited to the extremely old, there may be a selection bias for those animals that have survived to extreme old age in part due to exceptional immune function.[2] If the goal of the study is to identify how immune function becomes defective and leads to increased risk of disease in the aged, those with exceptional aging may not be appropriate. In geriatric horses, often actual age is not known, but estimated from dental wear, a process known to be highly inaccurate.[3] In the elderly, the presence of undiagnosed or subclinical disease is common and may have an impact on immune response.[4] Endocrine and metabolic abnormalities frequently affect old horses, and can be strong influencers of immune function.[5]

AGE-ASSOCIATED CHANGES IN IMMUNE FUNCTION

Cell Populations

Age-associated alterations in lymphocyte subset populations have been documented in several species including people, dogs, and rodents.[6–9] The most consistent change associated with age is a decrease in the number of naïve T cells (CD45RA), which has been documented in aged people, nonhuman primates, and rodents.[10–13] The decrease in naïve T cells has been postulated to be the result of thymic involution.[14] In addition, it has been suggested the loss of naïve T cells may be a consequence of chronic antigenic stimulation.[15,16] Immune response to lifelong latent infections by viruses, especially cytomegalovirus (CMV), are believed to contribute to depletion of the naïve lymphocyte pool.[17,18] Concurrent with the loss of naïve T cells, clonal expansion of CD8 memory cells specific for cytomegalovirus have been observed in the elderly.[18] Furthermore, CMV infection of specific pathogen-free mice was shown to reduce antiviral T-cell responses, reduce vaccination efficiency, and accelerate accumulation of effector memory CD8 T cells, lending direct evidence that exposure to pathogens can restructure the immune system, even in the absence of disease.[19] Due to a lack of available antibodies that can differentiate equine naïve from memory cells, changes in naïve T-cell populations have not been directly examined in the aging horse.

Other findings in human leukocyte populations include alterations in the total number of lymphocytes, CD4, CD8, and B cells. CD4/CD8 ratio, an indicator of an inflammatory versus immunosuppressive bias, has been reported to be altered in human geriatric populations.[20–22] Several studies have investigated lymphocyte populations in aged horses and ponies.[23–27] The total number of lymphocytes, CD4, CD8, and B cells all decrease in aged horses.[23–27] Total lymphocyte percentage also decreases, whereas the percentage of CD4 lymphocytes increases.[25,26] CD4/CD8 ratio was found to be increased in aged horses,[25] suggesting a proinflammatory state occurs in old horses as in aged people.

Cytokine and Acute-Phase Protein Profiles in the Aged Horse

Serum cytokine profiles in aged people typically favor a proinflammatory phenotype.[28,29] Aged horses also show similar cytokine profiles with increased gene expression of tumor necrosis factor (TNF)-α, interleukin (IL)-6, IL-1β, IL-8, interferon (IFN)-γ, IL-15, and IL-18,[26,30] and increased proinflammatory/anti-inflammatory cytokine ratios, including IL-6/IL-10 and TNF-α/IL-10.[30] When cytokine concentration was examined at the protein rather than gene expression level, serum cytokine concentration of TNF-α was increased in aged horses in one study[26] but not another.[30] Several confounding factors might affect serum TNF-α concentration, including concurrent