RAPID RISK ASSESSMENT

Acute encephalitis associated with infection with Borna disease virus 1, Germany

26 March 2018

Main conclusions and options for response

Borna disease virus 1 (BoDV-1) has been associated with human disease in four cases in Germany resulting in the death of three people. As three of the cases belong to a cluster of solid organ recipients from a single donor, donor-derived BoDV-1 transmission is possible. There is no evidence that the donor had any clinical manifestation of the disease.

BoDV-1 in humans occurs rarely; however considering the severity of this disease, Member States may consider adding BoDV-1 to the list of pathogens included in the differential diagnosis of causes of human encephalitis. The fact that the virus could be transmitted through solid organ transplantation raises concerns about the possibility of transmission through other types of substances of human origin (SoHO). This should be further investigated.

Clinicians and transplantation professionals should be aware of possible BoDV-1 related encephalitis and the possibility of transmission through donated organs, especially in areas where Borna disease is endemic. Endemic areas so far have been identified in central Europe including eastern and southern Germany, the eastern part of Switzerland, Liechtenstein, the most western federal state of Austria and more recently in Upper Austria [1,2].

The bicoloured white-toothed shrew (*Crocidura leucodon*) has been proposed as the animal reservoir of BoDV-1. The routes of transmission of BoDV-1 to humans from the animal reservoir remain unknown and the zoonotic transmission pathways should be further investigated.

Source and date of request

ECDC Internal Decision, 09 March 2018.

Public health issue

The investigation of four human cases of acute encephalitis associated with Borna disease virus 1 infection (BoDV-1, species *Mammalian 1 bornavirus)* in Germany, raises questions about the zoonotic spread of infection in the country and potential human-to-human transmission through organ transplantation.

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Consulted experts

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All experts have submitted declarations of interest and a review of these declarations did not reveal any conflicts of interest. Experts from the World Health Organization (WHO) Regional Office for Europe contributed to this risk assessment. Although experts from WHO reviewed the risk assessment, the views expressed in this document do not necessarily represent the views of WHO.

Disease background information

The causal agents of Borna disease (BD) are enveloped, spherical, 80 to 100 nm in diameter, non-segmented, single stranded, negative sense RNA viruses of the *Bornavirus* genus*, Bornaviridae* family, order Mononegavirales [3].

Taxonomy of *Bornavirus*

The genus *Bornavirus* includes eight species, according to the last International Committee on Taxonomy of Viruses (ICTV) accepted taxonomy, and 16 viruses. Five species include 12 avian bornaviruses *(Passeriform 1 bornavirus*, *Passeriform 2 bornavirus*, *Psittaciform 1 bornavirus*, *Psittaciform 2 bornavirus* and *Waterbird 1 bornavirus)*, one species includes one reptile virus (*Elapid 1 bornavirus*), and two species include three mammalian viruses *(Mammalian 1 bornavirus* and *Mammalian 2 bornavirus).* In the *Mammalian 1 bornavirus* species, there are two viruses: Borna disease virus 1 and 2 (BoDV-1 and BoDV-2); in the *Mammalian 2 bornavirus* species there is one virus: the variegated squirrel bornavirus 1 (VSBV-1) [3].

Borna disease in animals

Borna disease was first described in the eighteenth century and was named after the town of Borna, near Leipzig, Germany, where an epizootic condition was described in 1885 among military horses presenting with a fatal neurologic disease [4]. Borna disease is reported most frequently in horses and sheep. However many mammal species including farm animals (cattle and goats), zoo animals (llamas, hippopotamuses, alpacas, monkeys, etc.) and, rarely, companion animals (dogs and cats) can also be affected [5]. The disease has recently been seen in psittacine birds [6], Canada geese, trumpeter and mute swans [7], canary birds [8,9] and in reptiles [10].

In animals, the incubation period ranges from two weeks to several months. The infection may lead to a severe neurologic disorder characterised by an acute or sub-acute disease with meningo-encephalitis, or to mild manifestations with alteration or impairment of nerve-cell functions [4]. The specific disease syndromes depend on many host factors including the species, breed, age, and immunological status of the animal at the time of infection. Paralysis is common and death occurs within 1–5 weeks in the majority of animals. Recovery is possible with life-long altered behaviour [13].

Recently, the bicoloured white-toothed shrew *(Crocidura leucodon)* was proposed as the natural reservoir for BoDV-1 [11]. BoDV-1 occurrence in the reservoir hosts is only shown for Germany, Austria, Switzerland and Liechtenstein [1,2].

