Comparison of Bluetongue and Epizootic Hemorrhagic Disease Complex

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Introduction

Bluetongue (BT) and epizootic hemorrhagic disease (EHD) are caused by arthropod-borne orbiviruses that infect domestic, captive and free-ranging ruminants. These viruses are characterized by acute or subacute clinical courses in susceptible ruminants. Both serotypes of viruses have rarely been associated with clinical disease in postnatal animals. BT viruses (BTV) have been associated with reproductive infections and EHDV with experimental teratogenic lesions which has brought about speculation about the importance of these agents in reproductive failure. Of particular importance for the international markets has been the concern that BTV can be shed through semen. Furthermore, there is evidence that BTV infection in cattle is prolonged, lasting as long as 60 to 120 days. The duration of EHD viremia is not known in cattle. These observations and the fact that EHD is often a serious disease of free-ranging ruminants has lead to international restrictions or the threat of restrictions for trade of cattle and associated germplasm.

In the United States (US), both BT and EHD occur in separate as well as overlapping regions. BT is common with serological prevalence reaching 80% in cattle in western and southern US.[1] BT infections do not occur in the north central and northeastern regions of the US. On the other hand, EHDV has been reported in many parts of the US and southern Canada. This difference in distribution has been related to differences in the *Culicoides variipennis* subspecies which transmit the viruses in these regions.

The international trade concerns associated with these viruses warrant a review of the characteristics of the viruses and their host ranges.

The Viruses

Both serogroups, bluetongue and epizootic hemorrhagic disease viruses belong to the Reoviridae family and the genus Orbivirus.[2] There are 25 serotypes of BTV and 10 serotypes of EHDV worldwide. Both viruses consist of 10 genome segments which code for 7 structural and 3 nonstructural proteins. The viruses are double stranded RNA. The taxonomic grouping of the viruses is based on shared serogroup antigens. These are most commonly detected by complement fixation (CF), agar gel immunodiffusion (AGID) and ELISA tests which detect epitopes on VP7. Serotype specificity is based upon neutralizing epitopes found on VP2 identified by serotype specific antibodies. Occasionally, there may be cross reactions between BTV and EHDV group specific antibodies in the agar gel immunodiffusion test.

Distribution

BT viruses have been recognized on every continent except Antarctica. The viruses are more commonly found in the tropics and subtropical areas of the world. In the temperate climates, the presence and infectivity in animals occur seasonally. The seasonal distribution is dependent upon the culicoides vectors being active in the areas and transmitting the virus from animal to animal. In North America, the vector of greatest importance is *Culicoides variipennis var. sonorensis*; whereas it is *C. fulvis* and *C. wadai* in Australia and Asia and *C. immicola* in Africa and Europe.[3,4,5] The principal vector in Central and South America is *C. insignis*.[6] There is reasonably good evidence that the susceptibility of some of these vectors to oral infection is related to the products of genes which serve as receptors for the virus[7,8] This appears to be the case in the US with *C. variipennis var. sonorensis* and BTV in southern and western US and the absence of BTV where *C. variipennis var. variipennis* is found in the north central and northeastern US.[3] There is suggestive evidence that the BTV serotype distribution may be associated with the particular vector species. For instance, BTV serotype 2 appeared in the US only in the areas where C. *insignis* was distributed[5]; BTV-2 did not adapt to the *C. variipennis* subspecies in the US.

Paper presented at the XVIII World Buiatrics Congress, Bologna, Italy August 29 - September 2, 1994

The relationship of the various culicoides to EHDV has not been studied in the detail that has been the case with BTV. It is assumed that culicoides play a major role in the animal to animal spread of EHDV. In the US, EHDV has not been recognized in the northeast nor in the arid southwest, but it occurs in all other areas of the country.[9] Many of the Australian EHDV isolates were made from culicoides; however, virus has not been recovered from animals with clinical signs of disease.

