Review on marek's disease and its economic importance.

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Abstract

Marek's disease is a lymphoproliferative and neuropathic disease of domestic chickens, and less commonly, turkeys, quails and pheasants. It is caused by a highly contagious, cell- associated and oncogenic Alphaherpesvirus known as Marek's Disease Virus (MDV) or *Gallidherpes virus* 2 (GaHV-2). Marek's disease is named after JozsefMarek, a Hungarian veterinarian and has different names such as: Range paralysis, Skin leukosis, Neuralleukosis, Neural lymphomatosis and pearl eye. It is recently classified as OIE list disease and characterized by number of conditions such as: lymphomas of visceral organs (ovaries, liver, spleen and kidneys), unilateral or bilateral enlargement of nerves particularly sciatic nerve and brachial nerve due to infiltration of lymphoblasts. Graying of iris due to lymphoblastoid cell infiltration (ocular form) and cutaneous form characterized by nodular lesions at the base of feather follicles. Although the inhalation of infected dust from poultry houses remains the most common route of disease spread and other less common like darkling beetles (*Alphitobiusdiaperinus*), could also play minor roles in indirect transmission.It is not zoonotic and environmental factors, maternal antibody, genetics and age at exposure, virus strain, virus dose and route are the determinant of MD susceptibility. The disease is distributed throughout the world andan outbreak of marek's disease occurred in central Ethiopia and caused high mortality (46%) in commercial poultry farm .Since the disease causes a great economic loss, strict biosecurity, selectively breed chicken lines resistance against MD and vaccination are necessary for prevention and control of the disease. The aim of this paper is to review and present the available information on Marek's disease and its economic importance.

Keywords: *Marek's disease; Economic importance; Vaccination and diagnosis*.

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Introduction

Marek's disease is a lymphoproliferative and neuropathic disease of domestic chickens, and less commonly, turkeys, quails and pheasants. It is caused by a highly contagious, cell-associated and oncogenic *Alphaherpesvirus* known as Marek's Disease Virus (MDV) or *Gallidherpesvirus* 2/GaHV-2. Marek's disease is named after Jozsef Marek, a Hungarian veterinarian and has different names such as: Range paralysis, skin leukosis, Neurallymphomatosisand pearl eye. It is recently classified as OIE list disease and it is characterized by number of conditions such as: Lymphomas of visceral organs, unilateral or bilateral enlargement of nerves particularly sciatic nerve and brachial nerve due to infiltration of lymphoblasts. Graying of iris due to lymphoblastoid cell infiltration (ocular form) and cutaneous form characterized by nodular lesions at the base of feather follicles. Generally, young birds at any age are susceptible but in most cases susceptibility is seen at four weeks of age. Clinical signs appear at reported dead due to MD, clinical findings, vaccination about 2-5 months of age in immature birds. But status etc. was collected from all the poultry farms the disease has also been reported in adult birds [1].

A role for MDV in the etiology of multiple sclerosis of humans has been suggested but was later refuted. The presence of DNA sequences of the gD gene of MDV was described in sera from humans with and without exposure to poultry but genes unique to MDV were not analyzed in these studies. However, any MDV sequences were unable to be detected in 300 human plasma samples by quantitative real-time PCR and at this time, no compelling evidence suggests that MDV infects humans or adversely affects human health. The virus can remain alive in the environment for as long as eight months. It is shed from the feather follicles and spreads in fluff and dust, gaining entry when the bird breathes infected dust particles. It is not spread from the hen to the chicken through the egg and the virus is highly infectious. Once it is present in a flock, it spreads rapidly to unvaccinated poultry.

Healthy birds can be carriers and infect others. Marek's disease could be introduced by importation of live infected birds, hatching eggs and poultry products such as meat and feathers. Appropriate heat treatment can inactivate the virus. Marek's disease does not usually result in immediate death; instead, birds will often die of dehydration, starvation, and persecution from being weak and down. Birds will become progressively weaker and will begin losing weight. If affected birds are not paralyzed, they may suddenly die without warning from the internal tumors.

