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Review

Autoimmune disorders in horses: the role of Insect Bite Hypersensitivity (IBH) and other inciting factors

[1]*Onyiche T. E., [1]Malgwi, E. A., [1] Okoro D. O., [2]Boyi N., [1] Biu A. A. & [3]Thekisoe O.

[1]Department of Veterinary Parasitology and Entomology, Faculty of Veterinary Medicine, University of Maiduguri, Nigeria, [2]Department of Animal Science and Range Management, Modibbo Adama University of Technology, Yola, Nigeria, [3]Unit for Environmental Sciences and Management, North-West University, Potchefstroom 2531, South Africa.

*Corresponding author: et.onyiche@unimaid.edu.ng, +2348037035135

ABSTRACT

Autoimmune disorders are exaggerated immunologic responses to harmless antigens. The incidences of these conditions in animals specifically horses are on the increase. Autoimmune skin disorders of horses such as multi-systemic eosinophilic epitheliotrophic disease (MEED) and Pemphigus foliaceus (PF) are triggered by insect bite hypersensitivity principally due to *Culicoides* and *Simulium* species respectively. Other relatively uncommon skin disorders of horses include pemphigus vulgaris, cutaneous lupus erythematosus, bullous pemphigoid, systemic lupus erythematosus, and erythema multiforme. The roles of risk factors such as autoantibodies and changes associated with age in the immune system of equines such as immunosenescence and inflamm-aging, and the diagnosis, treatment, and management of some major autoimmune diseases of horses are discussed in this review. Additionally, we reviewed recent information on autoimmune thrombocytopenia in equines.

KeyWords: Autoimmune disorders, horses, hypersensitivity, insect bite related inciting factors.

INTRODUCTION

Autoimmunity just like other conditions such as infectious diseases, allergic disease, and developmental diseases is high on the list of pathogenic aetiology that is similar between humans and domestic animals (Gershwin, 2007). Autoimmune and allergic disorders simply denote exaggerated immune responses to harmless antigens which could either be from innocuous environmental organisms or from within one's body (Maizels, 2016). When tolerance to "self" antigens is lost, autoimmune disorders arise. Dysfunctional activation of B-cells as well as T-cells are pathways leading to inflammation and hence, autoimmune disease (Baranzini, 2013).

Autoimmune diseases are characterized by a multifactorial aetiology, in which environmental factors interact with genetic factors. Diverse genetic factors are associated not only with disease susceptibility but also with specific autoantibodies and disease phenotypes (Ceccarelli *et al*., 2016). Autoimmune diseases share several risk loci which suggest the involvement of common pathways to loss of tolerance. Therefore, this review aims to give an overview of the most common types of autoimmune diseases of horses including their clinical manifestations, diagnosis, and treatment. The role of insect bite hypersensitivity and other factors in triggering and modulating autoimmune diseases in equines are outlined.

INSECT BITE HYPERSENSITIVITY AS A TRIGGER OF AUTOIMMUNE DISEASES IN HORSES

There are a good number of blood-feeding insects that infest horses. These insects serve as vectors for fungal, bacterial, parasitic, and viral pathogens. The point of attachment to the host by these vectors may result in wounds that may serve as a portal for secondary infections. Also, skin irritation could occur which are a result of host immune reactions to the bite by these vectors. Common blood-feeding insects of horses include biting midges (*Culicoides* species), horseflies (*Tabanus* species), stable flies (*Stomoxys calcitrans*), black flies (*Simulium* species) and mosquitoes. (Hemmer & Wantke, 2020).

Insect bite hypersensitivity (IBH) is a recurrent chronic seasonal allergic dermatitis triggered by the bites of different

