Schmallenberg disease virus: An emerging disease in large and small ruminants.

Dr. Patrick Sylvester Craig

Introduction

Schmallenberg virus (SBV) is a novel emerging orthobunyavirus associated with reduced milk yield, inappetence and diarrhoea in adult ruminants, as well as malformations in aborted ruminants in Europe. Between August and October 2011, animals in a region at the border of Germany and the Netherlands were exhibiting unusual clinical signs characterised by mild to moderate fever, anorexia, significantly reduced milk yield, loss of condition and diarrhoea. Affected animals recovered within two to three weeks [1]. Following December 2011 and onwards, sheep, goats and cattle in Germany, the Netherlands and Belgium experienced abortions and stillbirths associated with foetal deformities predominantly of the limbs and skull. After ruling out the presence of other infectious agents, scientists in Germany isolated and sequenced viral genetic material from the affected cattle and identified a new virus. The virus was named after the German town in North Rhine-Westphalia, where it was first isolated.

Schmallenberg virus is an enveloped, negative-sense, segmented, single-stranded RNA virus, whose shape was similar to that of other bunyaviruses. Preliminary phylogenetic analyses classified SBV as a member of the genus *Orthobunyavirus* in the family Bunyaviridae, which is closely related to Akabane, Ainoa and Shamonda viruses. The genus *Orthobunyavirus* is the largest of five genera in the Bunyaviridae family which comprises over 170 named viruses, the majority of which are pathogenic to humans and animals [2]. SBV has been isolated or confirmed by polymerase chain reaction (PCR) in cattle, sheep, goats, bison, red deer and roe deer; whereas the serological presence of SBV antibodies has been detected in roe deer, red deer, alpaca, mouflons and water buffalo. The current data suggest that SBV in more efficient in sheep than in cattle [3].

Transmission

SBV is transmitted via haematophagus insect vectors, especially through *Culicoides* midges bites. The virus has been detected in pools of *Culicoides* biting midges and many *Culicoides* species including *C. absoletus* complex and *C. dewulfi*, *C. chiopterus*, *C. pulicaris* have been found to be positive for SBV. It is also of importance to note that *C. absoletus* is the primary

vector of Bluetongue virus (especially serotype 8; BTV-8). It has been suggested that insects may acquire the virus from infected animals and transmit it to other susceptible animals during blood feeding, as viral RNA has been detected in the blood of naïve animals for several days following infection with SBV [4]. The virus is also transmitted vertically across the placenta and this mode of transmission is of particular importance as SBV has been shown to be involved in congenital malformations in lambs, goat kids and calves [5].

Clinical and pathological manifestation of Schmallenberg

Acute infection in adult animals results in fever (>40°C). The viraemic stage is short and varies from one to six days and is followed by anorexia, impaired general condition, a significant reduction in milk yield of up to 50% and diarrhoea with full recovery with 2-3 weeks. These symptoms are mainly observed during the vector active season in Europe between April and November. Another manifestation if the disease is associated with abnormalities in animals born alive or dead at term, stillbirths or aborted following infection of the dam, affecting mainly sheep, but were also seen in cattle and goats. Congenital malformations in foetuses and newborns are the main clinical signs and are similar to those seen in Akabane virus infection. The congenital abnormalities are classified as arthrogryposis-hydranencephaly syndrome, which includes stillbirth, premature birth, mummified foetuses, arthrogryposis, hydranencephaly, ataxia, paralysis, muscle atrophy, joint malformations, torticollis, kyphosis, scoliosis, behavioural abnormalities and blindness. Transplacental transmission and infection with SBV leads to other abnormalities such as macrocephaly of the skull, brachygnathia inferior as well as variable malformations of the brain (hydanencephaly, porencephaly, cerebellar hypoplasia, hypoplasia of the brain stem), and other abnormalities of the spinal cord.

