Neuropathology, pathomechanism, and transmission in zoonotic Borna disease virus 1 infection: a systematic review

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Borna disease, which is a severe encephalitis that primarily affects horses and sheep, has been recognised for over two centuries. Borna disease virus 1 (BoDV-1) has been identified as a cause of a predominantly fatal encephalitis in humans. Little scientific data exist regarding the virus' transmission, entry portal, and excretion routes. Lesional patterns, immunological responses, and pathogenetic mechanisms remain largely unexplored in both reservoir and dead-end hosts. This systematic review compiles current knowledge on these aspects and provides guidance for future research. PubMed, ScienceDirect, and EBSCO were searched for publications from Jan 1, 2000, to April 30, 2024. 823 records were found, of which 41 studies were included. This systematic review discusses BoDV-1 transmission, pathogenesis, histopathological changes, and immunology in both reservoir and dead-end hosts, with special regard for humans. The exact propagation mechanisms, entry portal, and viral spread within the CNS are not entirely clear in humans. Although more data exist in animals, much remains hypothetical. Future research should focus on identifying potential entry sites and viral spread in dead-end hosts, which could help to clarify the pathogenesis and lesion distribution in the CNS, thereby contributing to a better understanding of BoDV-1 infection in humans and parallels with animal infections.

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Introduction

Borna disease virus 1 (BoDV-1) is a highly neurotropic virus that could serve as a model for other neurotropic viruses. Known for causing non-purulent meningoencephalitis in horses and sheep for over two centuries,[1,2] in 2018, BoDV-1 was identified as a cause of severe and often fatal encephalitis in humans.[3–5] The negative-sense, single-stranded RNA genome of the virus consists of approximately 8900 nucleotides, encoding six open reading frames for structural proteins (nucleocapsid protein, phosphoprotein, matrix protein, and glycoprotein), and non-structural proteins (regulatory X protein, and L-polymerase).[2]

BoDV-1 is zoonotic and harboured by the bicoloured white-toothed shrew (*Crocidura leucodon*) as a natural reservoir host,[6–8] in which the virus causes persistent infection with long-term infectious excretion.[7,9] Reports on BoDV-1 in other shrew species indicate that these shrew species could be dead-end hosts, rather than reservoir animals.[8] The classic accidental hosts, such as horses, sheep, and potentially humans, are believed to become infected via environmental contamination,[10,11] with BoDV-1 entering through the olfactory tract and spreading via the limbic system to other brain areas and the spinal cord.[12] The endemic area of BoDV-1 encompasses the eastern and southern parts of Germany and the neighbouring countries Switzerland, Austria, and Liechtenstein.[13]

As estimated by the Robert Koch Institute (Berlin, Germany), between two and seven new human cases of bornavirus encephalitis occur per year in Germany,[5] with currently just over 50 known cases.[14] Since the first confirmed human infections, the awareness of bornavirus encephalitis has grown, leading to a rise in diagnosed cases.[15] Clinically, it often starts with non-specific symptoms such as fever and headache, progressing to neurological impairments, and mostly resulting in death within weeks from the initial infection (figure 1).[5,10,16]

Bornavirus encephalitis remains an untreatable disease with many unknown aspects regarding transmission, virus entry routes, and immune response. This

Key messages

This systematic review has synthesised the current knowledge on Borna disease virus 1 (BoDV-1) infections, emphasising the pathomechanisms in humans and animals. The key conclusions are:

Transmission and entry

BoDV-1 transmission remains complex and is only partly understood. Reservoir hosts maintain persistent infections without symptoms and the exact entry site is difficult to establish due to diffuse virus distribution and lack of inflammation. The olfactory system and potential peripheral routes (such as scratches from territorial behaviour) are considered to be possible entry points. In dead-end hosts, the olfactory pathway seems to be the primary route, although direct evidence for environmental contamination as a transmission source is sparse.

Pathogenesis and lesional patterns

Reservoir hosts show no CNS lesions, which suggests immune tolerance, whereas dead-end hosts exhibit severe inflammation (particularly in the hippocampus) and a high neurotropism of the virus in both animals and humans. Future studies should explore the virus' distribution and interactions with CNS cells. The immune response to BoDV-1 in both host types is largely unexplored, and insights could inform therapeutic strategies and improve outcomes.

Spread to periphery

In reservoir hosts, BoDV-1 is found in neuronal and non-neuronal cells, allowing viral shedding through urine, faeces, and saliva, for example. In dead-end hosts, the virus is mainly confined to the CNS, with little peripheral nervous system (PNS) involvement and occasional detection in non-neuronal tissues. Human cases suggest BoDV-1 spread to the PNS and possible centripetal spread. Further research is needed to examine PNS involvement and viral shedding in humans by standardised investigations.

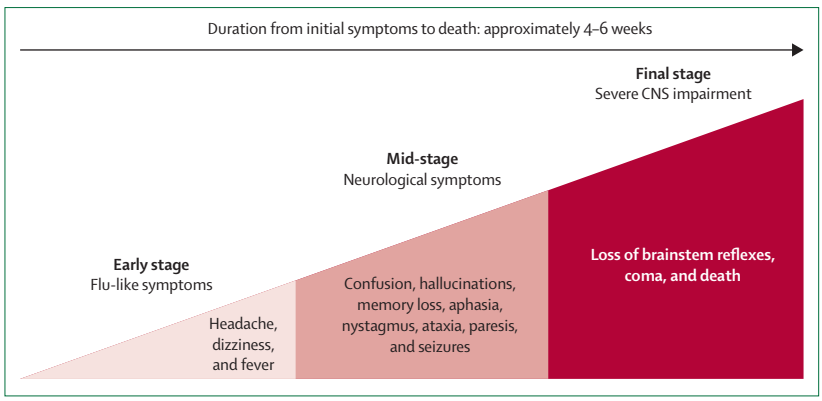

Figure 1: **Simplified course of human bornavirus encephalitis from initial symptoms to death**
Clear disease phases are often not discernible and early symptoms might already include fluctuating neurological signs and symptoms. Individual disease courses can be prolonged and depend on supportive care. Figure created with BioRender.com.

