Human Borna Disease Virus 1: An emerging neurotropic virus of concern

Hinh Ly[1] and Michaela Cain[1]

[1]University of Minnesota Twin Cities

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Letter to the editor

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Michaela Cain and Hinh Ly*

Department of Veterinary & Biomedical Sciences, College of Veterinary Medicine, University of Minnesota, Twin Cities, MN, USA

*Address correspondences to:

Hinh Ly, Ph.D.

University of Minnesota, Twin Cities, 1988 Fitch Ave., Ste. 295, St Paul, MN 55108

Phone: 612-625-3358

E-mail address: hly@umn.edu

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To the Editor:

Human Borna disease virus 1, BoDV-1, is a negative sense, single-stranded, enveloped RNA virus in the family *Bornaviridae*within the order Mononegavirales[1,2]. The viral genome has six known open reading frames that produce at least six proteins: nucleoprotein (N), phosphoprotein (P), putative matrix protein (M), type 1 membrane glycoprotein (G), and putative viral polymerase (L)[2,3]. Unique among all known RNA viruses, the replication and transcription process of BoDV-1 occurs in the host cell's nucleus and its genome is highly conserved[2]. BoDV-1 has been shown to replicate in cells of the central nervous system, including neurons, astrocytes and oligodendrocytes. The bicolored white-toothed shrew is the primary animal reservoir for BoDV-1, which can establish a persistent infection with broad tissue tropism, but without an overt clinical disease[4]. BoDV-1 infection is characterized by immune mediated meningoencephalitis that can often lead to severe complications and death in spillover hosts, such as horses and sheep[4]. BoDV-1 has also been found to induce behavioral changes in the animals, such as anxiety, aggression, cognitive defects, and hyperactivity in these animals and can lead to a form of neurotropic disease that is characterized by T lymphocyte-mediated encephalitis[4]. Borna disease in horses has been described since the 18th century, but only in 1885 that it was designated Borna disease following a major horse epidemic in Borna, which is a town in Saxony, Germany[5,6]. It is noteworthy that BoDV-1 has predominantly been found in regions of Germany, Liechtenstein (Switzerland), and Austria[7]. It is thought that some livestock can serve as intermediary hosts of BoDV-1; however, zoonotic transmissions of BoDV-1 have been suspected but not definitely confirmed.

It has been theorized that a substantial proportion of unidentified human fatal encephalitis cases are caused by BoDV-1, but due to difficulties in developing and validating a test for diagnosing BoDV-1 infection, human cases have not been definitively confirmed[7]. In a recent report published in the Emerging Microbes & Infection journal[8], Frank and colleagues developed and validated a workflow for rapid testing of BoDV-1 infections using serum and cerebrospinal fluid from at risk patients. The serological workflow uses an indirect immunofluorescence assay followed by a line blot assay, and utilizes the BoDV-1 phosphoprotein (P) antigen. In addition, qRT-PCR and next generation sequencing were conducted on some patients, who tested positive serologically for BoDV-1 infection. The authors also conducted histopathological characterization of positively confirmed BoDV-1 postmortem cases. Using these methods, they were able to recover the full-length BoDV-1 genome from the patient's brain tissue, and upon sequencing the viral genome, they were able to phylogenetically match the viral sequences to BoDV-1 strains found in shrews and domesticated animals of cluster 4 in central Germany[8].

The first human case of Borna disease that was serologically confirmed was reported in 1980s[9]. A recent study by Liesche and colleagues identified six cases of BoDV-1 infection in 6 females (17-65 years old) from 1999-2019, in brain tissue of encephalitis cases isolated in Bavaria, Germany[10]. All patients developed headache, fever, confusion, deep comas, and died within two months of symptom onset (Table 1). In addition, Niller and colleagues reported three previously known cases of encephalitis caused by BoDV-1 in solid-organ transplant, two of which were fatal[4]. Another study done in Germany from 2018-2020 examined 103 encephalitis cases of unknown etiology using qRT-PCR on CSF and brain tissues and found 3% prevalence of BoDV-1 infections[11]. All patients were from Bavaria, who developed encephalitis and fevers, and died within a month of the onset of symptoms (Table 1). Although more studies need to be done, these recent reported cases suggest an increased risk of BoDV-1 infections in Germany and the potential for severe outcomes in patients who contract the virus.

Interestingly, people who lived with and had been in close contact with infected patients neither showed signs of disease nor did they harbor BoDV-1 antibodies, which were tested serologically through fluorescence antibody tests and line blots[7]. The only confirmed human-to-human transmission of BoDV-1 was through solid organ transplantation, and it is theorized that all other human cases are spillover events from BoDV-1 infected animals. Due to the seemingly sporadic nature of BoDV-1 infections, it has been hypothesized that each human case represents an independent zoonotic transmission event.

There are significant gaps in knowledge about this virus, e.g., how it transmits within and between animal species (intraspecies and interspecies transmissions), and how it can cause disease (disease pathogenesis and pathology), etc. Although the incidence of Borna disease seems to be relatively low and is localized to some endemic regions in the world, it is important to conduct routine serological surveys of the virus and to study the disease that it causes, which can lead to very high and rapid mortality rate. Using new molecular tools, such as the reverse genetics system for BoDV-1[1], researchers have started to make some inroads into understanding the basic biology of this virus. Until more epidemiological, gross- and histo-pathological, virological, and immunological studies are done on BoDV-1 and the disease that it causes in humans, no prophylactic and therapeutic modalities can be developed to prevent or treat these emerging and fatal human viral infections.

Patient Age	**Patient Gender**	**Location**	**Profession**	**Time**	**Symptoms**	**Outcome**	**Reference**
55	Female	Bavaria	Part-time cleaner	Mid-January 2019	encephalitis, fever, headache, and coma	Death 3 weeks after onset of symptoms	11

Patient Age	Patient Gender	Location	Profession	Time	Symptoms	Outcome	Reference
11	Female	rural Bavaria	unknown	November 2019	encephalitis, fever, headache, and epileptic seizures	Death 4 weeks after onset of illness	11
79	Male	rural Bavaria	Farmer	June 2020	encephalitis, fever, and confusion	Death 4 weeks after the onset of symptoms	11
74	Female	Bavaria	*	*	Axonal motor neuropathy with Guillain-Barré syndrome-like spread	Death 14 weeks after onset of symptoms	10
21	Female	Bavaria	*	*	Fever, memory deficits, epileptic seizures, progressive loss of consciousness	Death 5 weeks after onset of symptoms	10
13	Female	Bavaria	*	*	Fever, Slurred speech, progressive loss of consciousness	Death 4 weeks after onset of symptoms	10
17	Female	Bavaria	*	*	Fever, headache, confusion, progressive loss of consciousness	Death 6 weeks after onset of symptoms	10
78	Female	Bavaria	*	*	Right-sided weakness, epileptic seizures, progressive loss of consciousness	Death 4 weeks after onset of symptoms	10

Patient Age	Patient Gender	Location	Profession	Time	Symptoms	Outcome	Reference
55	Female	Bavaria	*	*	Fever, headache, amnesic aphasia, progressive loss of consciousness	Death 2 weeks after onset of symptoms	10

*Not all patient data was available

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