THE DISEASE - Bluetongue Disease

Cattle

BTV rarely causes clinical disease in cattle. The appearance of clinical disease has been associated with a Type I Hypersensitivity.[10] Cattle display clinical signs of exudative dermatitis which is most pronounced in the cervical areas, hyperesthesia, coronitis and vesicular erosive lesions involving the oral mucosa. Nearly all of the cattle recover; however, the affected ones may have considerable weight loss. There is also elevation of vasoactive mediators and IgE in the serum and plasma. Histological changes in the skin include edema and infiltration of eosinophils, both of which are suggestive of a Type I Hypersensitivity.

Reproductive related lesions have been observed in cattle infected with BTV.[11,12] Abortions, premature births and calves born with neurological deficits have been associated with BTV infection of the pregnant cow during the first 4 to 5 months of gestation. There is some epidemiological evidence that BTV may be associated with infertility during the early embryonic period. Attempts to experimentally reproduce this phenomenon have not been successful. It has been demonstrated that BTV kills hatched embryos in *in vitro* studies.[13] Infection late in gestation with some strains of virus may result in premature delivery of small weak calves.[14] Late term abortions have been associated with fetal stress. Both natural and experimental infections have resulted in these patterns of disease. The typical neurological change is a severe case of hydranencephaly that results from destruction of undifferentiated neurological tissues in the first one-third of gestation.[12] Arthrogryposis is not associated with experimental bluetongue infections.

In the bull infected with BTV, there may be shedding of virus into the semen during viremia.[15] There have been reports that bulls with viremia may infect cows during breeding.[11] Often bulls with acute BTV infection are infertile.[15] This is usually a transient phenomenon. These observations lead to major international restrictions on the movement of cattle and their germplasm. The finding of virus in semen of serologically positive bulls is rare, occurring in 1 to 10,000 semen samples.[16] **The realization of the role that culicoides plays in the transmission of BTV rather than semen has lead to an easing of non-tariff trade restrictions for live animals and germplasm.**

Sheep

BTV is capable of causing the most severe forms of disease in sheep. The clinical signs are associated with high fever, facial edema, drooping ears, lameness, erosions of the oral mucosa, weight loss and breaks in the fleece. Morbidity and mortality are relatively high. Seminal shedding in rams may occur during viremia; however, these rams are usually temporarily infertile.[17] Congenital lesions associated with exposure of ewes to BTV during the first trimester of pregnancy may consist of hydranencephaly and porencephaly.

Wild Ruminants

A number of free-ranging and captive wild ruminants have been reported to be highly susceptible to BTV infections. The usual history is that these animals seek water and are often found moribund or dead close to watering holes. Most of the animals have widespread hemorrhages leading to the diagnosis of hemorrhagic disease.[9]

Canines

Recently, BTV was reported in pregnant bitches that received a modified live virus vaccine for canine distemper and parvovirus. The vaccine was found to be contaminated with BTV.[18,19] The pregnant bitches receiving the vaccine aborted or delivered stillborn puppies and then the bitches died. The vaccine has been removed from the market.

THE DISEASE - Epizootic Hemorrhagic Disease

Cattle

The association of EHDV with disease in cattle is extremely rare with few reports in the literature.[20] On the other hand, infection based upon serological tests in endemic areas where the culicoides are carrying EHDV are very high, sometimes approaching 80 to 90%. The clinical signs in cattle are essentially the same as reported for bluetongue.[22] There have been no reported cases of EHDV infections resulting in congenital lesions. Experimentally, EHDV is capable of causing congenital lesions such as hydranencephaly like those produced by BTV.[12] There have been no reports of EHDV being associated with viral shedding in the semen as occurs in bulls with BTV viremia.

Sheep

EHDV has rarely been recovered from sheep. No disease has ever been reported in sheep inoculated with EHDV or infected with field strains of EHDV.

Wild Ruminants

In North America, EHDV is considered one of the most important viral causes of disease in white-tailed deer (*Odocoileus virginianus*), mule deer (*O. hemionus hemionus*) and pronghorn antelope (*Antilocapra americanna*).[9] Clinical stages of disease include sudden death, widespread hemorrhages and dehydration. Chronic forms of the disease include lesions at the coronet of the hoof, oral and ruminal erosions and ulcerations.