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See Online for appendix

systematic review summarises current knowledge of BoDV-1 infection in animals and humans, and identifies substantial gaps in understanding of the disease, with guidance for future research in the field of BoDV-1 infections.

Methods

Search strategy and selection criteria

We searched PubMed, ScienceDirect, and EBSCO in May, 2024. Most foundational data on BoDV-1 infections in animals were obtained in the 1980s and 1990s; however, to focus on human infections and the intention to highlight more recent developments, we only included publications in English from Jan 1, 2000, to April 30, 2024. We used the search terms: "distribution pattern borna virus/distribution pattern borna virus human", "dissemination borna virus", "spread borna virus/spread borna virus human", "distribution borna virus/distribution borna virus human", "BoDV-1 distribution", "human bornavirus", and "human Borna disease virus 1". We focused exclusively on BoDV-1 to avoid confusion and maintain a clear and concise scope, and excluded records published before 2000 and publications that only included the words "virus" or "human", but did not have reference to BoDV-1. The inclusion of other *Bornaviridae* (such as the variegated squirrel bornavirus 1) would have complicated the narrative review and expanded the breadth of this systematic review beyond manageable limits. We did not exclude specific literature or document types. A detailed description of the search strategy and selection criteria can be found in the appendix (pp 1–2).

The scientific question of the present work contains the investigation of the distribution pattern in the nervous system and entry routes and the propagation mechanisms of BoDV-1 in humans and animals. After the literature search, a systematic review was done based on the PRISMA model by Page and colleagues.[17]

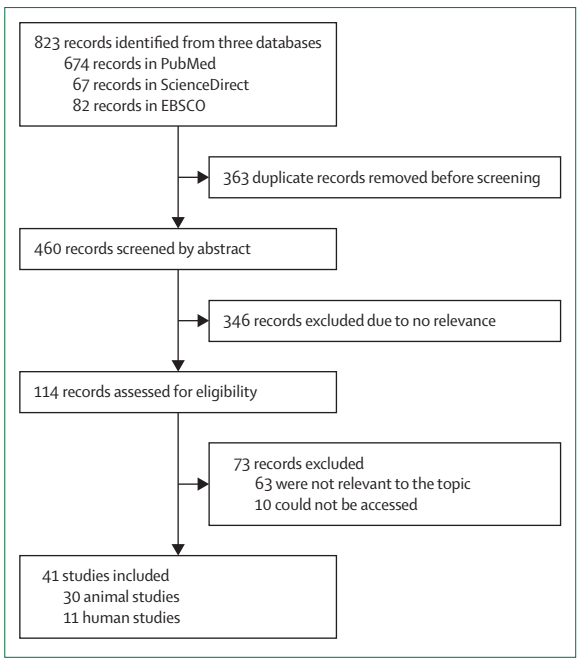

Figure 2: **Study selection**

Results

Overview of studies

The literature search generated 823 records, of which 114 were screened for inclusion (figure 2). 41 were included in this systematic review, consisting of 30 animal studies, and 11 human studies (appendix pp 3–31).

Transmission setting for BoDV-1 within animal reservoir hosts and to dead-end hosts

Reservoir hosts

Infection of the bicoloured white-toothed shrew (*C leucodon*; a primary BoDV-1 reservoir host) results in persistent infection with widespread virus presence throughout the animal, without causing inflammation or clinical signs.[18,19] *C leucodon* are primarily found in central Europe[6,18] and favour environments with moderate average temperatures, low forest cover, and urban areas, such as gardens and farmlands.[18,20]

Transmission routes among shrews remain to be elucidated. So far, intranasal, horizontal, and vertical transmission have been reported, along with excretion via urine, faeces, and possibly skin and fur, followed by nasal-olfactory uptake from the environment. The hypothesis of transmission through infected saliva during habitat defence has also been suggested.[7,19] The chain behaviour of young shrews (snout-to-tail bite; figure 3) might imply a faecal–oral or saliva–skin transmission, although oral transmission was unsuccessful in initial shrew infection studies.[21] Glands, keratinocytes, and nerve fibres within the skin can harbour viral antigens as a prerequisite for viral shedding.[19]

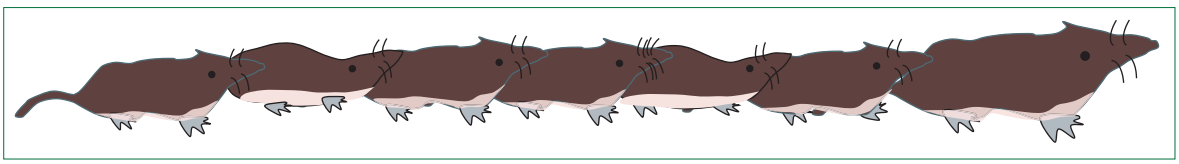

Figure 3: **Offspring transport in a family of bicoloured white-toothed shrews (*Crocidura leucodon*)**
Whether such behaviour contributes to the propagation of Borna virus disease 1 within the shrew population remains to be analysed.

Experimentally, intracerebral, subcutaneous, intraperitoneal, and intranasal infection routes have been successful.[21] Future studies should explore direct transmission through scratches or bites, vertical transmission, and environmental shedding.

