

GALLID HERPESVIRUS 2 (MAREK'S DISEASE VIRUS)

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GALLID HERPESVIRUS 2 (MAREK'S DISEASE VIRUS)

- MDV is an alphaherpesvirus belonging to:

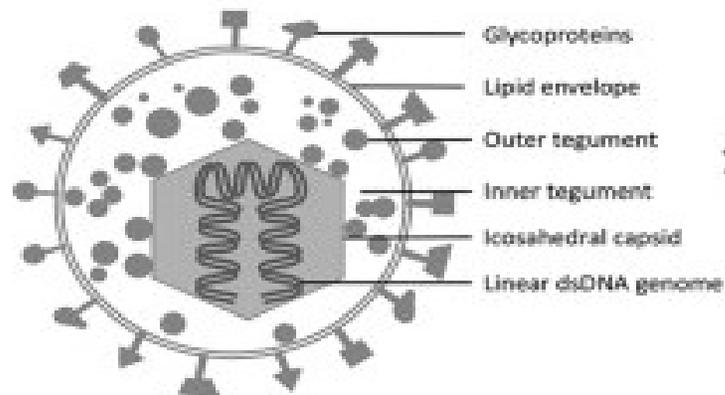
Order: *Herpesvirales*

Family: *Herpesviridae*

Subfamily: *Alphaherpesvirinae*

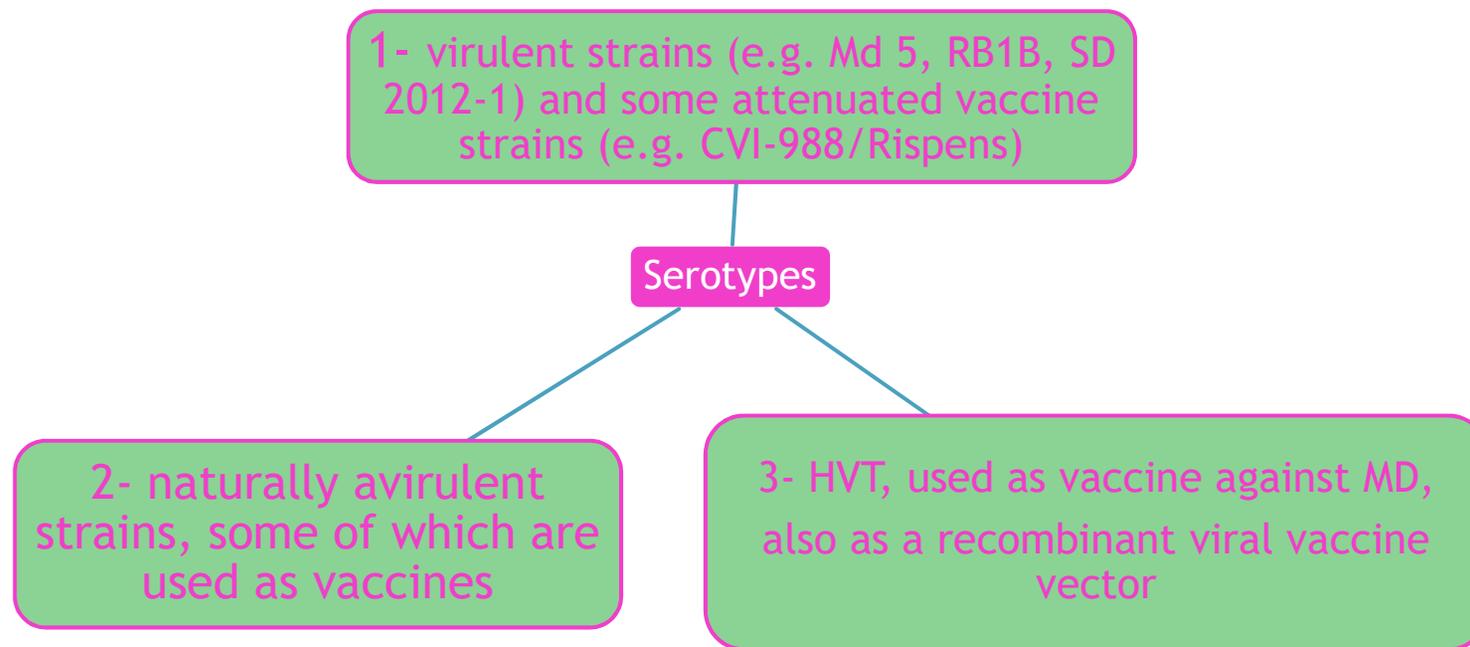
Genus: *Mardivirus*

- ▶ MDV - with linear dsDNA enclosed within an icosahedral nucleocapsid, surrounded by tegument proteins and the lipid envelope containing several viral glycoproteins