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species of blood feeding dipterous insects of the genus *Culicoides* and *Simulium*. IBH in horses is one of the most common allergic skin diseases incited by salivary allergens more specifically towards *Culicoides* species (Birras *et al*., 2021). This condition is an IgE-mediated allergic dermatitis. IBH is also known as *Culicoides* hypersensitivity, summer eczema, sweet itch, Queensland itch or Kasen (Anderson *et al*., 1993; Kurotaki *et al*., 1994; Miller *et al*., 2019; Birras *et al*., 2021). IBH was first described in 1840 and is currently regarded as the best characterized allergic disease in horses (Fettelschoss-Gabriel *et al*., 2018). IBH is widely distributed worldwide (Schaffartzik *et al*., 2012) and the prevalence range from 5-60% depending on the geographical region with high prevalence in countries such as Great Britain, Australia and Europe (Steinmann *et al*., 2003; Van Grevenhof *et al*., 2007; Schaffartzik *et al*., 2012); as well as the degree of exposure to the insect bite (Baselgia *et al*. 2006). In addition, the prevalence varies with the geographical distribution of *Culicoides* species (Anderson *et al*., 1988., Steinman *et al*., 2003; Schaffartzik *et al*., 2012). Clinically, IBH-affected horses experience weeping, hairless body conditions and ulcerative lesions during warmer months of the year. Affected lesions are characterized by lichenification, hyperkeratosis, swelling, bleeding and excoriations due to scratching and haemorrhagic crust formation which are mainly found in the dorsal and ventral line as seen in the tail area and mane (Schaffartzik *et al*., 2012; Jonsdottir *et al*., 2019). In some instances, there could be secondary infections with mites, bacteria and fungi which cause further local irritations (Fettelschoss-Gabriel *et al*., 2018).

Diverse breeds of horses are affected by IBH across the world and it has been attributed to underlying genetic components (Schurink *et al*., 2013). For example, the heritability estimates of IBH vary from 0.16 in Friesian horses, and in Swedish-born Icelandic horses, the estimates were given as 0.33. Knowledge regarding the genes responsible for this variability remains limited. Also, Icelandic horses do not suffer from IBH as horse-biting *Culicoides* species are absent in Iceland region. However, over 50% of adult Icelandic horses exported to continental Europe develop IBH within 2 years after exposure to *Culicoides*, while Icelandic horses born in Europe have lower prevalence of IBH compared to other breeds (Bjornsdottir *et al*., 2006; Jonsdottir *et al*., 2019). On the other hand, if the horses were born in Iceland and exported out of the country before seven months of age and exposed to *Culicoides*, such horses do have low risk of developing IBH just like the locally bred horses, suggesting that early exposure to *Culicoides* allergens is essential for the development of immune tolerance (Schaffartzik *et al*., 2012; Sommer-Locher *et al*., 2012). In a nutshell, the observations enumerated are largely due to lack of development of immunological tolerance in early life (Schaffartzik *et al*., 2012). In other words, the prevalence increases with the age of export (Sommer-Locher *et al*., 2012).

The bites and saliva of the female biting midge (*Culicoides* species), as well as that of the black flies (*Simulium* species), contain allergens that cause an immediate Type-1 hypersensitivity reaction (Wagner *et al*. 2009; Schaffartzik *et al*., 2010). Salivary proteins are allergens responsible for these immune reactions. Stable flies (*Stomoxys calcitrans*) and horse flies (*Tabanus* species) have also been implicated as likely causes besides *Culicoides* species and *Simulium* species which could be due to cross-reactivity between conserved allergen structures (Anderson *et al*., 1993). Additionally, environmental, genetic, and epigenetic factors are known to play some roles in the pathogenesis of IBH (Marti *et al*., 2008; Vychodilova *et al*., 2013). Allergic dermatitis arising from the bites of *Culicoides* species has been reported in other domestic animals like cattle and sheep (Yeruham *et al*., 1993). The allergic reaction triggers inflammation in the affected areas leading to itchy skin and hair loss most notably along the chest, tail, mane, shoulders, and midline of the abdomen (Figure 1) which are known preferred feeding sites for the insects (Schaffartzik *et al*., 2012; Fettelschoss-Gabriel *et al*., 2018). The estimated age of onset is within 2–4 years (Schurink *et al.,* 2013). Clinical

