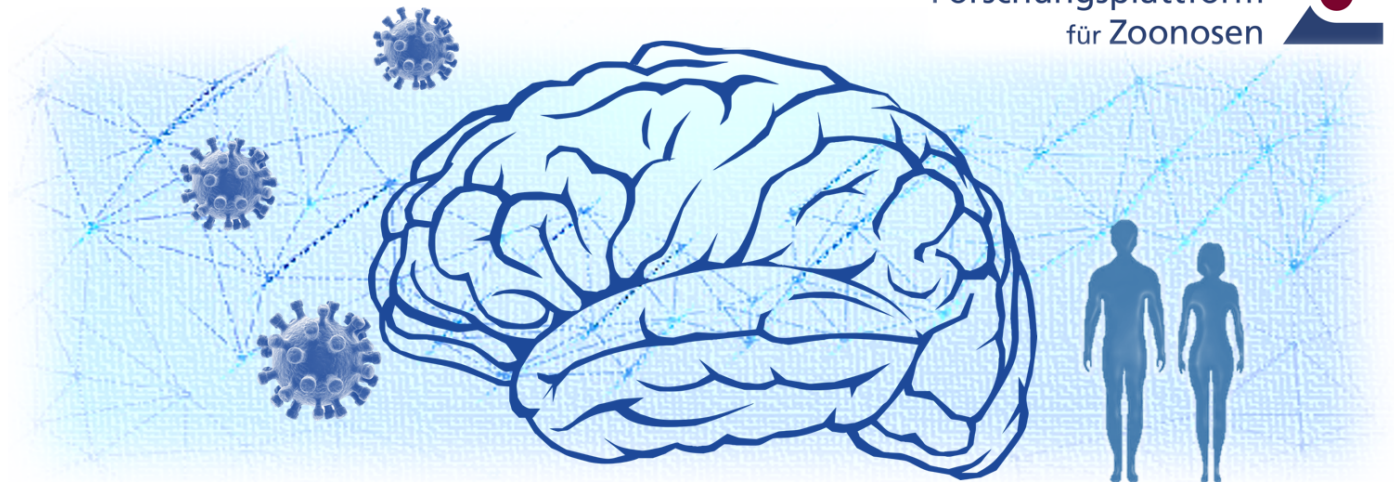


Borna Disease Virus 1 in Germany

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Graph: D. A. Thal

Zoonotic viruses are responsible for numerous human diseases, such as rabies, avian flu or Ebola fever. Researchers have now published that another zoonotic virus, the Borna Disease Virus-1 (BoDV-1), has been the cause of several fatal cases of encephalitis in humans in Germany in recent years (**the study**). This is remarkable in that until 2018 a zoonotic potential was only attributed to the Borna Disease virus from Variegated Squirrel Bornavirus-1 (VSBV-1), but not to other Borna viruses. Prof. Dr. Martin Beer, member of the Internal Advisory Board of the Zoonoses Platform and head of the Institute for Virus Diagnostics at the Friedrich-Loeffler-Institute on the Isle of Riems, was involved in the study. We asked him about the current state of research on Borna Disease Virus-1 in Germany.

ZOOP: Mr. Beer, in a study recently published in the journal "Lancet Infectious Diseases" you and your colleagues reported on several fatal encephalitis cases caused by Borna Disease Virus-1 in patients in Germany in recent years. How many cases are we talking about?

Beer: A total of 14 cases have been published so far, either acutely ill patients in the recent past or retrospectively identified patients in whom archived material could be examined. The cases cover a period from 1999 - 2019. Calculated over the years, the absolute number of severe BoDV-1 infections in humans in Germany is relatively low. However, with a few exceptions, the cases are fatal.

ZOOP: Already in the 1980s and 90s there were scientific publications on the detection of the virus in humans and there was a discussion about a potential connection between BoDV-1 infections and mental illness¹. How do you see these data today?

Beer: These data have to be questioned very critically. Analyses of animal samples have shown that the sequences of Borna viruses can be clustered very well according to their geographical origin. However, the published sequences of human samples in earlier studies did not show these geographical differentiations. Instead, they possess a great similarity to laboratory strains and viruses from animals from other regions. In addition, evidence was found in countries where the virus has never been detected

in animals and the methods used at the time, such as nested PCR, were highly susceptible to contamination and the serology tests used were not sufficiently specific. These shortcomings were recognised by some colleagues some years ago and published accordingly. (further details here ²)

ZOOP: How does the current study differ from earlier assumptions?

Beer: In our study we can establish a direct epidemiological link to the virus reservoir, the viral load is very high in the cases we are investigating, the antibody response is clear and we see very severe clinical courses associated with this. In addition, the detection of infection is based on several independent methods for direct and indirect virus detection. In contrast to earlier assumptions of a widespread occurrence of BoDV-1 infections in the population, our data show a low number of acute BoDV-1 infections in humans, but these are usually fatal.

ZOOP: What is the course of BoDV-1 infection in humans?

Beer: Based on the cases analysed so far, it can be assumed now that after an initial incubation period a short phase with unspecific flu-like symptoms such as headaches, increased temperature and reduced performance occurs. This is followed by clear neurological symptoms and a rapid deterioration in the patient's state of health up to coma and death.

It should be noted, however, that we have only examined the severely progressing cases. At the moment we cannot yet say whether asymptomatic or milder running infections can also occur in humans.

