Immunopathology, pathogenesis and epidemiology of Borna Disease Virus (BDV) infections in domestic animals.

Original title / Originaltitel
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Summary / Zusammenfassung
For more than a century, Borna Disease Virus (BDV) has been known to be the causative agent of a fatal meningo-encephalomyelitis in equines and small ruminants. Within the last 10 years, this disease and its causative agent were found to occur in other species such as rabbits, bovines, felines, ostriches, several zoo animals, as well as in a dog. Until now, Borna Disease in equines and ruminants are restricted to Central Europe, i.e. specific areas in Germany, Switzerland, Austria and the Principality of Liechtenstein. In recent years, a number of investigations from several countries and continents reported the occurrence of BDV antibodies and -RNA in human patients with psychiatric disorders such as schizophrenia and major depression. This led to the belief that BDV may be a potential human pathogen and stimulated research interest in numerous laboratories.

The epidemiological situation of BD and BDV in Switzerland appears to be relatively clear compared with other countries. The disease occurs in a well-defined area in the eastern part of Switzerland, mainly along the Rhine valley and the Swiss border to Austria and Liechtenstein. It occurs sporadically in horses, donkeys and mules as well as in sheep and goats. There are a few well-documented epidemic outbreaks in horses and sheep. In addition, we have diagnosed BD in two bovines (1 cow and 1 bull) that exhibited CNS disease and meningo-encephalitis. We assume that the number of undiagnosed cases of BD is low since awareness of the disease is high among owners and veterinarians in the affected area. This well-defined frame offers a good model for epidemiological studies.

Nevertheless, knowledge concerning the pathogenesis and epidemiology of BDV infection is scarce in spite of the situation described above. Most of the information on the pathogenesis of the disease is derived from experimentally infected rats and the immunopathogenesis in rats is well understood. In recent years, a few research groups have attempted to work experimentally with mice, but this species is less susceptible for BDV infection. Most of the information on the epidemiology of BDV infections in horses is based on sero-epidemiological studies but the sensitivity of testing methods and reproducibility of the results are highly controversial. The same is true for more recent studies based on molecular studies (RT-PCR) from peripheral blood leukocytes.

Objectives: The aims of our Borna Disease research group (Immunopathology group) are as follows:
1. Improve the methods for diagnosing BDV infections post mortem and in vivo.
2. Clarify the pathogenesis, especially immunopathogenesis of natural BD in domestic animals.
3. Investigate the epidemiology of BDV infections in domestic animals, based on natural outbreaks (i.e. detection of subclinical infections within affected herds and areas.)
4. Search for possible vectors (wild rodents, birds, ticks, etc.).

Methods: We have concentrated on the post mortem diagnosis of BD and BDV-infection, using immunohistochemistry as the gold standard to demonstrate BDV antigen in tissues. In addition, we are using a serological test for the demonstration of serum and tissue antibodies in co-operation
with the Virology Institute of our faculty. We also established in-situ hybridization technique and RT-PCR for the demonstration of BDV-RNA. Due to scarcity of time and labour we opted for collaboration with specialised virology laboratories (Vienna, Austria and Freiburg, Germany).

Results and Conclusions:
Immunopathogenesis: Based on the clinically affected and cases of BD confirmed post mortem in equines and ruminants, we were able to confirm that the morphological criteria suggestive of an immunopathological process leading to the disease is most likely the same as in the rat experiments. These investigations were the subject of the thesis by P. Caplazi.

Epidemiology: As early as 1990 we started to collect brain tissue and blood samples from slaughtered sheep, originating from the BD region (thesis A. Rohner-Cotti, 1991). By means of serology (indirect immunofluorescence), histology and immunohistology, we found that the number of BDV-infected sheep within the normal population is extremely low (1/183). This survey was repeated 8 years later, with samples from two other areas and additionally using RT-PCR technique (thesis R. Götzmann, in preparation, 2000). Again, we found very few sero-positive cases and no evidence of persistent BDV infection. Even within herds with recent BD cases, we rarely found inapparent infections. We concluded that the number of infected animals is generally low and that the infection is most likely not particularly contagious.

In a retrospective study (thesis K. Melzer, 1998), we looked for BDV in cats with CNS disease confirmed post mortem. We did not find any BDV antigen or BDV-RNA. Cats from an endemic region and cats from other areas were checked for serum antibodies against BDV. The former population had a relatively high prevalence of BDV-antibodies (31 %) whereas the latter had no significant increase.

In addition, in collaboration with a research group from the Medical School of the University of Zürich, we were involved in a study on BDV infection in individuals concomittent with HIV infection (Bachmann et al. 1999).

Future prospects:
In co-operation with the institute of Virology in our faculty, it was possible to establish a Real Time PCR to detect Borna Disease Virus. The method is specific and highly sensitive. It was possible to detect one BDV infected MDCK cell in 1 million non infected cells and furthermore the RT-PCR succeeded to detect 10 plasmid molecules, containing the sequence of p40. In addition it was possible to apply the method to biological material, such as frozen and paraffin embedded brain samples of sheep and horses suffering from BD. Another approach was the detection of BDV in ticks infected with the virus. After artificial feeding of Ixodid ticks with BDV the ticks were analysed with TaqMan PCR. With our tick model, it can be shown, that a very small virus amount is still detectable and that ticks are not likely to be a vector for BDV, because of the decrease of the virus after 20 to 30 days.

Publications / Publikationen


Die Borna'sche Krankheit in der Schweiz und im Fürstentum Liechtenstein
Schweiz. Arch. Tierheilk. 141, 521-527


Epidemiology of borna disease virus
Genetic clustering of Borna disease virus natural animal isolates, laboratory and vaccine strains strongly reflects their regional geographical origin.

Hofer MJ, Schindler AR, Ehrensperger F, Staeheli P, Pagenstecher A.
Absence of Borna disease virus in the CNS of epilepsy patients.

Shrews as reservoir hosts of borna disease virus.

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