PATHOGENESIS - Bluetongue Disease

Cattle

The pathogenesis of BTV in cattle is associated with prolonged viremias and hypersensitivity reactions.[10,21,22] The prolonged viremias which last as long as 90 days are the result of the BTV virus particles attaching to folds in the erythrocyte membrane.[22] This protects the virus from being attacked by antibodies and lymphocytes. The virus persists as long as the lifespan of the red blood cell.

Reproducing BTV disease in cattle is difficult. The most consistent way of causing lesions has been to sensitize cattle with vaccines and then challenge with virus.[10] This results in an IgE mediated hypersensitivity along with the release of vasoactive mediators. The disease has never been produced by inoculation of virus. Clinical BTV disease has also been associated with elevated IgE levels.[10]

The pathogenesis of BTV in bulls leading to the transient viremias has been associated with elevated temperatures. There is no evidence that the virus causes direct damage to the testes. Vasculitis has been observed in the epididymis and this is the probable route by which red blood cells and mononuclear cells carrying the virus find their way into the epididymal lumen.[17] The result is virus-contaminated cells being shed in the ejaculates.

Wild Ruminants

BTV in wild ruminants causes an acute hemorrhagic disease.[9] The virus affects endothelial cells where it causes local thrombosis of the vessels. As a consequence, the clotting cascade is activated, resulting in disseminated intravascular coagulopathy and widespread hemorrhages.

There is little information on the duration of viremia in wild ruminants. It is likely that the length of the viremia is shorter than in cattle and probably more similar to that of sheep.[9]

Canididae

The pathogenesis is not known at this time.

PATHOGENESIS - Epizootic Hemorrhagic Disease

Cattle

There is little definitive information on the duration of viremia in cattle infected with EHDV. There is a report in the literature that virus was found 28 days after infection in a field outbreak.[20] In experimental studies, viremias are usually no longer than 10 to 14 days.

Wild Ruminants

The pathogenesis of lesions with EHDV infection appears to be similar to those caused by BTV in wild ruminants. The duration of the viremia in EHDV infections in wild ruminants is relatively short usually not lasting more than 16 days.[9]

Diagnosis

Serology

There are group and neutralizing specific tests for both viruses. The group tests for BTV include CF, AGID, C-ELISA, and hemolysis in gel.[23] The accepted international tests are the AGID and C-ELISA.[24] Of these two, the C-ELISA is preferred since there are fewer cross reactions and the sensitivity and specificity are greater. The C-ELISA detects antibodies earlier and longer than the AGID. Commercial C-ELISA tests are available in North America. The most commonly used test for group specific responses in animals with EHDV infection is the AGID.

Neutralization tests are serotype specific and of longer duration that the group specific antibodies. These tests are better indicators of the range of the titers than the group tests. The usual procedures are the plaque reduction assays, or serial dilutions on a TCID50 serum neutralization assay. These assays are indicated for both BTV and EHDV.

Virus Identification

Virus identification can be done through virus isolation, immunoperoxidase staining of tissues, or identification of viral nucleic acids by the use of polymerase chain reaction (PCR) or hybridization. The best means of isolating BT virus is by inoculating a susceptible sheep or embryonating chicken eggs (ECE).[25] Cell culture systems have also been used; however they are not as reliable. Virus isolation of EHDV is best accomplished with cell cultures; however, embryonating chicken eggs can also be used. The main difference between BTV and EHDV in ECE is that BTV kills embryos in 2 to 4 days, and EHDV may require 6 to 10 days.[20]

Nucleic acid hybridization tests have been used to identify viral specific genetic codes of the virus.[25,26,27]

More recently, the use of PCR has greatly enhanced diagnostic capabilities. This technology utilizes identification of viral nucleic acids. It is rapid, bringing about diagnosis in 2 days as compared to 3 weeks for the conventional ECE.

Similar isolation procedures have been used for EHDV. The best systems are cell culture and PCR. ECE can be used; however embryo death or harvesting is done 6-10 days after inoculation.

Conclusions

BTV and EHDV are not particularly important disease problems of cattle. Occasional outbreaks may occur, and these have been described in discussion. On the other hand, other ruminant species are highly susceptible to the viruses. As a result, cattle and their germplasm, because of desire for global needs for breeds, have been under scrutiny as potential means of spread these diseases. To date, there is little or no evidence that cattle play a role in the international dissemination of these viruses.

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