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Characteristic of Flaviviridae and Diseases Caused by Viruses in this Family: A Briefing

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Abstract

Viruses are the sub-microscopic infectious agents and are the smallest and simplest of all life forms. The family Flaviviridae contains several important viruses that cause diseases in domestic and wild animals. Some of these viruses are emerging as very important not only for animal health but also for public health as they are highly zoonotic. The viruses of veterinary importance in this family belong either to the tick-borne virus group or the mosquito-borne virus group. So this article describes about the diseases caused by the family flaviviridae, its epidemiology, susceptible host, pathogenesis, clinical findings, diagnosis, prevention and treatment and its public health significance

General Features of the Family

The family Flaviviriade is named after '***yellow fever***', 'flavus; is the Latin word for yellow. These are also called ***group B arbovirus***.The viruses under Genus flavivirus of veterinary importance are Japanese B Encephalitis virus; Louping Ill virus; West Nile virus.The viruses under Genus Pestivirus of veterinary importance are Bovine viral diarrhoea virus; Border disease of sheep virus and Classical Swine Fever Virus. Host for Pestivirus include even toed ungulates. The virus in the family Flaviviridae is all inactivated easily by heat and disinfectants as they are enveloped viruses.

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Classification

Realm	Ribovira
Phylum	*incertasedis*
Family	*Flaviviridae*
Genera	*Hepacivirus, Flavivirus Pegivirus Pestivirus*

Virion Properties

Virions of the family Flaviviridae, regardless of Genus are spherical and consist of tightly adherent lipid envelope that may display distinct protein spikes surrounding nucleocapsid with icosahedral symmetry.

Genome consist of a single molecule of positive sense single stranded RNA of approximately 11, 12.3, 9.6-10.4, kb and 11.2 kb for flavivirus, Pestivirus, Hepacivirus and Pegivirus respectively. Flavivirus has a 5′ terminal cap whereas Pestivirus Hepacivirus and Pegivirus don't have cap, instead

they have an internal ribosomal entry site in 5′ end. Flavivirus don't have poly A tail at 3′ end of the genome.Genome of all members of family contains one ORF encoding 10 or more proteins that are created by co or post translational processing of single large polyprotein. Virions contains 3 structural proteins (genera: flavivirus, Hepacivirus and Pegivirus), or 4 structural proteins (Pestivirus) that are encoded at the 5′ end.

Structural proteins of flavivirus include C polypeptide, thenucleocapsid protein; envelope contain 2 virus encoded proteins ,the major and larger one is Envelope (E) protein, which is a major target site for neutralizing antibodies; smaller one is M protein, the transmembrane protein.M protein is generated from precursor polypeptide M(PrM). Pestivirus have 4 structural proteins including C (nucleocapsid protein) and Erns, E1 and E2 Envelope glycoprotein.

There are 7-8 virus encoded non- structural proteins including NS5, the RNA dependent RNA polymerase and NS3, which have several functions including helicase and protease activity in addition to contributing to RNA polymerase complex. NS2B and NS3 are largely responsible for cleavage of polyprotein and host cell proteases are responsible for rest of this processing. Flavivirus encodes only NS3 protease and Hepacivirus and Pestivirus encode a second protease in the NS2 region that cleaves between NS2 and NS3. Pestivirus also encode for a unique non-structural protein, Npro which auto catalytically releases itself from polyprotein.This protein is not responsible for viral replication in cell culture but modulates the interferon response in infected cells.

Diseases Caused by the Family Flaviviridae

Bovine Viral Diarrhoea

It is a sub-acute, acute, in apparent contagious disease of bovines characterized by high fever, diarrhoea and erosive lesions on mouth, oesophagus, rumen, abomasum and intestine. It is caused by Bovine Viral Diarrhoea Virus.

Epidemiology

It is one of themost significant infectious diseases in livestock industry with high prevalence, persistence and clinical consequences. It was first recognized in USA. BVDV-1 strain is the most predominant strain in the world. BVDV-2 was first isolated in UK in 2000. BVDV-3 has also been reported recently.It is responsible for significant economic losses in places like Africa, South and North America, Asia (India, Bangladesh, Pakistan, Burma, Sri Lanka)

Susceptible Host

Principal host of BVD is cattle of age group 6-24 months. Buffalo, pig and sheep also affected whereas deer, wild ruminants are also susceptible and often affected. BVD occurs in all seasons but most common in rainy and winter season.