ZOOP: Were the cases limited to certain regions in Germany?

Beer: Yes, so far the confirmed cases are exclusively patients from Bavaria. However, it is also conceivable that neighbouring regions could be affected, but hardly any samples have been examined there so far. However, within the framework of the "**Zoonotic Bornavirus Consortium**" (ZooBoCo) this will be pursued in the future. The consortium is part of the Research Network of Zoonotic Infectious Diseases, which is part of the German Research Platform for Zoonoses. Within this network, we are already successfully pursuing the cooperation between human and veterinary medicine as well as the transfer of results into the application of public health services.

ZOOP: How can humans be infected with the virus?

Beer: More than 10 years ago, the bicolored shrew (*Crocidura leucodon*) was identified as the natural host (reservoir host) of the virus. The infected bicolored shrew do not show any recognisable signs of disease themselves, but high viral loads are found in samples from these animals and they excrete the virus for example in saliva, faeces and urine. At the moment, we suspect that humans can become infected through contact with the virus-containing secretions of the bicolored shrew. Which contacts play a role is also a research goal of the ZooBoCo network.

ZOOP: Are there groups of people at particular risk?

Beer: Currently, we assume that especially people who spend a lot of time outdoors in the endemic area, who live in rural areas and thus may be exposed to bicolored shrews or their excrements, may become infected. What role bicolored shrews captured by cats and possibly brought to their owners play, we cannot yet say. Nevertheless, this could also be a risk factor. Known endemic areas of the virus are currently limited to some regions in Germany (Bavaria, Thuringia and Saxony-Anhalt and adjacent parts of neighbouring federal states) as well as in Austria, Lichtenstein and Switzerland, based on veterinary data. However, if we look at the case numbers to date, it can be assumed that the probability of infection is very low.

In terms of age or gender, no particularly endangered population groups have been identified so far.

ZOOP: Are there other animals that could possibly be vectors for the virus?

Beer: So far we have not been able to identify any other reservoir hosts of the Borna Disease 1 virus.

However, other animals such as sheep, horses, cattle, cats or alpacas can be infected with the virus. But just like humans, these animals are false hosts of the virus and therefore suffer from the infection but do not excrete any viruses (so-called "dead-end hosts"). Borna disease (named after the city of Borna near Leipzig, where the disease first appeared in horses at the end of the 19th century) affects the brain and

spinal cord of the animals, resulting in fever, sleeplessness, apathy, depression and movement disorders. The disease usually has a fatal course in horses. Current case numbers are not known, but this is expected to change with the introduction of a reporting obligation in 2020.

All “dead-end hosts”, including humans, do not excrete the virus and therefore, according to current knowledge, cannot transmit the virus to humans.

ZOOP: Does this mean that human-to-human transmission is not possible?

Beer: No, we can rule out classic human-to-human transmission at this point in time. An exception is the special case of organ transplantation. In 2016, three people fell ill after receiving an organ donation from an unidentified infected person. In this way, a nosocomial infection is therefore possible. The organ donor had no signs of Bornavirus infection and died for other reasons.

ZOOP: Is there any treatment for BoDV-1 infection?

Beer: At this time, we do not have any drugs approved for humans or animals.

ZOOP: Is Germany the only affected country in Europe?

Beer: Germany is the main endemic country and it is the only country in Europe so far where BoDV-1 infections in humans have been detected. However, there is also evidence of BoDV-1 in animals in parts of Austria, Switzerland and Liechtenstein.

ZOOP: How well is Germany prepared for the new zoonotic pathogen and what measures are being taken?

Beer: As of 01.03.2020, there is an obligation to report human infections with BoDV-1 in Germany. For animals, the introduction of a reporting obligation is also planned for this year. In addition, the Bavarian Ministry of Health has announced the establishment of a central office for research into BoDV-1 for the summer of 2020. In the project "Borna Focal Point Bavaria", science and the public health service are to cooperate closely. This project is supported by the research network for zoonoses. It is funded by the Federal Ministry of Education and Research (BMBF).

In addition, the research network "Zoonotic Bornavirus Consortium" (ZooBoCo) was already launched in October 2017 (see above). All the latest findings on the zoonotic character of BoDV-1 were developed within ZooBoCo, which must be considered a great success of this funding.

ZOOP: Where do you see the future challenges for zoonoses research with regard to Borna viruses?

Beer: There are still many unanswered questions and therefore a lot of research is still needed on Borna viruses. It is important to understand how the virus is transmitted and what risk factors for infection are. An important first step has already been the networking of human and veterinary medicine and the dialogue with the public health service. This "One Health" approach is a fundamental concept of modern zoonoses research.

ZOOP: Mr. Beer, we thank you for this interview.

Interview Dana Thal for the National Research Platform for Zoonoses (ZOOP)

¹Chalmers RM, Thomas DR, Salmon RL. Borna disease virus and the evidence for human pathogenicity: a systematic review. QJM. 2005 Apr;98(4):255-74. Epub 2005 Mar 10.

²Dürrwald, R., Kolodziejek, J., Herzog, S. and Nowotny, N. Meta-analysis of putative human bornavirus sequences fails to provide evidence implicating Borna disease virus in mental illness. Rev. Med. Virol., 2007, 17: 181-203. doi:10.1002/rmv.530