Pathogenesis of Schmallenberg

The pathogenesis of SBV is not fully studied, but experimental infection in cattle and sheep showed an incubation period of between one and four days with viraemia lasting for one to five days. One study revealed that the SBV is neurotropic in naturally *in utero*-infected lambs and calves [6]. Tissue section analysed from the brain and spinal cord of congenitally infected lambs and calves with arthrogryposis, brachygnathia inferior, torticollis and curvature of the spinal with accompanied muscle hypoplasia and demyelination using immunohistological methods revealed an abundance of SBV antigen in the cell body and processes of neurons in the grey matter of the brain and also in grey matter of the spinal cord,

suggesting that the SBV replicates in neurons of the central nervous system of animals naturally infected with the virus. Experimental infection in a mouse model showed that the virus also replicates abundantly in neurons where they cause malacia and vacuolation of the cerebral cortex, thus confirming the hypothesis of the neurotropism of SBV [6]. The neurons are the main target cells for viral replication in the developing foetus and ovine foetuses are susceptible to infection during days 28-50 of gestation, according to the European Food Safety Authority publication in 2012, and this time coincides with the development of the blood brain barrier (BBB). The BBB starts to develop in sheep between 50 and 60 days of gestation and reaches full development by day 123 [7]. This could probably account for the severe lesions observed in foetuses as opposed to adult animals.

Diagnosis

Clinical diagnosis of SBV is made on the basis of clinical signs of the disease which vary by animal species. EDTA-preserved blood as well as serum should be collected from adult animals with suspected acute infection and transported to the laboratory on ice. Samples should be collected preferably in the acute stage of clinical infection (fever, reduced milk yield, diarrhoea). In suspected cases of abortion, samples should be collected for histopathological examination (preferably cerebrum, cerebellum and brain stem and spleen) and virology as appropriate. Amniotic fluid and placenta are also suitable materials for diagnosis. Confirmation of infection is made by viral isolation and detection of SBV sequences using real time (RT)-PCR on tissues.

Differential diagnosis

Schmallenberg should be differentiated from diseases that cause high fever, diarrhoea, reduced milk yield and abortion and these include bluetongue, epizootic haemorrhagic disease, foot and mouth disease, bovine viral diarrhoea, border disease and other pestiviruses, bovine herpes virus 1 and other herpesviruses, Rift Valley fever, bovine ephemeral fever, toxic substances and genetic factors.

Prevention and control

There is presently no treatment or vaccine available for the control of SBV. Further studies are underway to determine what control measures are appropriate as this is a new disease. There are no movement restrictions since SBV is not a notifiable disease. Controlling

Culicoides vectors would be one possible option, i.e. controlling adult midges and removing larval sites.

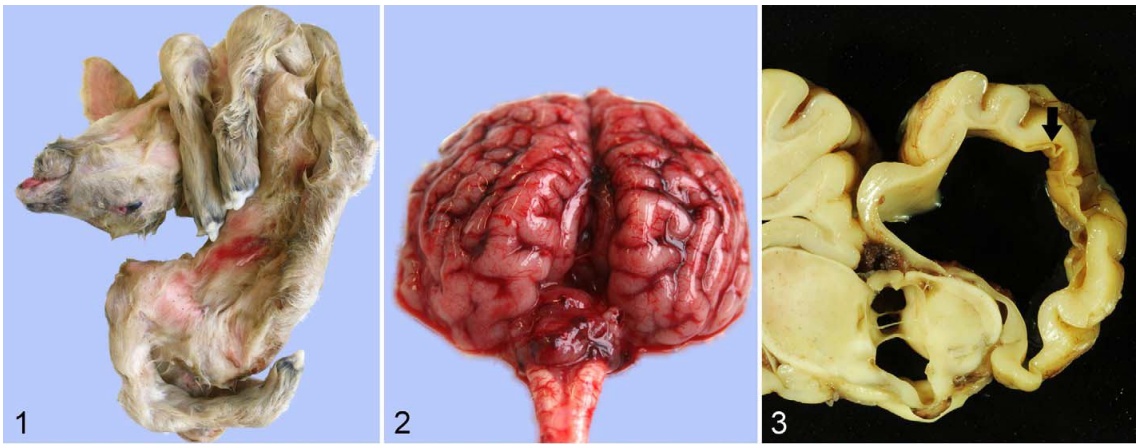

Figure 1. Aborted ovine foetus infected with Schmallenberg virus (SBV) has arthrogryposis, torticollis, and brachygnathia inferior. **Figure 2.** Cerebellar hypoplasia in an SBV-infected bovine foetus. **Figure 3**. Brain; SBV-infected bovine foetus. Unilateral loss of cerebral and thalamic parenchyma with eccentric dilation of the lateral and third ventricles. Note compressed cavitations (arrow) of porencephaly in adjacent cerebral parenchyma. Photographs taken from [8].

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