Soil samples should also be further analysed for the presence of BoDV-1, especially in and around shrew dwellings, along shrew tracks, and in areas where BoDV-1 has been detected in human or animal dead-end hosts. In this regard, chemical and physical aspects (ie, the pH value of the soil or temperature) that affect the stability and tenacity of the virus should also be considered.

The question regarding differences in the viral load in the organs of reservoir animals remains unresolved. The highest loads are found in the CNS. In chronically, persistently infected animals, the skin and salivary glands are also affected, with small amounts of the virus detectable in the kidney, which is sufficient for effective excretion of the virus. There seems to be no correlation between viral load in the excreting organs and the infectivity of the respective animal, which nonetheless raises the question of whether BoDV-1 excretion varies between individuals and which factors influence the viral load in the animals and their organs.

Animal dead-end hosts

BoDV-1 sporadically infects dead-end hosts (predominantly horses, sheep, and alpacas) during spillover events.[22] The specific ways in which the virus spreads among reservoir species and to dead-end hosts remain unclear, although evidence shows that infected shrews release the virus in their faeces and urine.[23,24] Viral sequence data of 100% identity from two *C leucodon* and a horse in the same stable strongly supports transmission from shrews to horses.[19] Direct contact with bodily fluids and contact with contaminated food and water could contribute to infectious virus transmission.[19,25]

Vertical transmission in horses has been reported but remains unconfirmed.[26,27] The potential for asymptomatic natural infection in horses has also been suggested by studying disruptions in glutamate and lipid metabolism in the hippocampi of BoDV-1 infected horses compared with uninfected controls.[28] Considering the geographical location of the study by Zhang and colleagues[28] (western China), which is outside the confirmed endemic area,[5,18,29] this result appears inconclusive and should be interpreted with caution.

Alpacas are particularly susceptible to BoDV-1, with atypical courses leading to sudden death and subclinical infections. The exact transmission route to alpacas is not yet clarified. In comparison to sheep and horses, in which typically either one or a few animals of the herd are affected, a substantial proportion of alpaca herds (approximately 40%) may be infected.[22,30,31] One hypothesis for the higher susceptibility of alpacas, among others, might be because they are obligate nasal breathers.[32]

Cats are occasionally implicated as a dead-end host and a potential risk factor for humans. A study by Lutz and colleagues[33] reported that cats can also be infected with BoDV-1. However, this conclusion needs to be critically evaluated, given that existing knowledge indicates that the so-called staggering disease in cats (previously associated with BoDV-1) is actually caused by rustrela virus (*Rubivirus strelense*).[34] As of 2024, only one confirmed case of BoDV-1 infection in a cat has been documented.[35] Nevertheless, the domesticated cat (*Felis catus*) could potentially serve as a passive vector between shrews and humans.

Cows are of particular interest, as they share a similar habitat with horses and sheep. However, only older studies with little data are available on the species. In 1994, Caplazi and colleagues reported the first natural BoDV-1 infection in a cow in Switzerland, but literature is sparse on BoDV-1 infection and transmission in cattle compared with horses.[36] Bode and colleagues described nine different cases of cattle in Germany, with each developing non-purulent encephalomyelitis.[37]

Early studies on BoDV-1 incidence in other mammals tested brain samples from various species, including cats, dogs, cattle, red foxes, badgers, squirrels, wild boars, deer, mice, and rats. There was only one positive result (in a dog), indicating the rarity of BoDV-1 infection.[38,39] Previous studies have inoculated various species of animals, including chickens, monkeys, and rabbits.[2] Nevertheless, future research should explore the different species of dead-end hosts to better understand how susceptible they are to BoDV-1 and what mechanisms might explain these differences. Lifestyle factors might provide a potential explanation, as discussed regarding the portal of entry. Domestic cats warrant particular attention due to their direct interaction with shrews (eg, hunting) by bringing them to the human interface.

As no infectious virus, viral RNA, or antigen is present in the peripheral organs of infected horses or sheep,

direct transmission between these species or from animal dead-end hosts to humans seems unlikely.[26,39]

Human dead-end hosts

Transmission of BoDV-1 to humans as dead-end hosts remains unclear, as people are usually diagnosed when already in severe clinical conditions or retrospectively from archived material. Therefore, identifying clues of transmission events, which can often only be obtained through relatives or close friends, is particularly challenging. Additionally, the interface between humans and the reservoir host is puzzling, as *C leucodon* is generally a nocturnal and fearful animal (of both other animals and humans).[11,40]

To our knowledge, Pörtner and colleagues did the first human risk factor study based on interviews with relatives of people who died and had been infected with BoDV-1, which revealed that living in rural, virus-endemic areas on the outskirts of settlements that were close to nature was a primary risk factor.[11] No circumscribed risk could be assigned to specific outdoor leisure activities (eg, gardening, jogging, or cycling), or agricultural work. Furthermore, no potentially relevant transmission route could be indicated. Direct contact with shrews was not reported, suggesting indirect transmission, possibly through contaminated soil, yet BoDV-1 RNA was not detected in garden samples from patients months after the infection. As previously mentioned, domestic cats could bring shrews infected with BoDV-1 into patients' homes, which would represent an obvious contact possibility. This hypothesis could not be confirmed in Pörtner and colleagues' case–control study,[11] but deserves further investigation.