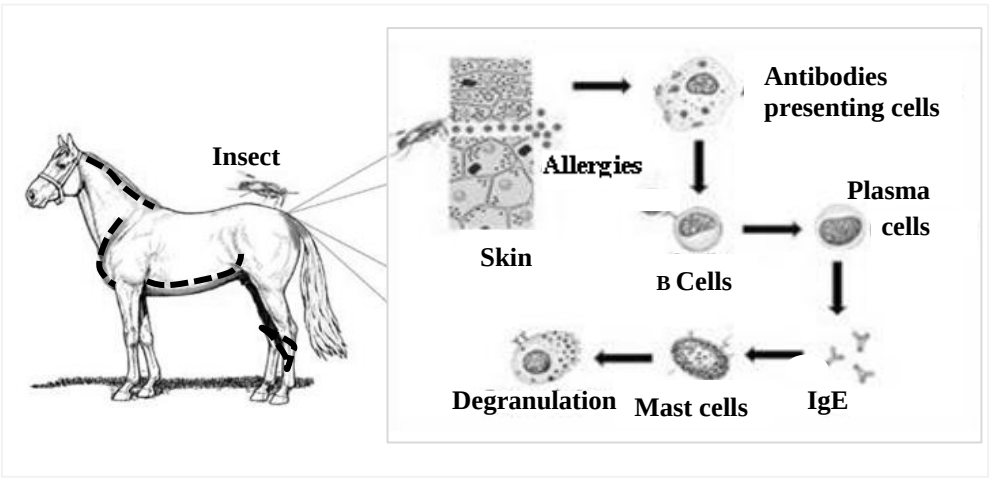

Figure 1: Schematic presentation of the mechanism of immune reaction in Insect Bite Hypersensitivity (IBH) in the horse (body areas marked with broken lines are the preferred biting sites). IgE; immunoglobulin E

manifestation of this condition becomes worse with an increase in the grazing season (Broström *et al*., 1987).

IMMUNOPATHOGENESIS AND CELLULAR RESPONSES IN IBH

Type I hypersensitivity reactions have been shown to play a major role in the pathogenesis of IBH. In the course of sensitization, cytokines such as interleukin (IL)-25, IL-33 and thymic stromal lymphopoietin (TSLP) are released from injured or inflamed epithelial cells inducing type 2 innate lymphoid cells (ILC2) to produce IL-5 and IL-13 (Eberl *et al*., 2015; Camelo *et al*., 2017). Under the effect of these cytokines, antigen presenting cells (APC) direct the immune response towards the production of IL-4 and IL-13 with the help of helper T cell (Th)2. Subsequently, B cells undergo class switch to produce allergen-specific IgE that binds to high affinity FcεRI receptors on mast cells and basophils leading to sensitization (Marti *et al*., 2021). When an allergic subject with prior exposure to the allergen, on re-exposure to the allergen, there is cross-linking of IgE bound to high affinity FcεRI receptors on mast cells leading to release of different mediators, causing the clinical signs of immediate hypersensitivity. Infiltration of leucocytes such as T helper 2 (Th2) cells, eosinophils and basophils at the site of the allergic reaction is followed by late-phase reaction peaking 24 h post exposure (Marti *et al*., 2021). Furthermore, with regards to earlier studies on the immunopathology of IBH, they was reported increase in the population of CD4+, Langerhans, and eosinophil cells in the skin (McKelvie *et al*., 1999). Lesions associated with IBH have increased numbers of IgE positive cells. Also, a substantial population of IgE mRNA expressing cells were observed indicating the involvement of IgE synthesizing plasma cells (Haegen, 2001). The increase in T-cells population is associated with a concomitant reduction of regulatory cells most importantly $CD4^+$ and Forkhead box P3 $(FOXP3)^+FoxP3^+$. Furthermore, it was observed in the skin lesions that the transcription patterns indicate reduced $FoxP3^+$, increased IL-13 expression, and absence of IL-4 transcription (Wilson, 2014). Additionally, the peripheral blood lymphocytes have a large population of IL-4 positive cells after activation by antigens of *Culicoides* species unlike in the healthy horses indicating the possible role of Th2 cells (Hamza *et al*., 2007). Further experiments demonstrated the activation of peripheral blood lymphocytes (PBL) and downregulation of IL-4 production in the healthy horses following the addition of supernatant from the culture of *Culicoides* species antigen (Jahn, 2006).

