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CORRESPONDENCE

# Severe bornavirus-encephalitis presenting as Guillain–Barré-syndrome

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The underlying cause of encephalitis and other inflammatory diseases of the human central nervous system remains unclear in a substantial number of cases. Not infrequently, these cases are then assigned an "autoimmune" or "probably infectious" etiology. Two species of bornaviruses are currently unequivocally associated with encephalitis in mammals including humans. Mammalian 2 orthobornavirus (variegated squirrel bornavirus, VSBV) was identified as the cause of encephalitis in breeders of imported squirrels [2]; Mammalian 1 orthobornavirus (BoDV-1 and -2) is the agent of zoonotic borna disease, an encephalitic disease characterized by disturbances of behavior and movements in warm-blooded animals [4] that is most often diagnosed in horses and sheep. Recently, we detected BoDV-1 as the cause of fatal encephalitis in a previously healthy young man [3], and it was found in a cluster of encephalitic disease in organ recipients that received organs of a single donor from southern Bavaria [6]. Due to these new findings, BoDV-1 has now to be considered in the differential diagnosis of human encephalitic CNS diseases.

After metagenomic sequencing led us to discover BoDV-1 in the CNS of a young patient who had died of encephalitis, we set out to test for the presence of this pathogen in other patients. For this purpose, we used real-time PCR to test brain biopsies and autopsy materials from cases with CNS disease of putative infectious origin that had been preserved at – 80 °C for years to decades. We detected high copy numbers of BoDV-1 RNA ($10e^7$ copies BoDV-1 per ~ 2000 cells) in a brain biopsy obtained in 1996 from a 31-year-old female patient, whereas samples from four other patients remained negative.

After about 10 days of non-specific prodromi (back pain; repeated vomiting attributed to antibiotic treatment for suspected kidney infection), the patient developed paraesthesias in hands, numbness in both legs, absent peripheral reflexes, and during the course paresis of both distal lower extremities. She was then admitted to a local hospital for possible Guillain–Barré-syndrome (GBS)/acute polyradiculitis. CSF analysis initially showed 10 leukocytes/µl and 90 mg/dl protein on day 1 with a clear albuminocytologic dissociation (total CSF protein up to 3050 mg/dl in follow-up lumbar punctures). Correspondingly, neurographical analysis revealed prolonged distal motor latency in lower extremities in the context of a demyelinating neuropathy.

Cranial MRI was normal on admission, but EEG showed general nonfocal abnormalities; with phases of frontal 3/s delta waves. She was treated with plasmapheresis (day 1 and 2), intravenous immunoglobulins (day 1 and 11, 25 g qd), intravenous aciclovir 250 mg t.i.d, ciprofloxacin 2 × 200 mg b.i.d, and amantadine-hemisulfate 200 mg/500 ml qd (for 12 days). On day 2, fever > 39 °C developed, intravenous ceftriaxone 2 g qd was given for 5 days and temperature was normalizing; on day 5/6 she was moved to ICU, and on day 14 she was transferred to our University hospital where she arrived in an unresponsive state.

Various diagnostic procedures and laboratory tests were performed but did not reveal an underlying cause. Biopsy of left *N. suralis* and *M. gastrocnemius* showed axonal

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inflammatory neuropathy with immune-mediated lesions of endoneural axon-related structures, but preserved muscular architecture without fibrosis or infiltration (Figure S1). The frontal brain biopsy that led us to the correct diagnosis was performed in week 12. Concordant with the earlier neuropathological diagnosis of disseminated lymphomonocytic meningoencephalitis, our immunohistochemistry showed infiltration of mononuclear CD3+ lymphocytes and CD68+ monocytes, and also the presence of BoDV-1 nucleoprotein (Fig. 1). Although earlier electron microscopy of ultrathin biopsy sections had not revealed viral structures, the high viral copy number and strong presence of viral antigen prompted us to attempt electron microscopy again on a small section of the biopsy. Indeed, we found intranuclear structures corresponding to viral replication centres [5], as well as ~ 80–100 nm virus-like particles, indicating active viral replication at this stage. The complete genomic sequence of the infecting BoDV-1 (Genbank accession MK574679) was obtained from overlapping RT-PCR amplicons. Phylogenetic analysis showed clustering with BoDV-1 isolates from southern Bavaria, and in particular with the strain we had detected in the other patient from our region 20 years later (Fig. S2). After 4 months without improvement, the patient was transferred to a local hospital closer