Böhmer and colleagues[41] did a One Health survey in a community where two paediatric cases of bornavirus encephalitis had occurred previously.[42] Environmental samples were collected from areas that had been frequented by the two children. Due to a lack of knowledge about the exact habitat of *C leucodon*, the collection of environmental samples proved challenging. Although BoDV-1 RNA was not detected in humans or environmental samples, a shrew was found in the vicinity. Phylogenetic analysis of the sequences of BoDV-1 from the two paediatric cases suggests that the infections were localised.[41] In other studies, barns or animal bedding were occasionally positive for the presence of BoDV-1 in horse or shrew holdings.[7,19]

Human-to-human transmission has been confirmed only once in an iatrogenic setting through solid organ transplantation, in which a Bavarian donor in whom death had been diagnosed based on neurological criteria transmitted BoDV-1 to three organ transplant recipients. The donor had not shown any symptoms or signs of neurological disease or infection. The cause of death was identified as cardiac arrest, but was not specified in more detail. Both kidney transplant recipients died. The liver transplant recipient developed postoperative cognitive impairments and facial palsy followed by severe leukoencephalopathy.[4] The source of the donor's infection remains undisclosed, and the absence of neurological symptoms raises several questions, including the possibility of atypical clinical courses. This case underscores the importance of investigating subclinical cases of BoDV-1 infection, particularly in peripheral organs, and the potential involvement of the autonomic nervous system.

Future studies should build on the works of Pörtner and colleagues,[11] Böhmer and colleagues,[41] and Grosse and colleagues,[42] which focused on soil samples from areas with *C leucodon* activity. Excreta within shrew burrows and oral or nasal intake of BoDV-1 by dead-end hosts should be further investigated, along with the option of airborne transmission through dust particles from infected shrews or their excreta. Studies on human infection risks should focus on leisure activities, seasonality, and geographical risk areas. The exact mode of transmission also requires further clarification.

Human bornavirus encephalitis is rare, and why only some patients develop the disease is unclear. Hypotheses include intrinsic factors, including genetic variations involving the immune system, or possibly protective endogenous bornavirus-like sequences, which are DNA sequences embedded in vertebrate genomes that originate from the mRNAs of ancient bornaviruses, and represent evidence of historical virus–host interactions.[43] Other factors, such as the minimal infectious dose and contact time with BoDV-1 combined with the specific portal of entry, probably have a key role. As a multifactorial setting is generally assumed, these aspects require clarification, with a focus on analysing the contact time and infectious dose needed for BoDV-1 infection, and investigating the duration of viral presence and the conditions necessary for transmission. Initially, in-vitro models could clarify the contact time needed for BoDV-1 to enter cells. Different cell types (eg, different kinds of epithelial cells) should be tested with various viral concentrations to draw conclusions regarding possible entry sites. Nevertheless, only suitable animal models can address the question of the actual contact duration needed for BoDV-1 to invade the organism. Moreover, human endogenous Bornavirus-like sequences based on the review of Horie[44] should be analysed for possible inactivating nucleotide insertions or deletions in patients with bornavirus encephalitis versus the unaffected population, or in people who live after bornavirus encephalitis.

In this context, the potential for postexposure prophylactic options should be explored, similar to Reinmiedl and colleagues' suggestions.[45] An investigation of the antiviral drug favipiravir in mice infected with rabies resulted in protection against rabies-related death when used alongside a vaccine.[46] Given the biological similarity between BoDV-1 and rabies,[26] this approach

warrants further investigation, especially because favipiravir has already shown antiviral activity against BoDV-1 in in-vitro models.[47]

Entry site and route of infection of BoDV-1 in reservoir and dead-end hosts

Reservoir animals

The absence of an inflammatory response and the diffuse distribution of BoDV-1 in the CNS makes determination of the exact entry site and infection route in reservoir animals difficult, because it represents the chronic persistent phase of infection.[7,18]

Shrew behaviour, especially regarding interactions such as scratching during territorial disputes, remains understudied, although it could provide clues to viral entry. Therefore, future research should focus on observing shrews in captivity and doing experimental studies with various inoculation routes (nasal, dermal, or oral). Ideally, this research should be done on shrews of different ages to establish whether the immune system of young shrews shows better tolerance than that of older shrews.

Animal dead-end hosts

In dead-end hosts, the mechanisms of viral entry into the CNS remain unclear.[30] The most common hypothesis is the olfactory pathway, which is similar to other neurotropic viruses (eg, herpes and rabies) and bypasses immune detection.[1] The olfactory epithelium, where neurons establish direct contact to the environment, is thought to be the main entry site for BoDV-1, since a targeted immune response appears to be absent.[1] BoDV-1 is thought to enter through the olfactory mucosa via open nerve endings, moving into the CNS via the olfactory nerve and pathway, and subsequently affecting neurons of the limbic system (especially the hippocampus).[2,48,49]

In horses, transmission was thought to occur via blood, due to BoDV-1 RNA and protein detection in peripheral blood mononuclear cells,[26] but recent analyses revealed no viraemia (Herden C, unpublished). Macrophages might uptake viral particles for antigen presentation, but the presence of infectious viruses in macrophages is doubtful.

Experimental infections in rats, mice, and sheep confirm that the olfactory route is the most efficient, yet subcutaneous and intravenous infections are possible.[1,39,50] Since BoDV-1 most likely requires nerve endings to anchor within the animal organism, the most inefficient route is considered to be by intravenous virus application.[51]

Studies in rhesus macaques (*Macaca mulatta*) provide a surrogate model for the human disease and support the olfactory pathway, with intracerebrally inoculated animals showing severe encephalitis, whereas peripherally inoculated animals showed a delayed onset of encephalitis.[24]

Beside the future experimental studies already discussed regarding the transmission of BoDV-1, viral shedding analyses in newly naturally infected animals should be done with a comprehensive swab testing of all accessible fluids and excrets (including salivia, nasal mucus, lacrimal fluid, faeces, urine, and skin secretions).

Human dead-end hosts

Due to the few human cases of bornavirus encephalitis, research remains largely descriptive, and BoDV-1 propagation mechanisms and entry routes are unclear.