THE ROLE OF AUTOANTIBODIES IN AUTOIMMUNE DISEASES

As earlier mentioned, the onset of autoimmune diseases (AID) is the result of interactions between environmental and genetic factors, which results in malfunctioning of the immune system. Autoimmune diseases are characterized by the presence of autoreactive T cells and autoantibodies (Hu & Deng, 2014). When this happens, the antimicrobial defenses of the immune system react against normal body components which result in systemic immunopathology. Therefore, one of the most consistent findings in AID is the presence of circulating autoantibodies. The arrival and detection of autoantibodies is a trademark of numerous autoimmune diseases (Shrestha *et al*., 2015). These autoantibodies provide diagnostic and prognostic clues for the care and management of AID (Hu & Deng, 2014).

AGE RELATED CHANGES IN THE IMMUNE SYSTEM OF EQUINES

Horses older than 20 years (geriatrics) slowly exhibit a general decline in body condition, muscle tone, and well-being (Pamplona *et al*., 1998). No clear evidence exists to link these changes with the decrease functions of the immune system (Hansen *et al*., 2013). As scientific evidence increases, it was obvious that as aging commences, there will be an overall decline in immune function commonly referred to as "immunosenescence" in older horses (Hansen *et al*., 2013). These horses were observed to exhibit exaggerated inflammatory responses known as inflamm-aging (Franceschi *et al*., 2000). In the elderly human population, Inflamm-aging is linked with increased morbidity and mortality in human elderly populations. Therefore, a similar outcome is expected in older horses (Hansen *et al*., 2013).

AGING OF THE INNATE AND ADAPTIVE IMMUNE SYSTEM IN HORSES

Discrepancies exist in the haematology in horses as they age. The most notable change is the decrease in the total white blood cells (WBC) (Horohov *et al*., 2002). Increased levels of apoptotic WBC in geriatric horses have been observed without a corresponding age-related change in the antioxidant's status (Williams *et al*., 2008). Furthermore, contradictory evidence indicates changes to the population of lymphocytes in the equine as age increases. An increase in the population of CD5+ and CD4+ cells has been observed in geriatric horses (Adams *et al*., 2008). Additionally, the results of the CD4/CD8 ratio in aging horses are conflicting. In one study, they observe no differences in this ratio (Adams *et al*., 2008); while two other studies demonstrated a higher ratio (Guirnalda *et al*., 2001; Horohov *et al*., 2002). Furthermore, it was observed in geriatric horses that the peripheral blood mononuclear cells (PBMCs) decrease during the proliferative response *in vitro* to different mitogens (Horohov *et al*., 2002; Adams *et al*., 2008; Katepalli *et al*., 2008). Also, horses with lower proliferative capacity resulting in fewer diving cells in response to mitogens were experiencing cell senescence due to aging

(Adams *et al*., 2008; Horohov *et al*., 1999). Age-related increase in Interferon gamma (IFN- γ) expression in equine lymphocytes has been recognized in non-dividing CD4+T-cells (Adams *et al*., 2008). Finally, an age-related decrease in the population of B-cells in the equine has been determined without changes in serum concentration of immunoglobulins such as IgG, IgM, IgG(T) or IgA (McFarlane *et al*., 2001) but it was observed in another study, a decline in IgG with age (Katepalli *et al*., 2008)

AUTOIMMUNE DISEASES OF HORSES: MULTISYSTEMIC EOSINOPHILIC EPITHELIOTROPHIC DISEASE (MEED)

It is a chronic wasting disease of horses characterized by the development and presence of granulomas (nodules or masses) in several organs. Inflammatory cells principally eosinophils constitute these granulomas (Black & Mace, 2004). The pathogenesis and causes are still largely unknown. But it is believed to be connected to a type 1 hypersensitivity response to nematode parasites as a possible cause. Furthermore, hypersensitivity to *Culicoides* species has also been speculated to trigger MEED in horses (Laisse *et al*., 2017). Bites by *Culicoides* species have been known to lead to a type I hypersensitivity (immediate) reaction (Craig, 2011). Furthermore, regular occurrences of type I hypersensitivity due to inhaled or ingested antigens of the parasites have been speculated to be involved in the development of MEED (Mauldin & Peters-Kennedy, 2016). Hypersensitivity, parasitism, lymphoma, and genetic disorders are frequently associated with eosinophilia (Wilkie *et al*., 1985; La Perle *et al*., 1998). Younger horses are affected predominantly and no breed or sex predisposition or specific geographic incidence (Laisse *et al*., 2017). Both thoroughbred and standardbred horses are most frequently affected (Black & Mace, 2004; Mauldin & Peters-Kennedy, 2016). MEED has been sporadically reported in the United States (Mccue *et al*., 2003; Pucheu-haston & Del Piero, 2013); United Kingdom (Henson *et al.,* 2002); Canada (Wilkie *et al*., 1985); New Zealand (Black & Mace, 2004) and Brazil (Laisse *et al*., 2017).