Genus Mardivirus

- ▶ Includes three species (serotypes) designated as
- ▶ Gallid herpesvirus 2 (serotype 1)
- ▶ Gallid herpesvirus 3 (serotype 2)
- ▶ Meleagrid herpesvirus 1 or herpesvirus of turkeys (HVT) (serotype 3)
- ▶ Virulent GaHV-2 strains further classified as weakly virulent, mildly virulent, virulent, very virulent and very virulent plus



Serotypes

Serotype 1

- ▶ Includes all the **pathogenic strains** of the virus
- ▶ very virulent plus (e.g. 648A)
- ▶ very virulent (e.g. Md/5, Md/11, Ala-8, RB-1B)
- ▶ virulent (e.g. HPRS-16, JM GA)
- ▶ mildly virulent (e.g. HPRS-B14, Conn A)
- ▶ weakly virulent (e.g. CU-2, CVI-988)

These strains **may be attenuated by passage in tissue culture**, with loss of pathogenic properties but retention of immunogenicity, to provide strains **used as vaccines**

Serotype 2

- ▶ Includes **naturally avirulent strains** of MDV (e.g. SB-1, HPRS-24, 301B/1, HN-1)
- ▶ Several of these have been shown to **provide protection against virulent strains**

Serotype 3

- ❑ Contains strains of **naturally avirulent HVT** (e.g. FC126, PB1)
- ❑ Widely used as a **monovalent vaccine**
- ❑ Also used in combination with serotype 1 and 2 strains in **bivalent or trivalent vaccines** against the very virulent strains of MDV

Marek's Disease

- ▶ Marek's disease (MD) is a contagious, lymphoproliferative disease of chickens
- ▶ Ubiquitous, worldwide distribution, of major economic significance in poultry industry
- ▶ Josef Marek, Hungarian Veterinary pathologist first described the disease in 1907
- ▶ Identification of causative agent as a herpesvirus was established in 1967
- ▶ First and most important disease model in which a neoplastic condition was successfully controlled by vaccination

Transmission

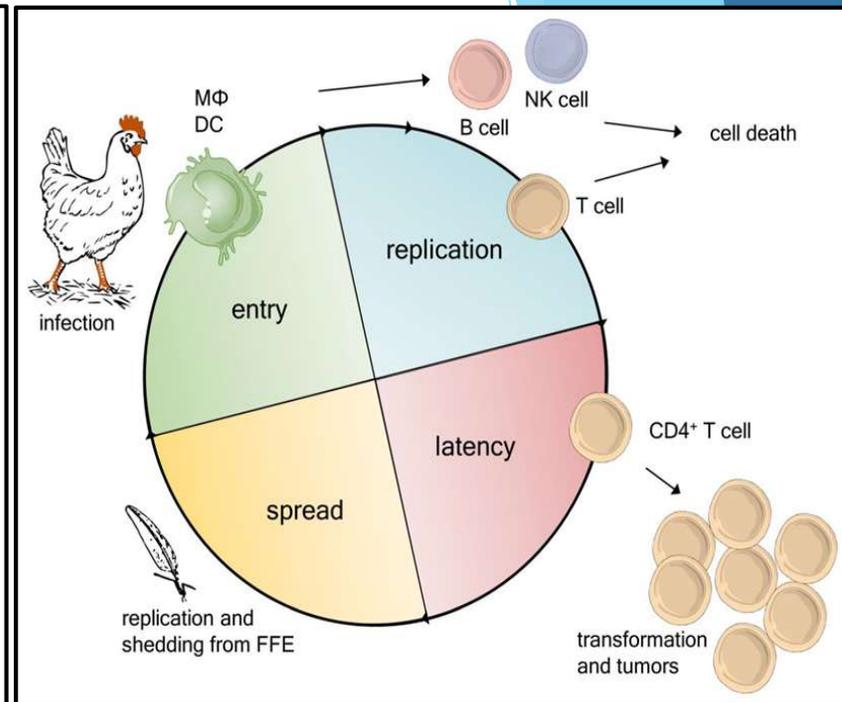
- ▶ Natural route of MD infection is **through inhalation** of cell-free virus particles by chickens
- ▶ **Cell-free infectious virus is only produced in the feather follicle epithelium** from which it is shed into the environment along with desquamated cells
- ▶ This dander can remain infective for several months in dust and litter in poultry houses
- ▶ Infected birds remain carriers for life