Literature Review

Etiology

MDV is a cell-associated *Herpesvirus* with lymphotropic properties similar to those of *Gammaherpesviruses*. However,

its molecular structure and genomic organization are similar to Alphaherpesviruses. As per the recent classification by the International Committee on Taxonomy of Viruses (ICTV) all MDV serotypes are grouped together ingenus of *Mardivirus* within the subfamily *Alphaherpesvirinae*. Members of the genus *Mardivirus* described as belonging to the 3 serotypes arenow grouped as the 3 species. These are Gallidherpesvirus 2 (serotype 1), *Gallidherpesvirus* 3 (serotype 2) and *Meleagridherpes* virus 1 (serotype 3). Serotype 1 MDV is the prototype virus for this group of avian viruses and MDV refers to serotype 1 virus. On the basis of their virulence, serotype 1 strains are further divided into pathotypeswhich are often referred to as mild (m) MDV, virulent (v) MDV, very virulent (vv) MDV and very virulent plus (vv+) MDV strains. The serotypic classification for MDV and HVT strain has recently been justified based on the complete sequence for serotype 2 HPRS-24 and serotype 3 FC126 virus strains.

Host range

Chickens are by far the most important natural host with wide differences in genetic susceptibility among the breeds. Natural out breaks of MD are relatively common in Japanese quail. Tumors have occasionally been reported in turkeys but more recently severe outbreaks have been reported in these birds in France and Israel.MD has also been reported in pheasants.

Epidemiology

Distribution: The disease is distributed throughout the world. It is identified in Europe in 1907. It soon appeared in North America and then in other countries depending on the thoroughness of health surveillance which was best on large, modern poultry farms and in specialized abattoirs.

Virus Strain: The virulence of MDV strains varies widely and appears to have increased over time. All virulent or oncogenic strains of MDV belong to serotype 1 and currently four pathotype are recognized as follows: Mild MDV (mMDV) strains cause mainly neural MD and sometimes a low incidence of mainly ovarian lymphomas in genetically susceptible chickens and their pathogenic effects are preventable by HVT vaccine. Virulent MDV (vMDV) strains cause high incidence of visceral and neural lymphomas and their effects are preventable by HVT vaccine. Unlike mMDV and vMDV the vvMDV (very virulent MDV) strains are oncogenic in HVT vaccinated birds and in birds that are genetically resistant to less virulent viruses and their effects are preventable by bivalent vaccine. Very virulent plus MDV (vv +MDV) strains are oncogenic even in birds vaccinated with bivalent vaccines and increasing virulence in this sense appears to be related to increased oncogenicity. Lymphoma formation in adult birds also appears to be associated with increased virulence [2].

Virus dose and route: Dosage may influence disease frequency under natural conditions. The MD response in genetically susceptible birds given virulent virus was found to be maximal even when a limiting dilution of virus was inoculated. Route of exposure probably functions in the same manner because less efficient routes may effectively decrease the dose to the bird.

Transmission of infection: The transmission of MDV occurs by direct or indirect contact, apparently by the airborne route. The epithelial cells in the keratinizing layer of the feather follicle replicate fully infectious virus and serve as a source of contamination of the environment. The shedding of the infected material occurs approximately two to four weeks after infection, prior to the appearance of the clinical disease, and can continue throughout the life of the bird. The virus associated with feather debris and dander found in dust in the contaminated poultry house can remain infectious for several months. Although the inhalation of infected dust from poultry houses remains the most common route of disease spread, other less common like darkling beetles (*Alphitobiusdiaperinus*), could also play minor roles in indirect transmission(PayneandVenugopal, 2000).

Pathogenesis: The pathogenesis of MD is complex. The infection is thought to be transmitted by the respiratory route from the inhalation of infected dust in poultry houses. Although the very early events in the disease are not yet clear, the pattern of events after infection with an oncogenic MDV in susceptible birds can be divided into the following stages: early cytolytic infection, latent infection, late cytolytic infection with immunosuppression and neoplastic transformation.