Mode of Transmission

It can be spread by ddirect and indirect contact. Incidence of BVD is more in crowded herd. Virus is normally present in nasal secretionsoral dischargeurine. Other sources like transport vehicles, farm appliances, contaminated feed and water etc can also serve as a potential means to spread the virus.Ingestion of contaminated materials of diseased animals can also spread the virus. Sheep and swine no role in disease transmissionCalves harboring cytopathic strain act as principal source of infection

Clinical Features

Clinical manifestation of the disease depends upon the age of animal infected and pregnancy status of the animal. Three types of situation arise that include post natal infection in non-pregnant cattle, infections in pregnant cows and persistent infections in calves and Mucosal disease (MD).

Post Natal Infection in Non-Pregnant Cattle

All age groups susceptible (8-24 months common). In some animals there may be explosive diarrhea. Nasal and ocular discharge and erosive stomatitis, considerable drop in milk yield in dairy herds. Due to immunosuppression, there may be opportunistic respiratory and intestinal infections.

Infection in Pregnant Cows

High frequency of transplacental spread depending on age of fetus and strain of virus. Infection very early in pregnancy results in death, resorption of fetus. Infection before immunological maturity (80-125 days) results in fetal death or low birth weight(weak calf syndrome), defective organogenesis like congenital defects in eye (retinal dysplasia) and C.N.S defects like cerebellar hypoplasia and cavitations of cerebrum. Surviving calves become persistently infected. (seronegative in all test); responsible for shedding virus throughout life. Their dams are called 'Trojan dams'. They have high probability of developing MD. Foetus infected after 125 days of gestation, usually survive.

Persistentinfections in Calves and Mucosal Disease

PI calves areillthrify and smaller than their peers. They continuously shed virus. Virus transmitted poorly from acutely infected cattle butefficiently from persistent cattle. PI dam always gives rise to PI calves. Only 20% PI survive up to 2 years of age. PI cattle that survive are susceptible to MD (fatal). If the PI animal is super infected with a cytopathic strain of BVDV due to mutation of non-cytopathic strain already circulating in the animal, develop MD.

Diagnosis

Diagnosis is made by observing the typical signs and syndromes, gross and microscopic lesions, leukopenia etc. Confirmatory diagnosis can be made by isolating and identifying the virus from suspected materials like blood, spleen and lymph node. Animal inoculation tests can also be performed. Cytopathogenic effects like degeneration of cytoplasm pyknosis ballooning elongation vaculation granulation of lymphoblastic cells can be looked for. Other tests like Viral Neutralization Test, CFT, and ELISA can be used. Serum conjugates against Hog Cholera can be used in FA test for BVDV. BVD must be differentially diagnosed from Malignant catarrhal fever FMD, Rinderpest, IBRJohne's disease, heavy parasitism etc.

Prevention and Control

Proper hygiene and sanitation must be followed. Chloroform, ether and trypsin kill them. Mild case recovered spontaneously with durable immunity. Modified live viral vaccine/Killed vaccine used to prevent the disease (first vaccination ~ 6 months, booster required for proper immune response).

Difference Between Cytopathic and Non-Cytopathic Bvdv Strains:

CYTOPATHIC	NON-CYTOPATHIC
Produces cytopathic effects in MDBK cell line->vaculation being the earliest morphological change	No cytopathic change in MBBK cell line
Fail to establish chains of infections and unable to cause PI rather they are responsible for mucosal disease	Responsible for persistent infections and associated changes
Not common in occurrence as compared to cytopathic strains	More common in field condition
Emergence of cytopathic virus from non-cytopathic virus is attributed to mutations that are unique to each virus [Recombinant initiations within host-cell mRNA, gene translocations, duplications, point mutations]	NCP strains undergo mutation to cytopathic strain
It illustrates a case of viral emergence to extinction	Persistence of virus helps its survival inside host
Able to induce Type I interferon in infected cultured cells	Fails to induce INF type I in cultured cells
Show production of NS 3 proteins by mutation of NS2 gene	NS3 not expressed