Disease

- The outcome of infection of chickens by Marek's disease virus is influenced by-
 - Virus strain, dose and route of infection
 - By the age, sex, immune status and genetic susceptibility of the chickens
- Transportation, vaccination, handling and beak trimming are stress factors which increase susceptibility to disease
- Chickens are the main target species of MD; also, it can infect other species such as turkeys, quail, and pheasant
- MD can occur at any time, beginning at 3-4 weeks of age or older, sometimes even well after the onset of egg production

Pathogenesis and Pathology

- ▶ The first target cell in the chicken after virus uptake - dendritic cells and macrophages
- ▶ Productive infection of lymphoid cells in lymphoid organs (thymus, bursa of Fabricius, spleen) results in virus amplification and immunosuppression
- ▶ From about 4 days after infection, there is a persistent cell associated viremia followed by a proliferation of CD4⁺ T cells, a transformed to produce T-cell lymphomas
- ▶ A surface antigen, expressed on transformed lymphocytes, formerly called Marek's disease tumour-associated antigen (MATSA) is now considered as marker for activated T cells.



Cell free virus is released from the feather follicles epithelium

Clinical signs of MD

- ▶ Progressive disease with several overlapping signs and pathological syndromes
- ▶ Mortality rates up to 100% in unvaccinated chickens
- ▶ Lymphoproliferative syndromes are the most frequent
- ▶ Described as:
 - ▶ Classical MD (Fowl Paralysis)
 - ▶ Acute MD (Transient paralysis)
 - ▶ Ocular Lymphomatosis
 - ▶ Cutaneous MD
 - ▶ Immunosuppression



Classical MD (Neurolymphomatosis or Fowl Paralysis)

- ▶ Characterised mainly by involvement of nerves, mortality rarely exceeds 10-15% and can occur over a few weeks or many months
- ▶ The most common clinical sign is partial or complete paralysis of the legs and wings
- ▶ Characterized by one leg held forward and other backward
- ▶ The characteristic finding is enlargement of one or more peripheral nerves



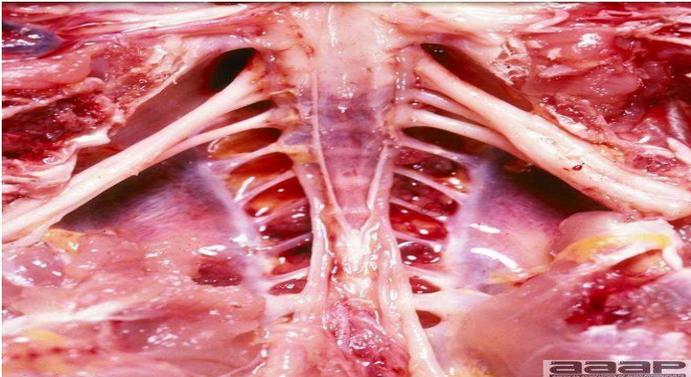
- ▶ If the vagus nerve is involved, there may be dilation of the crop and gasping

- ▶ Affected nerves are often
 - ❑ Two or three times their normal thickness
 - ❑ Normal cross-striated and glistening appearance absent
 - ❑ The nerve may appear greyish or yellowish
 - ❑ Sometimes oedematous