Grosse and colleagues studied two paediatric cases in southeast Bavaria, and found the highest viral loads in the limbic system, the olfactory tract, and the thalamus.[42] These findings support the olfactory route as a potential entry site, with a centripetal spread pattern suggested by high virus concentrations in the olfactory bulb.[42]

A multicentre MRI study highlighted early inflammatory involvement in the gyrus rectus, which runs along the olfactory bulb.[52] Nevertheless, its involvement appears to be secondary, with origin occurring in the basal ganglia. Due to the strong accentuation of the basal nuclei, a possible haematogenous spread was also discussed on a purely hypothetical basis.[52]

Bayas and colleagues describe the ^{18}fluorodeoxyglucose PET/CT findings of a patient with bornavirus encephalitis.[53] An upregulated metabolism in the basal ganglia, temporomesial lobes, and cerebellum was revealed. Clear hypometabolism was observed in areas of the frontal and parietal lateral cortex.[53] The strong involvement of the cerebellum was notably a new aspect of the presentation of BoVD-1 in humans. Previously, the cerebellum was regarded as a location that is only involved at a later stage of BoDV-1 infection, with the virus being rarely detected at autopsy.[15,52] The earlier involvement of the cerebellum raises questions on the circumstances that led to its specific earlier presentation in this case. An alternative infection route could be a possible explanation, or the early high-dose steroid therapy of the patient,[16] thereby marking a modification of the viral spread pattern.

Despite the assumption of olfactory involvement, no altered sense of smell has been reported in any clinical case, possibly due to the rapid progression of the disease, preventing a full assessment of symptoms and long-term effects.

Although the olfactory tract is considered the primary entry point, alternative routes (eg, the oral cavity and gustatory pathway) should not be ruled out, especially due to the slight differences of the distribution pattern compared with animal dead-end hosts (figure 4).

Immunopathology and propagation mechanism in the brain of BoDV-1 infected reservoir and dead-end hosts

Reservoir hosts

In natural reservoir hosts, all components of the CNS (including neurons, glial cells, and their processes) are infected by BoDV-1,[18] without showing pathological lesions.[7,9]

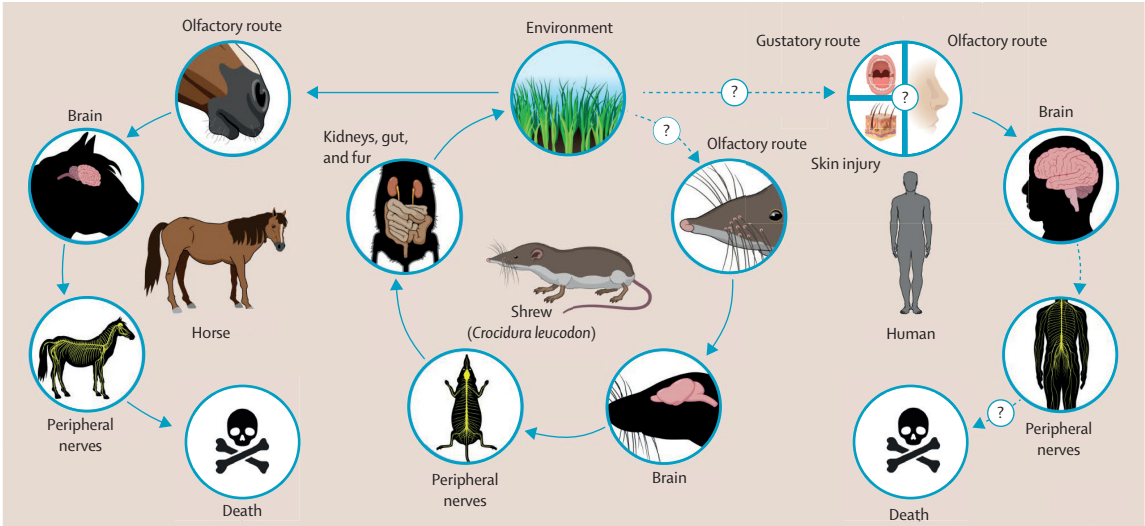

Figure 4: **Possible Borna disease virus 1 infection cycle in reservoir and dead-end hosts**
Borna virus disease 1 transmission from the reservoir host *Crocidura leucodon* with assumed route of spread to the CNS and peripheral nervous system and organs, and environmental transmission to dead-end hosts (eg, horses and humans). Figure created with hegasy.de and BioRender.com.

Future studies should explore the origin of immune tolerance in shrews, as what happens when adult shrews with no previous exposure are infected with BoDV-1 remains unclear. Preliminary data suggest that adult shrews have temporary weight loss but no other clinical signs, with high viral loads in the CNS and no inflammatory response. Additionally, shrews with manifest disease caused by BoDV-1 possibly remain undetected due to their elusive nature. Further research is needed to understand their immune system, which might differ from that in rodents, as shrews belong to the order *Eulipotyphla* (formerly *insectivore*).[7,9]

Animal dead-end hosts

Naturally infected horses develop a non-purulent meningoencephalomyelitis with severe inflammatory lesions, particularly in the hippocampus, cerebral cortex, nucleus caudatus, mesencephalon, and thalamus. The lesions are characterised by mononuclear perivascular and parenchymal infiltrates, mainly $CD4^+$ T cells, with fewer parenchymal $CD8^+$ cells, and later, an increase in plasma cells. The highest viral loads are detected in the hippocampus, with the lowest values being detected in the cerebellum. Joest–Degen intranuclear inclusion bodies are key markers of BoDV-1 infection.[23,54–57]

In a study of alpacas, BoDV-1 infection leads to a chronic, multifocal non-purulent meningoencephalitis with the detection of Joest–Degen intranuclear inclusion bodies.[22] Highest viral titres were detectable in the hippocampus, brainstem, and olfactory bulb. Additionally, the cerebellum, spinal cord, retina, and optic nerve were affected. Lower concentrations were found in peripheral nerves.[22]