Marek's disease virus is a lymphotropic virus and targets lymphocytes, the principal cells of the immune system. B lymphocytes, the cells of the antibody-forming arm of the immune system, are first targeted by the virus in a lytic infection. Following this, cytolytic infection occurs in the activated T-lymphocytes that are involved in cell-mediated immune responses. These early cytolytic events result in atrophic changes in the bursa of Fabricius and thymus, leading to severe debilitation of the immune system and marked immunosuppression. The cell-associated viraemia that develops during this period is believed to be the route by which the virus spreads throughout the body and feather follicle epithelium. FFE is the only site where a fully productive infection occurs which allows shedding of the virus into the environment. After the early cytolytic phase, the infection switches to a latent phase in the infected T cells and the regressive changes in the lymphoid organs start resolving, largely restoring the architecture of these lymphoid organs. Following this, some of the latently infected T cells become targets for neoplastic transformation resulting in lymphomatous lesions in various visceral organs. Due to the complex nature of the pathogenesis with varying periods of latency, the incubation period of MD from the point of infection to the onset of clinical disease can vary from a few weeks to several months [3].

Pathology

Macroscopic lesions: In the classical form of Marek's disease, the characteristic finding is the enlargement of one or more peripheral nerves. The most commonly affected nerves that are easily seen on post- mortem examination are the brachial and

sciatic plexus and nerve trunks, coeliac plexus, abdominal vagus and intercostal nerves. The affected nerves are grossly enlarged and often two or three times their normal thickness. The normal cross-striated and glistening appearance of the nerves is lost. They have a greyish or yellowish appearance and are oedematous. Lymphomas are sometimes present in this form of the disease, most frequently as small, soft, grey tumours in the ovary, kidney, heart, liver and other tissues. In the acute form, the typical lesion is the widespread, diffuse lymphomatous involvement of visceral organs such as the liver, spleen, ovary, kidney, heart and proventriculus.

Sometimes lymphomas are also seen in the skin around the feather follicles and in the skeletal muscles. Affected birds may also show involvement of the peripheral nerves similar to that seen in the classical form. The liver enlargement in younger birds is usually moderate compared with that in adult birds, where the liver is greatly enlarged and the gross appearance is very similar to that seen in lymphoid leukosis. In the acute cytolytic form of the disease caused by some of the virulent isolates, extensive atrophic changes may result in the complete disappearance of the thymus and bursa of Fabricius.

Microscopic lesions: Although gross lesions can provide indications of the nature of the neoplasm, histopathological examination is essential for accurate diagnosis. For this, it is important that fresh tissues are collected into fixative from several cases from an affected flock. The useful set of tissues to collect for the diagnosis of Marek's disease include the liver, spleen, bursa of Fabricius, thymus, heart, proventriculus, kidney, gonads, kidney, nerves, skin and other gross tumour tissues. Nerves with B-type lesions show oedema and infiltration by small lymphocytes and plasma cells with Schwann cell proliferation, and the lesion appears to be inflammatory. The C-type lesion consists of a mild scattering of small lymphocytes and plasma cells, often seen in birds that show no gross lesions or clinical signs, and is thought to be a regressive inflammatory lesion.

Demyelination, which is frequently seen in nerves, is responsible for the paralytic symptoms. Birds showing signs of acute transient paralysis have extensive vasculitis involving cerebellum, cerebrum and optic lobes. Lymphomas seen in the visceral organs and other tissues are similar cytologically to the lymphoproliferations in the nerve A-type lesions. The lymphoid cells are usually of the mixed type, with a preponderance of small and medium lymphocytes. But sometimes, especially in adult birds, large lymphocytes and lymphoblasts may predominate. The polymorphic population of the lymphoid cells, as seen in impression smears or tissue sections of Marek's disease lymphomas, is an important feature in differentiating it from lymphoid leucosis. The thymus and bursa of Fabricius in birds with acute cytolytic disease show severe atrophic changes replacing most of the lymphoid cells. Neoplastic lymphomatous lesions can also develop in these organs. Rarely, arterial lesions showing proliferative changes in the aortic, coronary, coeliac and mesenteric arteries are reported in cases of MDV-associated atherosclerosis [4].