CLINICAL MANIFESTATIONS

The pathogenesis of this condition in horses remains unclear, based on the organs affected, and varied associated clinical signs. Common clinical signs include anorexia, weight loss, diarrhea, exfoliative dermatitis, and pruritus (Gehlen *et al*., 2003)**.** The gastrointestinal tract and the skin are most commonly affected. Cutaneous lesions begin with dry, scaly cracks in the coronary bands and the oral mucosa is inflamed. Then subsequently, it becomes widespread with crusting and exudation over the limbs, face, and ventral abdomen. It may later progress to alopecia (hair loss), thickening/cracking of the skin as well as pruritus. These cutaneous lesions have been observed in over 60% of MEED cases (Schumacher *et al.,* 2000). However, it is important to note that this must be differentiated from other skin lesions. Horses with MEED also present cutaneous signs such as epidermal ulcerations, lichenification, and hyperkeratosis. The head and lower parts most especially the coronary bands, are always involved (Wilkie *et al*., 1985; Maudin & Peters-kennedy, 2016). Cutaneous manifestations of MEED have also been attributed to some factors which include malabsorption of fat-soluble vitamins (Wilkie *et al.,* 1985). Gastrointestinal manifestations include inappetence, severe weight loss, and diarrhea. Furthermore, MEED must be separated from other chronic inflammatory bowel diseases of horses including lymphoplasmacytic enterocolitis, granulomatous enteritis, and idiopathic eosinophilic enterocolitis. One notable difference between MEED and other chronic inflammatory bowel diseases of horses is chronic pancreatitis (Schumacher *et al*., 2000). Finally, horses with MEED most often presents hypoproteinemia (La perle *et al*., 1998; Gehlen *et al*., 2003; Roufosse *et al*., 2004).

DIAGNOSIS

There are no specific diagnostic tests for clinical confirmation of cases of MEED in horses. Diagnosis is primarily arrived using the principle of exclusion. The histopathological examination has been proven to be very effective and reliable in the diagnosis. But this can only be done following death or euthanasia of the affected horse. Differential diagnoses are systemic lupus erythematosus, granulomatous enteritis, and Pemphigus foliaceous. Others are lymphoma with dermal and systemic involvement.

TREATMENT

Treatments for MEED include the use of antibiotics, corticosteroids, and anthelminthic agents (Schumacher *et al.,* 2000). Single or combined treatment with prednisolone (Henson *et al*., 2002) and dexamethasone with trimethoprim-sulfamethoxazole have also been used. The use of antihistamine is also necessary (Mccue *et al*., 2003) as this is helpful and improves the horse's condition at the early onset of the disease. Laisse *et al.,*. (2017) noted marked clinical improvement following treatment with enrofloxacin and triamcinolone. The majority of affected horses with MEED die or are euthanized due to poor prognosis as a result of a lack of response to treatment (Gehlen *et al*., 2003; Black & Mace, 2004).

PEMPHIGUS FOLIACEUS (PF)

This is the most common and potentially life-threatening autoimmune skin disease of horses (Zabel *et al*., 2005). The affected animal makes antibodies against his skin. These antibodies destroy the intracellular cohesion that holds the skin cells together. This leads to acantholysis of the skin leading to oedema of the skin and the formation of blister or

pustule within the epidermis (Laing *et al*., 1992; Scott *et al*., 2003). This condition is common in horses from 2 months - 25 years of age (Vandenabeele *et al*., 2004). Various researchers have reported no predilection based on breed, age, or sex (Scott *et al*., 1983; Pascal *et al*., 1995; von Tscharner *et al*., 2000).