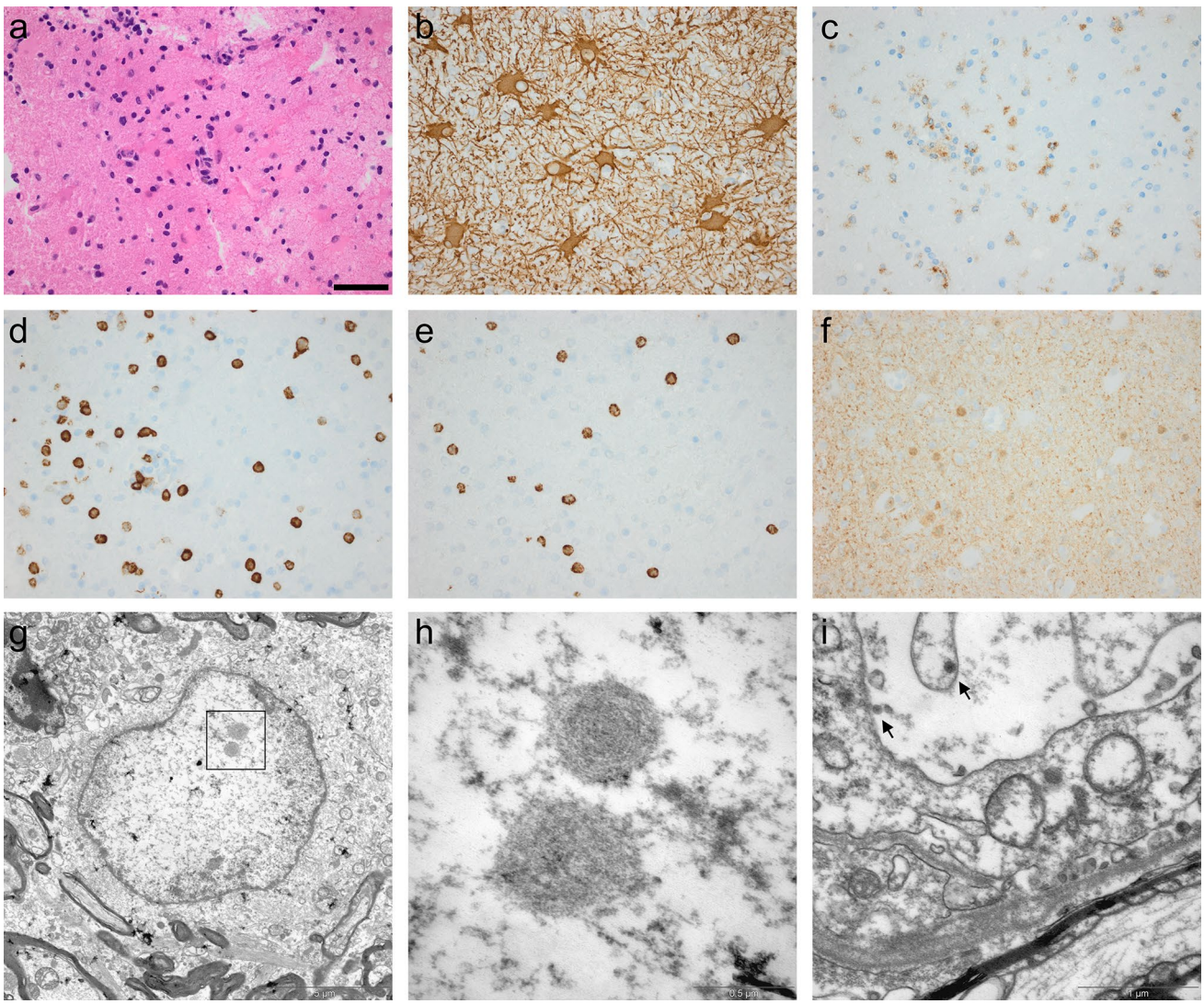


**Fig. 1** Hematoxylin and eosin (HE) staining (**a**) demonstrates a chronic inflammatory process with gliosis and lymphomonocytic cells as indicators of encephalitis. Immunohistochemistry of glial fibrillary acidic protein (GFAP) highlights numerous reactive astrocytes with prominent cell bodies (**b**). Abundant macrophages and microglia/microglia nodules (CD68) (**c**), and T-lymphocytic infiltrates (CD3) (**d**) with a strong component of cytotoxic T cells (CD8) (**e**) are present. Immunohistochemistry using mouse monoclonal Bo18 antibody directed against BoDV-1 nucleoprotein (**f**). Scale bar in **a** 50 µm, also applies for **b**–**f**. Electron microscopy presenting intranuclear viral replication centres (**g**), boxed area enlarged and rotated 180° (**h**). In another area (**i**), two 80–100 nm virus-like particles are marked (black arrows)

to the family, and another 6 weeks later released into the care of the family in a palliative situation with mechanical respiration.

An initial presentation of BoDV-1 infection as GBS has been described in two of three immunosuppressed patients who were infected by solid organ transplantation [6]. The case reported here shows that this can also occur in previously healthy individuals. Interestingly, the patient´s disease progressed despite high-dose amantadine treatment, supporting studies that showed ineffectiveness of amantadine in borna disease (reviewed in [1]). Although BoDV-1 can now be considered as a causative agent in cases of acute encephalitis, and (para-infectious) Guillain Barré polyradiculitis, in many cases of human CNS inflammation the etiology remains obscure, and systematic efforts to increase the rate of correct diagnosis of infections are warranted in these severe and often fatal or disabling diseases.