A 2024 study by Fürstenau and colleagues[30] compared the pathology and viral distribution of BoDV-1 in alpacas and horses. Differences in inflammatory infiltrates and tissue distribution were noted, which were possibly related to illness duration. Lymphocytes, plasma cells, and macrophages were present in alpacas, with BoDV-1 primarily detected in the CNS and rarely in extraneural organs, being largely confined to nerves. This pattern is consistent with other spillover hosts, indicating that alpacas are most likely dead-end hosts that neither shed nor transmit BoDV-1. Additionally, BoDV-1 was found in non-neuronal glandular cells of the adenohypophyseal intermediate lobe of both alpacas and horses.[30] BoDV-1 detection in the anterior (glandular) but not the posterior (nervous) part of the pituitary gland has also been reported in cattle,[58] which is surprising considering the otherwise strong neurotropism of the virus.

Experimental studies have shown BoDV-1 replication in the nuclei of infected cells,[2,59,60] initially at the site of inoculation, such as at the olfactory nerve or nerve endings in the pharyngeal region.[26] From there, the virus moves intra-axonally and centripetally as a ribonucleoprotein complex to the brain.[26,50,51,61] The delay in disease onset depends on the distance between the inoculation site and the CNS.[26] In experimentally infected rats and voles, BoDV-1 replicates in glial cells and neurons (particularly in the hippocampus), before spreading throughout the CNS and later to the peripheral and autonomic nervous system.[2,62] In experimentally and naturally infected animals, the virus is found in neurons, astrocytes, oligodendrocytes, ependymal cells, and Schwann cells, but not in microglia.[23,25]

Rats are a key animal model for studying BoDV-1 pathogenesis. Experimental infection of adult rats mirrors the disease seen in dead-end hosts with strict

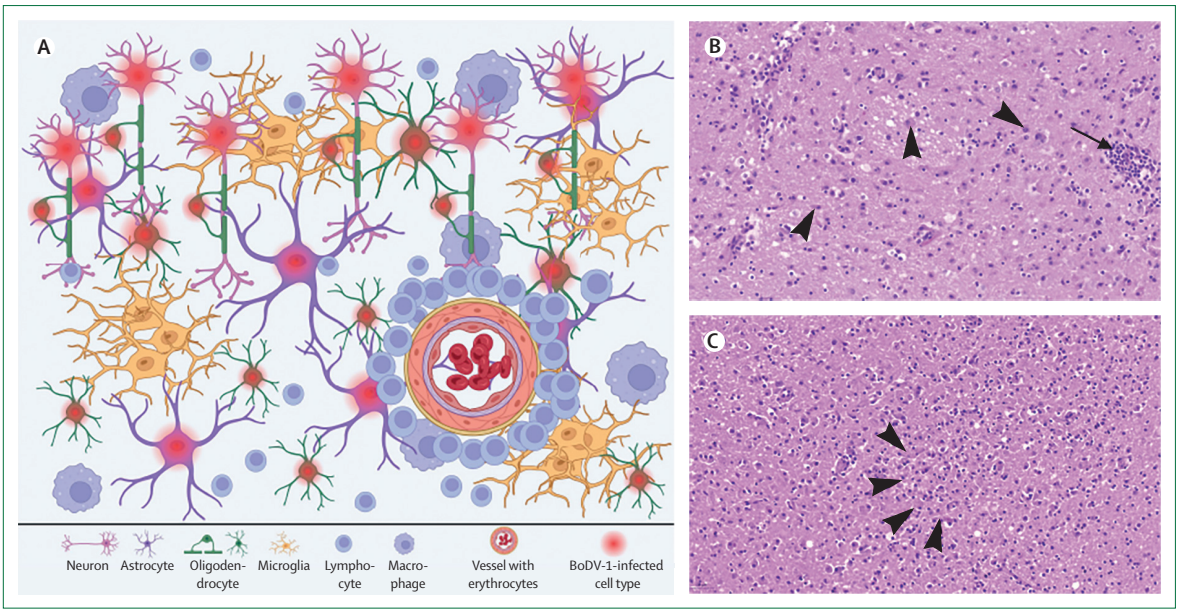

Figure 5: **Neuropathology of human bornavirus encephalitis**
(A) Schematic summary of the neuropathological changes as sclerosing lymphocytic panencephalitis with microglial nodules, including a vessel showing perivascularly accentuated lymphocytic infiltrates. Neurons, astrocytes, and oligodendrocytes are infected by BoDV-1. (B) Brain histology of a deceased patient with bornavirus encephalitis showing perivascularly accentuated lymphocytic infiltrates (black arrow), reactive astrocytes (arrow heads), and (C) microglial nodules (arrow heads). Figure created with BioRender.com. BoDV-1=Borna disease virus 1.

neurotropism and severe meningoencephalitis. By contrast, immunoincompetent neonatal rats show a persistent, symptomless infection similar to reservoir hosts, with viral shedding.[2,63,64] BoDV-1 primarily targets neurons, but astrocytes and other neuroectodermal cells are also involved.[2,63,64] Infected neonatal rats show a loss of Purkinje cells,[65] and clinically show deficits in learning and memory. In neonatal Lewis rats, BoDV-1 spreads to the periphery with viral shedding but they develop BoDV-1 specific serum antibodies instead of inflammatory lesions, which is similar to infected shrews.[2,63] Ovanesov and colleagues[66,67] showed that BoDV-1 infection in a neonatal rat model can disrupt astrocyte–neuron interactions. Using neuron-glia-microglia mixed cultures, they showed that the virus' activation of microglia relies on the presence of astrocytes.[66,67]

Intracerebrally infected adult Lewis rats, however, show the same pathologies as naturally infected horses and sheep, with $CD4^+$ and $CD8^+$ T cell, and macrophage infiltration,[49,68] and long-lasting astrocyte and microglia activation.[2,63,69] Immunosuppressive drugs have been shown to prevent T-cell mediated immunopathology.[2,70]

Experimental studies provide valuable insights into the understanding of BoDV-1 infection. The infection of neonatal rats shares similarities with the disease in reservoir animals, and the infection of adult rats with the disease presentation observed in dead-end hosts.