The exact etiology of Pemphigus foliaceous remains unclear. Some experts believe sensitivity to black flies as well as *Culicoides* gnats can be inciting factors. The condition seems to reoccur or worsen during warm weather, suggesting the involvement of seasonal allergens such as pollens and ultraviolet light in some cases (Scott, 1989; White, 1992). Furthermore, veterinarians believe drugs such as antibiotics, vaccines, and some supplements can trigger the condition. The clinical condition in other species does appear to have a genetic predisposition (White, 1992; von Tscharner *et al*., 2000). Finally, Pemphigus foliaceous is speculated to be associated with hypothyroidism in horses (Peter *et al*., 1981).

CLINICAL MANIFESTATIONS

Various nonspecific systemic signs including fever, anorexia, depression, lethargy, and weight loss are associated with this condition. Non-regenerative anaemia, neutrophilia, and hypoalbuminaemia are some of the clinicopathological findings that have been reported (White 1992). Lesions seen are usually fragile vesicles, bullae and pustules. Others signs include erosions, alopecia, epidermal collarettes, crusts, exudation, and scaling (Scott *et al*., 2003). These lesions are often seen in the head and lower extremities (von Tscharner *et al*., 2000; Scott *et al*., 2003) with subsequent dissemination to other areas within a short period usually 1-3 months (Scott *et al*., 2003). Oedema may develop in the ventral abdomen and lower extremities (Scott 1989; White 1992), and notably in the hind limbs (von Tscharner *et al*., 2000) but spreads to other areas within 1-3 months (Scott *et al*., 2003). The face and coronary band may show changes and, in some cases, maybe the only site affected (von Tscharner *et al*., 2000); and in some, the mammary gland or the prepuce may also be affected (Johnson, 1997; Scott *et al*., 2003). The lesions on the coronary band are so painful that the affected horses are reluctant to move (von Tscharner *et al*., 2000).

DIAGNOSIS

Several diagnostic tests such as direct smears, histopathology, and skin biopsies are helpful in the diagnosis of PF in horses. Others useful test including immunofluorescence or immunohistochemical can be employed (Scott *et al*., 2003). Cytological examination reveals large numbers of neutrophils and acantholytic cells in samples collected from crusted areas (von Tscharner *et al*., 2000). Cytology should be complemented by histopathological evaluation. Histological changes observed so far include subcorneal and/or intraepidermal pustules and marked acantholysis (Yaeger & Scott 1993, von Tscharner *et al*., 2000). Several biopsies are needed from intact pustules or crusts to confirm the diagnosis (von Tscharner *et al*., 2000). Pustules are fragile and easily rupture giving rise to surface crusting. Finally, direct immunofluorescence is a reliable diagnostic test. Other useful findings include the presence of immunoglobulin and complement (C_3) in occasional situations in the intercellular spaces (Rosser Jr *et al*., 1983, Day & Penhale, 1986). In the horse, any diagnosed condition(s) characterized by scaling and crusting are differential diagnoses of PF (von Tscharner *et al*., 2000).

TREATMENT

Long-term glucocorticoid administration (prednisolone or dexamethasone) has been proven to be helpful. Additionally, the administration of omega fatty acid, supplementation of vitamin E, restriction of the affected animal to sunlight, and addressing any underlying causative factors including fly bite allergies, diets, and drug administration are also helpful in the management of this condition. Horses that fail to respond to the above treatment regimen might require treatment with injectable gold salts, azathioprine, and/or oral pentoxifylline (von Tscharner *et al*., 2000). Euthanization is the last option when treatments fail or following development of laminitis secondary to treatment, or the treatment costs become prohibitive. The prognosis in affected horses largely depends on the age of onset (Zabel *et al*., 2005). Younger horses less than one year of age have been proven to have a better prognosis (von Tscharner *et al*., 2000). However, horses older than five years have poorer prognosis requiring aggressive treatment (von Tscharner *et al*., 2000). Remission has been reported but it is rare (Scott *et al*., 2013).