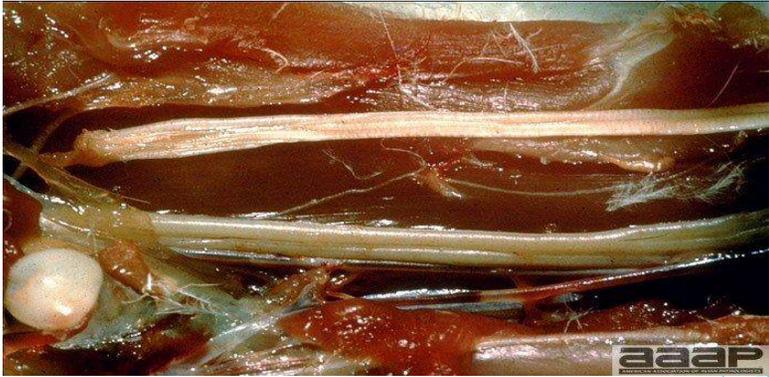
- ▶ Lymphomas sometimes present
 - ▶ Most frequently as small, soft, grey tumours in the ovary
 - ▶ Sometimes also in the lungs, kidneys, heart, liver and other tissues

Lesions in MD

(Image source -Google)



Sciatic plexus enlargement



Nerve enlargement & loss of striations



Infiltration of feather follicles



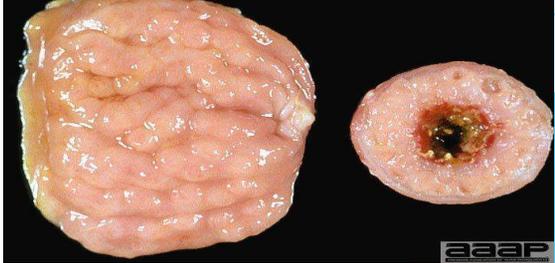
Visceral tumors



Heart tumors



Kidney tumors



Proventricular tumor

Acute form

- ▶ Occurs in sudden outbreaks with the neck and limb paralysis
- ▶ usually characterised by visceral lymphomas in multiple organs (liver, gonads, spleen, kidneys, lungs, proventriculus and heart)
- ▶ Sometimes lymphomas also arise in the skin around the feather follicles and in the skeletal muscles
- ▶ Affected birds usually have enlarged peripheral nerves, as is seen in the classical form

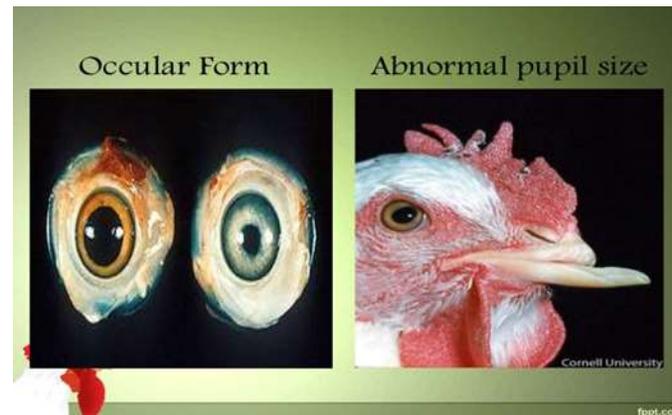
- ▶ In younger birds, liver enlargement usually moderate
- ▶ But in adult birds the liver may be greatly enlarged and the gross appearance identical to that seen in lymphoid leukosis, from which the disease must be differentiated
- ▶ Nerve lesions are often absent in adult birds with MD
- ▶ Birds are often severely depressed and some may die without showing signs of clinical disease
- ▶ Disease incidence to 10- 30% in the flock and outbreaks involving up to 70% can occur

Transit paralysis

- ▶ Transient paralysis from brain edema
- ▶ Relatively **common with newer and more virulent virus strains** (vvMDV or vv+ MDV strains)
- ▶ Characterized by the onset of neurologic signs 9-10 days post-infection
- ▶ **Symptoms related to brain lesions** and include flaccid paralysis of neck and limbs
- ▶ Regularly result in full clinical MD after several weeks, death occurs
- ▶ Death typically occurs 1-3 days after the onset of clinical signs

Ocular lymphomatosis

- ▶ Rare syndrome
- ▶ Leads to graying of iris of one or both eyes (Grey eye) due to infiltration of transformed (neoplastic) lymphocytes
- ▶ Pupil irregular and eccentric, consequently partial or total blindness may happen



- ▶ Mortality is rare and usually older birds are infected, may be the only presenting sign