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## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

## References

1. Herden C, Briese T, Lipkin WI, Richt JA (2013) Bornaviridae. In: Fields BN, Knipe DM, Howley PM (eds) Fields virology, 6th edn. Wolters Kluwer Health/Lippincott Williams & Wilkins, Philadelphia, pp 1124–1148
2. Hoffmann B, Tappe D, Hoper D, Herden C, Boldt A, Mawrin C et al (2015) A variegated squirrel bornavirus associated with fatal human encephalitis. N Engl J Med 373:154–162. https://doi.org/10.1056/NEJMoa1415627
3. Korn K, Coras R, Bobinger T, Herzog SM, Lucking H, Stohr R et al (2018) Fatal encephalitis associated with borna disease virus 1. N Engl J Med 379:1375–1377. https://doi.org/10.1056/NEJMc1800724
4. Ludlow M, Kortekaas J, Herden C, Hoffmann B, Tappe D, Trebst C et al (2016) Neurotropic virus infections as the cause of immediate and delayed neuropathology. Acta Neuropathol 131:159–184. https://doi.org/10.1007/s00401-015-1511-3
5. Matsumoto Y, Hayashi Y, Omori H, Honda T, Daito T, Horie M et al (2012) Bornavirus closely associates and segregates with host chromosomes to ensure persistent intranuclear infection. Cell Host Microbe 11:492–503. https://doi.org/10.1016/j.chom.2012.04.009
6. Schlottau K, Forth L, Angstwurm K, Hoper D, Zecher D, Liesche F et al (2018) Fatal encephalitic borna disease virus 1 in solid-organ transplant recipients. N Engl J Med 379:1377–1379. https://doi.org/10.1056/NEJMc1803115

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