EQUINE AUTOIMMUNE THROMBOCYTOPENIA (EAT)

Thrombocytopenia is a condition due to either decreased platelet production from the bone marrow, increased peripheral platelet destruction, increased platelet utilization, or platelet sequestration (Sellon *et al*., 1996b). Immune-mediated thrombocytopenia (IMT) is a result of any or combination of the following namely, increase platelet destruction leading to a decrease in peripheral thrombocytes number and the presence of antibodies associated with platelets. These antibodies (IgG) bind to the surface of platelets resulting in premature platelet destruction (Newman *et al*., 1989). In horses, the condition may be due to idiopathic thrombocytopenic purpura and autoimmune thrombocytopenia (Larson *et al*., 1983) or secondarily sequel to another disorder (Sellon *et al*., 1996a; Cohen & Carter, 1991). Equine infectious anemia virus has also been found to be associated with IMT (Sellon *et al*., 1996b). This disease is characterized by the formation of an immune complex consisting of Equine Infectious Anaemia (EIA) virus

particles and antibodies deposited on the platelets (Clabough *et al*., 1991; Sellon *et al*., 1996b). Immune-mediated thrombocytopenia (IMT) has been reported in horses with idiopathic disorder (Sellon *et al*., 1996a) and lymphosarcoma (Reef *et al*., 1984). Idiopathic thrombocytopenia purpura in the horse is characterized by a decrease in the number of circulating platelets in the absence of other recognizable haemostatic dysfunction. The Platelet life span is shortened either by indirect involvement in an immune reaction or directly by the reticuloendothelial organs when specific antibodies are directed against them (Sellon, 1998). Generally, age, sex, and breed predisposition do not play any role in the degree of susceptibility although it is more prevalent among young adult thoroughbreds. In horses, clinical signs include mucosal petechiae, haemorrhage and mild dependent oedema (Sellon *et al*., 1996a).

DIAGNOSIS

Clinical signs such as petechiation, anaemia and severe thrombocytopenia are seen. Others include platelet clumping, increased platelet volume, and activated partial thromboplastin time (Cohen & Carter, 1991). Variation in the megakaryocytes numbers in the bone marrow aspirates is a useful indication of IMT (Wardrop *et al*., 1996). Among other, clinical and laboratory assessment in suspected cases of thrombocytopenia is vital to assess the presence of platelet-associated immunoglobulin (PAIgG). This is because patients suffering from other autoimmune diseases like systemic lupus erythematous or IMT have PAIgG (George, 1990). Platelet-associated immunoglobulin (PAIgG) is measured using the flow approach by measuring the total IgG (which is the sum of surface IgG and a total of IgG contained in alpha-granules). These two fractions increase in patients with IMT. However, total IgG also increases in non-immune thrombocytopenia (NIT) patients (George & Raskob, 1998).

TREATMENT

The use of immunosuppressive therapy is the approach for the clinical management of EAT. Affected horses show an increase in platelet count after intramuscular administration of dexamethasone in 4-7 days (Morris, 1988). Prednisolone may be used as a substitute for dexamethasone (Morris, 1998; Sellon, 1998).

OTHER UNCOMMON AUTOIMMUNE SKIN DISEASES OF HORSES

Other uncommon autoimmune skin diseases of horses include Pemphigus vulgaris which is a rare autoimmune skin disease in horses (Winfield *et al*., 2013), Systemic lupus erythematosus, and cutaneous lupus erythematosus are recognized in horses but they are rare (Clark, 1988). Bullous pemphigoid is another rare autoimmune disease in horses caused by an immunologic attack of the basement membrane zone by autoantibodies (Olivry *et al*., 2000). Finally, erythema multiforme is an immunologic reaction in the skin in which keratinocyte cell death is the prominent change seen on biopsy (Marshal, 1991).

CONCLUSION

A strong genetic susceptibility is suggested for most autoimmune diseases. In addition, appropriate environmental triggers are indispensable for the initiation of autoimmunity. It has been suggested that loss of tolerance occurs immediately following some inciting events. Insect bite hypersensitivity (IBH) has been recognized as one of such triggers of autoimmune disease of horses. We are of the opinion that with improved knowledge and understanding of some of these events, solutions will be proffered to manage and prevent some of these diseases in equine worldwide.

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