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Marek's Disease

Zeinab M. S. Amin Girh[1], Nagwa S. Rabie[1] and Mona S. Zaki[2]

[1]Department of Poultry Diseases, National Research Centre, Dokki, Giza, Egypt.
[2]Hydrobiology Department, National Research Centre, Dokki, Giza Egypt.
Drmonazaki@yahoo.com

Abstract: Marek's Disease (MD), caused by Marek's Disease Virus (MDV) which is a highly contagious oncogenic and neuropathic disease of chickens. It is responsible for great economic losses to the poultry industry all around the world and characterized by development of CD4+T cell lymphomas as well as infiltration of nerves and visceral organs by lymphocytes. MD is one of the most common lymphoproliferative diseases of chickens which cause mononuclear cell infiltration in one or more of the following tissues: peripheral nerves, gonads, lymphoid organs, iris, muscle, skin and other visceral organs resulting into development of tumors in visceral organs, paralysis of legs, wings and neck, grey eye (iris) or irregular pupil, vision impairment, blindness, skin lesions and immunosuppression, all of which can be accompanied by non-specific signs such as anorexia, weight loss and poor performance. Thus MD poses a big challenge to the welfare and wellbeing of the poultry with increased condemnation of carcass, loss of productivity and quality products, leading to huge economic losses. It is also an immunosuppressive disease and causes increased susceptibility to other infections. The present review discusses in brief about the Marek's disease, its etiology, conventional and advance tools and techniques being used for its diagnosis, prevention and control strategies in poultry.
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Introduction

Marek's Disease (MD) is a highly contagious oncogenic and neuropathic disease of chickens. It is caused by Marek's Disease Virus (MDV) and is responsible for great economic losses to the poultry industry worldwide. Sporadic outbreaks of MD have been reported recently throughout the world even in vaccinated flocks (Powell and Lombardini, 1986; Kuria *et al*., 2001; Okwor and Eze, 2011; Lobago and Woldemeskel, 2004), including India (Rajkhowa, 2005; Bineesh *et al*., 2007; Jadhav *et al*., 2007; Kamaldeep *et al*., 2007; Raja *et al*., 2009;Arulmozhi *et al*., 2011; Gopal *et al*., 2012). The disease is characterized by development of CD4+ T cell lymphomas as well as infiltration of nerves and visceral organs by lymphocytes. Dr. Jozsef Marek first recognized the disease as a paralysis of roosters in the year 1907. MD almost devastated the poultry industry in the 1960s but the disease was brought under control after Marek's disease Herpes Virus of Turkey (HVT) was identified and live vaccines were developed in 1970's. Thereafter, variant MD viruses evolved with increased pathogenicity. Subsequently, many MD outbreaks have been reported worldwide and new vaccines developed to combat MD viruses with higher virulence. Earlier it is considered as paralytic disease but now-a-days, it is manifested as an acute disease with tumors in multiple visceral organs. Marek's disease (MD) is one of the most economically important and devastating diseases of poultry **(Hassanin *et al*., 2013).** It was first described by a Hungarian veterinary pathologist Jozsef Marek in the last century **(Pastoret, 2004; Biggs and Nair, 2012).** MD is caused by MD virus (MDV) which is a highly infectious, cell associated, and potent oncogenic herpes virus **(Nair and Fadly, 2013).** MDV belongs to the family *Herpesviridae*, subfamily *Alphaherpesvirinae*, and genus *Mardivirus* **(Davison, 2010; Hassanin *et al*., 2013).** The genus *Mardivirus* has three members that are serologically related but distinct species: Gallidherpesvirus 2 (serotype 1), Gallidherpesvirus 3 (serotype 2), and Meleagrid herpes virus 1 (Herpesvirus of turkey [HVT], serotype 3) **(Gimeno and Pandiri, 2013; Lv *et al*., 2017).** All the virulent or oncogenic strains of MDV belong to serotype 1 **(Schat, 2016).** Currently, four pathotypes have been identified which include: mild (m) MDV, virulent (v) MDV, very virulent (vv) MDV, and very virulent plus (vv+) MDV strains **(Schat and Nair, 2013)**. The MDV serotype 2 and 3 are not