Swine Fever

Swine fever is also known as Hog cholera, pig typhoid, Schweine pest (German) Pestedupore (French) Pestesuina (Italian), Peste porcine. It is a highly fatal, highly infectious viral disease affecting pigs of all age groups. Pigs are the natural host and the only animal to be affected by the disease naturally. The disease is characterized by septicaemia, haemorrhages, leukopenia, ataxia, skin discolouration, reproductive failure, pneumonia, vomition, diarrhoean etc. It is caused by Swine Fever Virus which was previously considered as G- ve bacteria, ***Salmonella cholerasuis.*** Dorset et al identified Swine fever virus in 1904.It has anumber of strains with wide virulence and antigenicity which is a reason for vaccine outbreak. It has antigenic similarity with **BVDV**.

Epidemiology

Worldwide in distribution and occur in severe outbreak form Morbidity may be up to 100%. It is eradicated successful by primary policy of slaughter and quarantine in countries like Canada Australia New Zealand South Africa UK USA.

Susceptible Host

It is one of the most costly diseases affecting pig. Mortality is very high. Pigs of all breeds, sex and

ages are susceptible to it. Suckling white mice and rabbits are used as laboratory animals. Virus does not grow in chick embryo Cultivated in tissue cultureWild pigs remain as carrier.

Mode of Transmission

Present in blood stream. All organs and all dischargesare infective Urine, dung, eye discharge and breathecan be the mode of transmission. It is excreted in urine for 2-3 weeks.The host gets infection, mostly byingestion of garbage or contaminated feed and water.Virus can enter respiratory tract through inhalation. It is a very contagious disease and can spread rapidly with direct contact. *Recovered pigs may act as carrier and carrier pigs and vaccinated pigs are potent source of infection.* In pregnant sows, it can pass or cross placental barrier leading to still birth, abnormal piglets. Transmission through breeding Insects flies. One peculiar method of transmission seen in case of this disease is that the virus is present in eggs of lung worm of affected pigs and when the earthworm ingests lung worm egg, it gets the virus and when in turn eaten by healthy pigs, the pigs get infected by the virus.

Pathogensis

The virusmostly enters body through upper digestive tracts through ingestion or respiratory tract by breathe. It localises in tonsils which is the site of primary viral replication. It enters into blood through tonsilartissue. Secondary replication of the virus occurs in the endothelial cells, lymphoid organs, and bone marrow leading to haemorrhages, profound leukopenia and thrombocytopenia. Blood vessels undergo changes like hyaline degeneration, infiltration by lymphocytes, macrophages & plasma cellshaemorrhages necrosis, infarction in various organs. Inflammation in the lungs along with secondary bacterial infection (Salmonella choleraesuis Pasteurella suiseptica) can also occur.

Clinical Findings

The disease can occur in per acute, acute and chronic form. Incubation period varies from three days to three weeks (commonly seven days).

Classical Form of Swine Fever

In its Classical form, hog cholera is an acute infection. Common signs after IP of 2 to 4 days include high fever, depression, anorexia and conjunctivitis. Vomition, diarrhea, constipation is also seen.

Nervous dysfunctions like paresis, paralysis, tremor, circling etc can be seen.Light skinned swine show hyperemia,purpuria on abdomen and ears. Severe leucopenia may occur. Mortality may reach 100%.

Chronic Form

Chronic form is less severe with prolonged IP. Signs like Runting, chronic diarrhea, dermatitis, purpuria, secondary bacterial infections and death are generally seen. This form is associated with virus of moderate virulence. Infection in pregnant cows leads to foetal, embryonic death, abortion, mummification, still birth. New born piglets may die or survive with tremors, runting and progressive disease leading to death

Some Characteristic Clinical Signs of The Disease

Infarction of spleen is pathognomonic. DIC, thrombosis of small vessels is commonly seen. Most prominent lesion in swine dying of hog cholera is general exhaustion of immune system. There is complete *atrophy of thymus*, and germinal centers in spleen and lymph node. Live piglets (healthy\infected) remain *persistently infected, immunologically tolerant and are the lifelong shedders of the virus.*

Diagnosis

Diagnosis is done byhistory and clinical signs, histopathologic findings isolation and identification from specimens like spleen, tonsils, lymph nodes and blood.