Human dead-end hosts

Liesche and colleagues provided the first neuropathological findings from an autopsy study of six cases of bornavirus encephalitis, revealing a distribution pattern in humans that differs slightly from animals, with a notable accentuation of the basal ganglia.[15] The neuropathological changes were described as sclerosing lymphocytic panencephalitis with microglial nodules and intranuclear eosinophilic inclusion bodies (figure 5).[15] BoDV-1 RNA was found in neurons, astrocytes, oligodendrocytes and ependymal cells, whereas macrophages, microglial cells, and lymphocytes remained negative for BoDV-1.[15] Liesche-Starnecker and colleagues later reported BoDV-1-positive endothelial cells under particular conditions, which were linked to hypoxic vessel damage.[71]

Building on the autoptic findings of Liesche and colleagues, Finck and colleagues[52] initially defined the macroscopic morphology of bornavirus encephalitis in humans, correlating imaging abnormalities with histopathological findings from 55 MRI scans of 19 patients with bornavirus encephalitis. They observed early hyperintensities in the caudate nucleus and insula, subsequently spreading to the limbic system, and later the brainstem.[52] Despite these findings, current histomorphological investigations suggest that BoDV-1 spreads via anatomical pathways rather than a strict continuous route.[72]

Generally, little is known about immunopathological mechanisms, especially in humans. BoDV-1 is not cytolytic, and tissue destruction seems to be mediated by specific $CD4^+$ and $CD8^+$ T-lymphocytes.[63,73] Astrocytes have also been implicated in the immunopathogenesis.[73] Therapeutic immunosuppression can extend survival.[40,42,73]

Serum and cerebrospinal fluid samples from ten patients with bornavirus encephalitis revealed a proinflammatory cytokine profile, with increases in interferon γ and interleukin-6 and decreased interleukin-13, which reflects ongoing immune cell attraction and contributes to tissue damage. This proinflammatory environment could impair astrocyte function, potentially leading to excitotoxicity in neurons due to glutamate excess.[73]

Future research should track BoDV-1 spread through detailed mapping of BoDV-1-positive anatomical pathways and further characterise the cellular composition in affected regions, with a particular focus on the role of the massively reactive microglia subtypes. This research will enhance pathomechanistic understanding of bornavirus encephalitis and the potential of this disease as a model for other neurotropic virus infections.

Furthermore, the precise localisation of BoDV-1 within cells and the virus' association to cellular structures should be established with confocal microscopy. This experimental setting could be realised in a similar way to the study by Werner-Keiss and colleagues,[74] who investigated viral RNA in the brains of experimentally infected Lewis rats, and Petzold and colleagues,[75] who provided important data on the distribution of variegated squirrel bornavirus-1 in naturally infected variegated and Prevost's squirrels. To confirm the hypothesis that viral dissemination occurs via cell-to-cell contact,[48,76] intercellular connections could be highlighted by immunofluorescence, for instance. Moreover, investigation into viral movement within and between cells should be pursued. Tomonaga and colleagues[77] emphasised the understanding of the molecular biology of BoDV-1, including viral protein function, nuclear infection persistence, and viral gene regulation. Developing infectious molecular clones through reverse genetics will advance knowledge of the neurotropism and role in neurodevelopmental damage of BoVD-1.

Spread of BoDV-1 to the peripheral nervous system (PNS) and viral excretion in reservoir and dead-end hosts

Reservoir hosts

Reservoir hosts exhibit evidence of BoDV-1 in the nervous system and in non-neuronal cells, affecting mesenchymal and epithelial cells in almost every organ, which includes the urinary tract, oral system, salivary gland, respiratory tract, and keratinocytes of the skin.[7,9,15,18,19] The virus is believed to be shed mainly through urine, faeces, saliva,[7,23] and possibly skin (scaling of epidermal cells) of the shrews.[7]

Nevertheless, future investigations should further examine viral distribution in the PNS. In reservoir species, neurovirulence seems to be reduced to promote viral shedding through epithelial tissues into the environment.

Animal dead-end hosts

Naturally BoDV-1 infected animals (eg, sheep and horses) rarely show signs of PNS involvement.[15] In alpacas, however, the virus was found not only in the CNS, but also in large peripheral nerves, the trigeminal ganglion, the retina, the optic nerve, and neuronal structures of the gastrointestinal tract.[22,30] In horses, viral antigens were found in large peripheral nerves and in the eye.[30]

Despite these data, a systematic analysis of PNS infection is needed and should be addressed in future research through comprehensive autopsy sampling. The intra-axonal spread from the olfactory epithelium to the brain (as shown in rat studies)[78] underscores the importance of exploring intranasal transmission in dead-end hosts.

In neonatal rats infected with BoDV-1, viral RNA was detected in all examined peripheral nerves.[23] In neonatally infected immunocompetent rats, infection also led to viral spread to peripheral organs after CNS dissemination. In adult rats, BoDV-1 spread to the PNS and autonomic nervous system during the later stages of disease, with detection in the lungs and gastrointestinal tract.[79] Earlier studies suggested that non-neural tissues such as bone marrow, thymus, and peripheral blood mononuclear cells might be affected, but current knowledge indicates that these show only background signals, rather than actual infection.