pathogenic and are used as candidates for the production of vaccines against MD **(Schat, 2016)**. Similarly, a MDV-1 strain known as MDV Rispens CVI998 is the most effective vaccine strain available which can be used alone or in combination with HVT **(Diaz, 2014).** MDV Rispens CVI988 strain can be differentiated from oncogenic MDV-1 strains by the molecular techniques **(Renz *et al*., 2013; Gimeno *et al*., 2014).** However, one of the fascinating discoveries about MD is that vaccination does not produce sterilizing immunity **(Read *et al*., 2015).** That is, MD vaccines protects the hosts from the clinical disease, but neither prevents them from becoming infected, or block transmission or shedding of virulent MDV strains **(Gimeno, 2008; Pandey *et al*., 2016; Reddy *et al*., 2017).** Chickens are the most important natural host for MD, but the disease has been reported in turkeys, Japanese quails, pheasants, owls, ducks, geese, swans, kestrels, crested partridges, and red-crowned cranes **(Schat and Nair, 2013; Schock *et al*., 2016; Lian *et al*., 2018)**. Virtually, all the chickens, including game fowl and jungle fowl, are susceptible to MDV infection and tumor development (Schat and Nair, 2013). MD is distributed worldwide and it is of serious economic importance in all the countries with well-developed or developing poultry industry (**Biggs and Nair, 2012).** Clinical MD is characterized by depression, death, stunting lethargy, characteristic unilateral paralysis of the legs, and mortality **(Gimeno and Pandiri, 2013).** Because of the ubiquitous nature of MDV, and hence the presence of the virus in many poultry farms, detection of virus, viral antigens, or nucleic acids in the absence of clinical disease does not confirm the occurrence of MD (**Nair, 2018).** Clinical signs of MD accompanied with tumors in multiple organs, and enlarged peripheral nerves at PM may suffice to make a tentative diagnosis **(Nair, 2018).** However, confirmatory diagnosis can be done by immunohistochemistry, histopathology and, Polymerase chain reaction (PCR)-based molecular techniques **(Gimeno and Pandiri, 2013).**

Etiological Agent (Mdv)

The causative agent of the diseases is Marek's Disease Virus (MDV) and as per the recent classification by the International Committee on Taxonomy of Viruses (**ICTV, 2011**), it is placed in Order *Herpesvirales,* family Herpesviridae, subfamily Alphaherpesvirinae and genus *Mardivirus* (Marek's disease-like viruses). MDV is a cell associated herpes virus consisting of a linear, double stranded DNA of 160-180 kbp in size. MDV-Herpes virus group has been divided into three serotypes based on their biological properties viz. serotype 1, 2 and 3. Serotype 1 MDV is virulent and oncogenic whereas serotype 2 and 3 (HVT) are non-pathogenic vaccine strains. Serotype 1 MDV strain viruses are further classified into pathotypes (**Witter *et al.*, 2005**) based on induction of lymphoproliferative lesions and severity of disease in vaccinated chickens.

Economic importance

Neoplastic diseases, and the viruses that cause them, are important in poultry for several reasons. The presence of thevims or the neoplasm causes economic loss from mortality and depressed performance. For Marek's disease (MD), additional costs arise from the development, production and use of vaccines for disease control, and for avian leukosis, from the implementation of virus eradication programmes, particularly by primary breeding companies. The viruses are prevalent throughout the world, but new strains arise periodically in particular locations (especially strains of MDV but also of ALV). If these spread between countries, national disease control measures can be undermined. Before the introduction of vaccination of commercial flocks in1971, MD was a major global disease of chickens. Vaccination dramatically reduced losses, but the disease remains one of significant economic importance, particularly because of the periodic appearance of new strains of MDV against which existing vaccines provide suboptimal protection. This has required the continued development of new vaccines and vaccination strategies **(Calnek and Witter 1997)**. In 1984, the total world-wide economic loss caused by MD, including the cost of vaccination, was estimated at US$943 million **(Purchase, 1985)**. The *International Animal Health Code* of the Office International Epizooties (OIE) places MD on List B, comprised of those diseases which have socio-economic and/or public health importance within countries and which are significant to international trade of animals and animal products **(OIE 1999).**

Virus structure and replication

The isolation of cell-associated herpes virus from MD tumors in the late 1960s **(Churchill and Biggs 1967)** was an important historical landmark which led to an improved understanding of the disease and development of effective vaccines. Due to the lymphotropicnature of the virus, MDV was originally classified as agammaherpesvirus together with Epstein-Barr virus, and the oncogenic herpes viruses of non-human primates, herpesvirussaimiriِ and herpesvirusateles. However, on the basis of the genomic organization, MDV is currently classified together with alphaherpesviruses such as the herpes simplex vims (HSV) in the family *Herpesviridae.* The deoxyribonucleic acid (DNA) of MDV is a linear double-stranded molecule of approximately 170 kilobases, consisting of a unique long region **(UL)** flanked by a set of inverted repeat (TRL and IRL) regions and a unique short region **(US)** flanked by another set of inverted repeat regions (IRS and TRS)

(Ross,. 1999). Thus, the genomic structure of MDV from left to right can be described as **TRL-UL-IRL-IRS-US-TRS** and is similar to that of other alphaherpesviruses. The viral genomes in the infected cells are maintained either as circular episomes or as integrated forms. The viral genome has the capacity to encode at least seventy proteins sixty of which have counterparts in HSV, including structural proteins, metabolic enzymes and transactivating proteins such as VP 16 and ICP4 **(Ross,. 1999).**

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