FA Test is the fastest and most reliable can be applied to cryostat sections of spleen and lymph node.Animal inoculation (susceptible and immune swine inoculated with the infected materials) can also be done. Lab tests like acute leucopenia, late stage leukocytosis can help in diagnosis.

Treatment

As it is a viral disease, there is no specific treatment. Hyper immune serum,fluid therapy can be used for treating the animals.

Prevention and Control

It is destroyed by heat at 60-70°C%, cresol, and 3% sodium hydroxide. It *survives in frozen pork for many years.* It can be preserved in 50% glycerin saline for 7 months. ***Garbage feeding prohibitions and garbage cooking regulationsare adopted by most of the developed countries where it is eradicated.*** Strict and rigorous sanitary prophylaxis as per ***OIE Terrestrial Animal Health Code is applied in order***

to check the spread of the disease. Eradication by ***"Test and Slaughter" followed by safe disposal of carcass and thorough disinfection of the area.***

Control by Vaccination

Attenuated lapinizedviral vaccine were used previously that provided immunity for 3- 6 months. ***Crystal violet vaccine*** which is a killed vaccine with efficacy 60% shows good results. Recently, Indian scientists at ICAR's IVRI developed Classical Swine Fever (CSF) cell culture based vaccine which provides immunity for about 2 years. Intervet swine fever vaccines, which is an attenuated, freeze dried, and tissue culture based vaccine is available in 5 ml vial. Blanket vaccination of pigs over 2 weeks of age can be done where the infection is endemic. Piglets born to vaccinated sows, can be vaccinated at 8 weeks age. New generation MLV (Modified Live Vaccine **'Marker Vaccine'** based ***on major envelope glycoprotein (E2-Subunit)*** is also available.

Border Disease of Sheep

Border disease was first described on the border between England and Wales, hence the name used in Great Britain and North America. It is known as "hairy shaker disease:, in Australia and New Zealand due to its clinical signs

Clinical Features

It appears as a congenital disease in lambs characterized by low birth weight, poor viability and poor conformation, tremors and excessively hairy birth coat in normally smooth-coated wood breeds.

Pathogenesis

In adult sheep, infection is always subclinical, but infection in pregnant ewes results in foetal death or delivery of dead, deformed or mummified lambs. There is defective myelination of the nerve fibres in CNS which is manifested clinically by neurological signs. In some lambs, there is development of immune response whereas in others there is persistent infection, immunological; tolerance and seronegativity to the virus permanently. These organs become life time carriers of the virus and shed the virus in all body secretions and excretions whether they are showing clinical signs or not

Louping Ill

It is an infectious ovine encephalomyelitis, a tick born disease in sheep and cattle caused by Louping ill virus (under genus Flavivirus). It occurs mostly in the British Isles and Iberian Peninsula.

Pathogenesis

Louping ill is seen most commonly in sheepless than 2 years of age. Adult sheep are either immune or show a sub clinical infection. The disease is characterized by fever, CNS involvement, in coordination of movement, ataxia and paralysis. Gross lesions are not seen in infected sheep but microscopic lesions like meningoencephalitis is seen with damage to the Purkinje cells and Perivascular cuffing. The disease gains its name from peculiar leaping gail of ataxic sheep. Natural infection can occur in a variety domestic animals like horse, whereas rabbits and guinea pig are resistant.

Prevention and Control

Formalin inactive vaccine provides effective immunity, antibody exist up to 3 years. Recently tissue culture vaccine is also developed. Acaricides can be used to control ticks which are the main vectors of the disease.

Public Health Significance

Louping ill is zoonotic and it is transmitted to humans by ticks or occasionally by contact with infected sheep and sheep tissues. In humans, the disease is biphasic, the first phase is influenza type and the other phase is meningoencephalitis syndrome that usually resolves without sequel in 4- 10 days.

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