Cutaneous Marek's disease

- ▶ Recognized readily after plucking of feathers, **round nodular lesions** up to 1 cm in diameter are seen particularly around feather follicles
- ▶ Non-feathered area of legs may have a distinct red coloration
- ▶ MD is therefore sometimes called “**redleg syndrome**”

Immunosuppression form of MD

- ▶ Includes both humoral and cellular host immune defense systems
- ▶ Early cytolytic infection of B lymphocytes
- ▶ Latent infection of both B and T lymphocytes
- ▶ Late cytolytic infection and transformation of T lymphocytes results in severe immunosuppression state

Diagnosis

Clinical signs and pathological findings

- ▶ Paralysis of legs and wings in conjunction with thickening of the peripheral nerves is typical of Marek's disease
- ▶ Nerve involvement is not always evident in adult birds, in these circumstances, differentiation from lymphoid leukosis is particularly important

Antigen detection

- ▶ Viral antigen can be detected in preparations of skin or feather tips, using a radial precipitin test

Demonstration of Serum antibodies to GaHV-2

- ▶ Using AGID, ELISA, immunofluorescence or virus neutralization

Virus isolation

- ▶ Virus can be isolated from the buffy coat of blood samples from infected birds
- ▶ Chicken kidney cells or duck embryo fibroblasts can be used for isolation of the virus
- ▶ Another, less commonly used source of MDV for diagnostic purposes is feather tips, from which cell free MDV can be extracted

PCR assays

- ▶ Enable differentiation of oncogenic and non-oncogenic strains of serotype 1 MDV, and of MDV vaccine strains of serotypes 2 and 3

Immunity, Prevention and Control

- ▶ Vaccination is the principal method of control
- ▶ MDV vaccine inhibits development of MDV-induced lymphoma but does not prevent infection and replication of pathogenic strains of MDV
- ▶ The standard method- to vaccinate 1-day-old chicks or in *ovo vaccination* at 18 days of embryo development
- ▶ Vaccine available as either using herpesvirus of turkeys, gallid herpesvirus 3, live-attenuated Marek's disease virus
- ▶ Although a **single dose of virus injected into day-old chicks provides good lifelong protection**, it does not prevent super-infection with virulent field viruses
- ▶ CVI-988-Rispens strain vaccine is effective in providing protection against the very virulent MDV

Vaccine

- ▶ Commercially used vaccine include attenuated HPRS-16 and CVI-988 (Rispens) strains
- ▶ Attenuated variants of very virulent stains (Md11/75C/R2/23) used in experimental vaccines to protect against the variant form of acute MD caused by the very virulent stains
- ▶ Naturally avirulent strains SB-1 and 301B/1 commercially used, particularly with HVT, in bivalent vaccines for protection against the very virulent strains
- ▶ Naturally avirulent HVT (e.g. FC126, PB1), widely used as monovalent vaccine, and also in combination with serotype 1 and 2 strains in bivalent or trivalent vaccines against the very virulent strains of MDV

Use of appropriate management strategies

- ▶ The production of chickens on the “all-in all-out” principle, improves the efficacy of vaccination as a control measure
- ▶ Rearing young chicks away from older birds for the first two or three months of life reduce exposure to infection
- ▶ Removal of litter and cleaning/disinfection of the housing after each production cycle

Features differentiating MD and lymphoid leukemia

Feature	Marek's disease	Lymphoid leukemia
Age	Any age. Usually 6 weeks or older	Not under 16 weeks
Signs	Frequently paralysis	Non-specific
Incidence	Frequently above 5% in unvaccinated flocks Rare in vaccinated flocks	Rarely above 5%
Macroscopic lesions		
Neural involvement	Frequent	Absent
Bursa of Fabricius	Diffuse enlargement or atrophy	Nodular tumours
Tumours in skin, muscle and proventriculus, 'grey eye'	May be present	Usually absent
Microscopic lesions		
Neural involvement	Yes	No
Liver tumours	Often perivascular	Focal or diffuse
Spleen	Diffuse	Often focal
Bursa of Fabricius	Interfollicular tumour and/or atrophy of follicles	Intrafollicular tumour
Central nervous system	Yes	No
Lymphoid proliferation in skin and feather follicles	Yes	No
Cytology of tumours	Pleomorphic lymphoid cells, Rarely only lymphoblasts	Lymphoblasts
Category of neoplastic lymphoid cell	T cell	B cell