In experimentally intracerebrally infected rodents, a centrifugal spread of BoDV-1 via peripheral nerves has been observed. Hallensleben and colleagues noted severe neurological disease in infected newborn mice, with hind limb abnormalities and paraparesis appearing 4–6 weeks after infection, which was caused by a cytotoxic T-cell mediated immunopathological process.[80] Kinnunen and colleagues detected BoDV-1 antigen in the axons of peripheral nerves of the mediastinum, mesentery, the bladder, and skeletal muscles, and also in the smooth muscle cells of the urinary bladder, extraneuronal cells (such as chromaffin cells in the adrenal medulla), myocytes of the heart, and skeletal muscles of bank voles.[62] In BoDV-1-infected rats, viral RNA has been found in peripheral nerves,[23] including those innervating the digestive tract, salivary glands, urinary bladder, and smooth musculature.[51]

In bovines, Sukmak and colleagues reported that BoDV-1 spreads to non-neural tissue via the PNS, with detection in the adrenal gland, spleen, liver, ovary, sciatic ganglion, parasympathetic ganglion, trigeminal ganglion, and sinus node.[58]

Human dead-end hosts

Literature on the viral dissemination of BoDV-1 from the CNS to PNS in humans remains sparse. In the retrospective study of Liesche and colleagues, strong BoDV-1 positivity in the Schwann cells was reported.[15] As there was only sufficient material in the PNS of one patient, systematic analyses of PNS infection was not

possible. In another study by Grosse and colleagues, BoDV-1 RNA was found in tear fluid and saliva, indicating the presence of the virus in human serous secretions.[42] These glands are controlled by cranial nerves (glossopharyngeal nerve and the intermediate part of the facial nerve) that originate from parasympathetic nuclei, where clinically significant viral loads were detected, suggesting a centripetal spread from the brainstem.[42] However, all cranial nerves showed viral loads in this study. Furthermore, additional cases of BoDV-1 should be examined, focusing on people with high viral loads in the olfactory bulb, followed by comparison and analysis with other brain regions and cranial nerves.

Whether BoDV-1 can also be excreted by humans—if infected individuals were to survive longer and receive immunosuppression—should be tested. In previous cases, the disease progressed too quickly, and the virus did not spread far enough into non-neuronal tissues to be excreted in amounts sufficient for transmission.

Systematic investigations into BoDV-1 distribution are absent in the human PNS and in animal dead-end hosts. Given the few cases and the fact that many cases are only retrospectively discovered, comprehensive investigation of new autopsy cases is crucial, focusing on viral distribution in the PNS and peripheral organs. Centralising autopsies in centres with high expertise in human bornavirus encephalitis should be pursued to ensure standardised investigation.

In this context, future studies should focus on analysing the local immune response to BoDV-1 infection in the PNS. Additionally, future research should focus on the development of specialised in-situ detectors, for example. By using various sensors, brain regions can be examined for specific proteins to identify areas that have been most effectively infected or show persistent or ongoing infection. These studies could reveal where viral replication occurs, and which regions are primarily impacted.

The analysis of human tissue presents unique challenges compared with animals due to varied treatments, differing evaluations by multiple centres, and the wide range of disease stages among individuals, making direct comparisons complex. Further limitations are outlined in the panel.

Discussion

BoDV-1 has been recognised in animal infections for over two centuries, yet was only identified as a human pathogen in 2018, with many aspects of the infection mechanisms being poorly understood. This systematic review highlights the paucity of knowledge regarding the cellular transport, entry routes, and propagation mechanisms of BoDV-1, particularly in humans, in whom research is substantially less advanced than for animal studies. Although hypotheses regarding the primary entry route through the olfactory tract have been made, alternative routes (eg, the gustatory pathway) warrant consideration due to anatomical connections that could facilitate viral entry. Pathological findings of bornavirus encephalitis include lymphocytic panencephalitis, pronounced astrogliosis, and microglial nodules, with distribution focusing on the basal ganglia, hippocampus, and brainstem.

The current body of knowledge remains sparse, relying largely on assumptions rather than evidence-based conclusions. To advance the understanding of BoDV-1 pathogenesis, future research should prioritise clarifying viral entry routes, transmission mechanisms, and risk factors. Such insights are essential not only for understanding the nature of BoDV-1 infection (especially for preventive measures and improving clinical outcome), but also for broader application in studying other neurotropic viruses.

***Panel:* Limitations**

Despite the comprehensive nature of this systematic review, several limitations should be considered:

Scarcity of human data
The paucity of studies on Borna disease virus 1 in humans restricts the ability to draw definitive conclusions. More research is needed to confirm animal findings in human hosts.

Heterogeneity of studies
Variations in methodologies, sample sizes, and study focus areas introduce biases and complicate synthesis, thereby potentially affecting overall conclusions.

Temporal scope
The literature search focused on studies from Jan 1, 2000 to April 30, 2024. Although this timeframe captures recent advancements, relevant earlier studies might be excluded.

Database selection
Although three databases and varied search strings were used, relevant studies in other databases or unpublished data from other sources could have been missed.

Speculative nature of findings
Much of the current understanding remains hypothetical, which highlights the need for more rigorous and experimentally validated research.

Contributors
NJ, YV, DT, and FL-S searched the literature and did the analysis. NJ, DT, and FL-S drafted the initial manuscript and created the illustrations with Biorender.com. DT and FL-S provided supervision. YV, TM, PG, JS, TS, BM, CH, and KM edited, reviewed, and approved the manuscript. NJ, YV, TM, PG, JS, TS, BM, CH, KM, DT, and FL-S formulated new hypotheses and future research directions.

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