Borna disease in humans

The first demonstrated human infections with a member of the genus *Bornavirus* were reported in 2015. The involved virus was variegated squirrel bornavirus 1 (VSBV-1). Between 2011 and 2013, three men from the same geographical area (Saxony-Anhalt, Germany) developed a progressive fatal encephalitis and died 2–4 months after the onset of the symptoms (fever and/or shivers, confusion, unsteady gait, myoclonus and/or ocular paresis, progressive psychomotor slowing and coma) [12]. All three men were breeders of variegated squirrels *(Sciurus variegatoides)* and they exchanged their animals on different occasions. By the use of metagenomics approaches, a previously unknown bornavirus (VSBV-1) was detected in CNS samples from the three patients, and in a squirrel that had been in contact with them [12,13].

Event background information

On 7 March 2018, Germany reported four human cases of acute encephalitis or encephalopathy associated with infection with BoDV-1 through an Early Warning and Response System (EWRS) message. This virus is clearly distinct from VSBV-1. On 8 March 2018 the event was described in the epidemiological bulletin of the Robert Koch Institute by the Friedrich Loeffler Institute, the Federal Research Institute for Animal Health [14].

Three of the cases relate to a cluster of solid organ recipients from a single donor from southern Germany, and two of the recipients died. One additional case of encephalitis due to BoDV-1, who also died, was found in southern Germany.

The organ donor passed away for reasons that seem to be unrelated to a neurological disease. Approximately 100 days after receiving the organ transplants, the three transplant recipients (two kidney and the one liver transplant) developed severe encephalitis/encephalopathy while being on standard immunosuppression therapy for organ recipients. The other organs of the donor were not used. Both recipients of the kidney transplants fell into a coma and passed away. The recipient of the liver transplant survived with residual degenerative optic nerve atrophy. The donor and the recipient patients lived and were treated in different cities/states. Apart from the fact that these three cases received organs from one single donor, no other common risk factors were identified.

The initial laboratory investigations were carried out by the Friedrich Loeffler Institute which confirmed BoDV-1 genome in both kidney transplant recipients by RT-qPCR and next-generation-sequencing. BoDV-1-specific seroconversion was detected in all patients and confirmed at the University of Freiburg and the Bernhard Nocht Institute. Immunohistochemistry and *in-situ*-hybridization at the University of Giessen confirmed the presence of BoDV-1 antigens and RNA. BoDV-1-specific seroconversion with high antibody titres was observed in the liver transplant recipient.

The additional case of encephalitis due to BoDV-1 was found during the investigation of this transmission cluster. No epidemiological link could be identified between this isolated case and the transplantation cluster. Another patient with encephalitis is currently under investigation; this patient has not received any organ transplantation either.

ECDC threat assessment for the EU

BoDV-1 zoonotic transmission

Zoonotic transmission of VSBV-1 was evidenced by the cluster among variegated squirrels breeders in 2011–2013 in Germany [12,13]. Plausible routes of transmission were through bites or scratches, but transmission through direct deposition on the mucous membranes or inhalation of particles contaminated by faeces or urine of infected animals was not excluded.

The bicoloured white-toothed shrew *(Crocidura leucodon)* has been proposed as the animal reservoir of BoDV-1 [11,15-17]. The routes of transmission from the animal reservoir to humans are unknown and the zoonotic transmission pathways should be further investigated.

There is no information about possible exposure of the organ donor to animals and shrew in particular.

BoDV-1 and SoHO safety

This is the first time that a possible BoDV-1 transmission through organ transplantation has been reported. Although information on the status of BoDV-1 infection and other clinical data of the organ donor are unknown, all BoDV-1 infected recipients developed severe clinical symptoms resulting in two of them dying. No other commonalities between the donor and the recipients other than the solid organ transplantations were reported, which suggests donor-derived virus transmission. It has to be noted that BoVD-1 genome could not be detected in the blood of any of the recipients.

Experimental transfer of infection through lymphocytes from the brain of Borna disease affected to immuno-compromised rats [18] has been previously documented, demonstrating that transmission through transplantation might be possible.

Although this event strongly suggests the possibility of BoDV-1 transmission through solid organ transplantation, further investigations will be necessary to understand the epidemiology of the disease, including the possibility of transmission through other SoHO.

Disclaimer

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This report was written under the coordination of an Internal Response Team at ECDC. All data published in this risk assessment are correct to the best of our knowledge on 22 March 2018. Maps and figures published do not represent a statement on the part of ECDC or its partners on the legal or border status of the countries and territories shown.

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