Clinical signs

Classical form: It occurs in birds aged 12-24 weeks and affects primarily the peripheral nerves or nerve plexuses resulting in varying degrees of paralysis of particular or several parts of the body. Involvement of sciatic results in progressive lameness of one or both legs and the birds lies on the ground with a tendency to hold one leg stretched forward and the other backward. Paralyzed bird is unable to reach feed and water and usually die from starvation or dehydration. Involvement of the brachial plexus is indicated by droopiness of the wings. Affection of the vagus and intercostal nerves lead to difficult breath (gasping) while affectionsof nerves supplying the digestive tract may be manifested by digestive disturbances as flaccid croup and diarrhea. Occasionally when the cervical nerves are involved there is torticollis, locomotors disturbances are often associated with loss of weight paleness of the comb and wattles and diarrhea although the appetite may remain good.

Ocular form: Ocular form characterized by depigmentation or diffuse grayish fading of the iris of one or both eyes and irregular pupil (serration, slight or pinheaded like) which show progressive loss of light accommodation or blindness.

Cutaneous form: Lesions or deformities at the feather follicles which can be minor to severe and can range from large bumpy nodules to crusty looking lesions and they may be rounded orhard.

Diagnosis

Conventional method: Primary diagnosis is based on age, clinical signs, history and gross and microscopic lesions. Diagnosis of MD is easier in general in chickens younger than 14 weeks of age, although non-bursal tumors could be caused by REV which must be excluded. However, REV non-bursal tumors are generally not recorded in commercial flocks below 14 weeks of age. Lymphoid leukosis is the most likely to be diagnosed in older birds with bursal tumors, but MD virus and REV both can cause bursal tumors. Occurrence of tumours in older birds in the absence of bursaltumors, MD is the most probable diagnosis. Grossly, the disease is characterized by paralysis of legs, wings and neck, and tumor nodules in visceral organs depending upon the tissue or organ involved. Other observations include gray eye (iris) or irregular pupil, vision impairment, blindness, skin lesions and immunosuppressant. Microscopically, mononuclear cell infiltration in one or more of the following tissues: peripheral nerves, gonads, lymphoid organs, iris, muscle, skin and other visceral organs areobserved.

Differential diagnosis: Three grossly similar looking diseases MD, Lymphoid Leukosisand Reticuloendotheliosis (RE) should be differentially diagnosed. The MDV infection is ubiquitous, but the disease is not. The principal methods to identify the presence of infection are isolation of the MDV virus, demonstration of viral DNA or antigens in tissues, and detection of antibody. Infection by MDV in a flock may be detected by isolating the virus from the tissues of infected chickens. However, the ubiquitous nature of MDV must be

taken into consideration and the diagnosis of MD should be based on a combination of MDV isolation or detection of the genome by very sensitive Polymerase Chain Reaction (PCR) and clinical disease [5].

Prevention and control

Biosecurity: Since vertical transmission of infection does not occur in Marek's disease, chickens hatched and reared in isolation will be free of MDV. However, because of the highly infectious and ubiquitous nature of the virus, it is often difficult to maintain freedom from disease without vaccination programs. Nevertheless, the use of vaccines should not be an alternative to good management or implementation of effective biosecurity measures. Management measures followed adequately should delay and lessen the seriousness of the disease. Young chicks should be reared in isolation from older flocks for the first 2-3 months, when the infection is most likely to have serious consequences. An 'all-in/all-out' policy should be the preferred option for the whole site. This would make it possible to break the infection cycle by disinfection when the houses are empty. Removal of used litter and disinfection of buildings are important aspects of disease control, especially in view of the possibility of selection for pathogens with increased virulence. Furthermore, placing the chickens in an environment heavily contaminated with virus before they have developed a solid immunity as it can lead to vaccination breaks. Strict biosecurity is also necessary to prevent the introduction of new MDV strains into a farm. Because insects could act as reservoirs of infection, treatment of premises with insecticides is desirable.

Vaccination: Vaccines are highly effective, often achieving more than 90% protection under commercial conditions. Herpes virus of turkey strain FC-126 is widely used and is highly effective against virulent MD virus. A bivalent vaccine consisting of HVT and a serotype-2 strain SB-1 have been found to have synergistic effect and provide better protection against virulent MDV. In- ovo vaccination is the method of choice due to no requirement of chick handling and immunity develops within two weeks. Because vaccination does not prevent infection with the virus, the MDV has evolved with increased virulence and resistance to this vaccine. As a result, current vaccines used are a combination of vaccines using HVT and *Gallidherpesvirus* type 3 or attenuated MDV strain, CVI988/Rispens. The widespread vaccination provided the host with another important weapon against the virus and the losses from the disease decreased dramatically by over 99%.

An attenuated MDV strain, CVI988, is considered to be the most protective vaccine currently available and has been introduced in many countries. MDV vaccines are administered in-vivo at Embryonation Day (ED). The automatic injectors deposit the vaccine inoculum into the amniotic fluid of the majority of the eggs. However, with increase in cases of vaccination failure and the emergence of more virulent pathogens, the disease poses a severe threat to the poultry industry and challenges the control strategies. Though MD vaccines have efficacy more than 95% they have many inherent drawbacks. The most important one is their inability to induce a 'sterile immunity' in the vaccinated host. This allows the virulent virus strains to replicate and be shed into the environment in spite of the vaccination status of the host. CVI988/Rispens vaccine is useful in turkeys against MD, but HVT was not protective against MD in this species.

Economic Importance

*Prior to the use of vaccines, MD constituted a serious economic threat to the poultry industry causing up to 60% mortality in layer flocks and 10% condemnations in broiler flocks. Because vaccines are not 100% effective, sporadic losses still occur, but they are no longer as serious problem. Purchase (1985) estimated that mortality and condemnation losses due to MD totaled about $12 million in the United States in 1984. When combined with economic loss from the costs of vaccine and application and reduced egg production, however, the total was about $169 million in the United States and $943 million worldwide.) Current worldwide, annual losses in the range of US$ 1 to 2 billion, but they indicated that these figures are impossible to verify. The disease remains a major concern for the poultry industry due to the unpredictability of outbreaks and the possibility that vaccines may ultimately fail as a consequence of the evolution of mo*re virulent strains of MD virus. *In Ethiopia, MD was first diagnosed in 1983 and incidence rate of 3% in industrial poultry farms was reported for the years 1983-1986. An outbreak of marek's disease occurred in central Ethiopia and caused high mortality (46%) in commercial poultry farm, indicating its potential significance for modern chicken production in the country.* During the 3.5 months of outbreak an estimated loss of 76000 birr was incurred during mortality. At present, chickens in Ethiopia are not vaccinated against MD and it is considered as disease of economic significance in chicken production in Ethiopia.

Conclusion and Recommendations

Marek's disease is a disease of chickens produced by a herpesvirus that produces a reduction in the immune response in acutely infected birds followed by the production of tumors in many of the infected birds. It has no zoonotic importance. Very virulent strains ($vvMDV^{+}$) have been reported in a number of countries around the world and have affected broilers, breeders and commercial layers. This disease extensively limits the productivity of both egg producing and meat producing birds resulting in great economic impact in poultry industry. Vaccination, in conjunction with good farm cleaning and disinfection, proper reception practices, all-in/all-out policy, accurate vaccination programs adapted to the type of bird and field situation, good vaccine preparation and administration practices and strict biosecurity measures can greatly reduce the incidence of Marek's disease and thereby prevent the economic losses due to the disease. Based on above conclusion I recommended that:

- *Breeding of genetically resistant poultry should be encouraged.*
- *Strict biosecurity should be followed.*

- *Vaccination program should be implemented in farms.*
- *Governments should backup veterinarian and society both in capital and facility to minimize economic loss.*

References

1. Abdul-Careem MF, Hunter BD, Nagy E, et al. Development of a real-time PCR assay using SYBR green chemistry for monitoring Marek's disease virus genome load in feather tips. J Virol Methods. 2006;133:34-40.
2. Afonso CL, Tulman ER, Lu Z, et al. The genome of turkey herpesvirus. J Virol. 2001;75:971-8.
3. Buscaglia C, Calnek BW, Schat KA, et al. Effect of immune competence on the establishment and maintenance of latency with Marek's disease herpesvirus. J Gen Virol. 1988;69:1067-77.
4. Calnek BW. Pathogenesis of Marek's disease virus infection. Curr Top Microbiol Immunol. 2001;255:25-55.
5. Calnek BW. Marek's disease--a model for herpesvirus oncology. Crit Rev Microbiol. 1986;12:293-320.

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