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A potential role for early hyponatremia in the diagnosis of Borna-virus encephalitis?

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Case Report

Keywords: Borna Virus-1, fatal encephalitis, meningoencephalitis, viral, infection, brainstem dysfunction, neurohypophysis, hyponatremia

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Abstract

Background

The first case of fatal Borna Virus-1 encephalitis (BoDV-1) was reported in 2018. Here, we report another fatal case of BoDV-1 encephalitis with early severe hyponatremia, indicative of neurohypophysial dysfunction.

Case presentation:

A 77-year-old female living in southern Germany was admitted to hospital in 2020 due to rapidly progressing word-finding difficulties, personality changes, global disorientation, diffuse cognitive slowness, and gait ataxia, initially without fever. After a rapid deterioration with fever, gait instability and ataxia, rapid cognitive decline, meningism, epileptic seizures, aphasia, and signs of latent right hemiparesis, the suspicion of a (meningo-)encephalitis was set. Furthermore, an unexplained, severe hyponatremia had been present since admission. Laboratory workup in cerebrovascular fluid (CSF) and serum as well as brain imaging was negative. Despite extensive empirical antiviral, antimicrobial, and immunosuppressive treatment efforts, the patient fell into coma (day 5), lost all brainstem functions (day 18), and remained fully dependent on invasive mechanical ventilation. Finally, she clinically developed a status of brain death and died 42 days after initial admission. Brain autopsy confirmed an extensive, diffuse, and severe affection of neocortical, subcortical and cerebellar structures as well as the neurohypophysis due to infection with BoDV-1. In light of the autopsy results, the hyponatremia could imply an early basal brain involvement, which could narrow down the initial differential diagnosis.

Conclusion

The diagnosis of BoDV-1 encephalitis remains clinically challenging. The disease progresses quickly to irreversible brain damage. An early, unexplained, hyponatremia in the presence of severe and rapidly evolving encephalitis may narrow down the diagnosis.

Introduction

Since the first reports of fatal Borna Virus-1 (BoDV-1) encephalitis in 2018 [1, 2], the number of such cases is gradually increasing to a few per year. Clinical suspicion and diagnosis remain challenging because the disease symptoms are usually diffuse, while the disease rapidly progresses to irreversible and (usually) fatal brain damage. In such cases, a negative extended diagnostic panel of common viral, autoimmune, or paraneoplastic etiologies [3–6] usually leads to the diagnosis of an "encephalitis of unknown etiology" [6]. However, as the mortality of BoDV-1 encephalitis reaches 95–100%, any clinical sign or laboratory test that facilitates its early diagnosis is desirable to support early treatment efforts.

Here, we report a fatal case of BoDV-1 encephalitis with rapidly progressive and severe basal brain and brainstem failure. The clinical picture was accompanied by an, early, unexplained, treatment-resistant, hyponatremia. Based on the autopsy results and a critical review of all reported cases, we suggest a potential diagnostic algorithm to promote a prompt diagnosis of BoDV-1.

Case Presentation

A 77-year-old female living in southern Germany developed in May 2020 nausea, vomiting, and flu-like symptoms for 3 days. Within the following 2 days she developed neurological symptoms, with onset of word-finding difficulties, gait ataxia, global disorientation, personality changes, and diffuse cognitive slowness. She was admitted to the hospital 5 days after her first symptoms. Her previous neurological status had been normal for her age.

On admission, the neurological examination (day 0) displayed a disoriented patient with cognitive slowness, unspecific personality changes, mild word-finding deficits, and diffuse cerebellar symptoms (mild gait-ataxia and dysmetria, saccadic eye pursuit). Peripheral systems were intact. The acute brain CT-scan (with CT-angiography) was normal. Chest CT scan was also unremarkable. On day 2 after admission, an MRI-scan of the brain showed preexisting microangiopathic alterations, without signs of encephalitis or an acute vascular event. Blood chemistry at this stage revealed mild leukocytosis (up to 11300/µl) along with severe and unexplained hyponatremia (121mmol/l). The electroencephalogram (EEG) on day 2 showed a theta-slowing without any sign of epileptic activity or triphasic waves. The lumbar puncture found a clear cerebrospinal fluid (CSF) with relatively mild pleocytosis (8 cells/µl), elevated protein (62mg/dl), mildly elevated lactate (3.0mmol/l), and signs of mild blood-brain-barrier (BBB) -leakage without signs of intrathecal IgG production, cumulatively indicative of a non-bacterial inflammatory process. A viral encephalitis was suspected and a corresponding CSF-diagnostic panel was ordered [6].

A therapy with aciclovir, levetiracetam, and methylprednisolone was empirically initiated until availability of the CSF results, yet without any treatment success. Hyponatremia was appropriately substituted, but did not return to normal levels. On day 3, the patient further deteriorated with development of fever, aggravated gait-ataxia, deterioration of cognitive functions (somnolence), meningism, epileptic seizures, global aphasia, and signs of latent right hemiparesis. She now fulfilled the criteria for confirmed encephalitis[6]. Due to further development of tachypnea, hypoxia, and lactate, she was admitted to the intensive care unit (ICU).

At that stage, the clinical and laboratory data supported a rapidly progressive (meningo-) encephalitis of yet unknown etiology, that manifested as a diffuse cortical process with additional diencephalic, brainstem, and cerebellar insult (severe hyponatremia, saccadic movement disorder, ataxia).

On day 5, the patient became comatose and was intubated for ventilator support. All repeatedly performed chest- and brain-CT scans remained unremarkable. The brain MRI scan on day 12 (Fig. 1-b1) revealed an atypical insular signal enhancement on the FLAIR sequence and discrete punctuate contrast-agent enhancement in the frontal and temporal lobes without corresponding correlates in FLAIR sequences. Remarkably, the patient remained comatose despite complete cessation of any analgosedation, showing rapidly progressive loss of cranial nerve and brainstem functions by day 14. Her hyponatremia also persisted.

On day 18, while being still comatose and dependent on invasive mechanical ventilation, the patient had a complete absence of brainstem reflexes (pupillary, corneal, ciliar, and pharyngeal/laryngeal brainstem reflexes). The EEG continued to deteriorate, showing a generalized theta-delta rhythm with spontaneous Burst-Suppression on day 21 (Fig. 1). Due to irresponsiveness to prior treatments, a quadruple anti-tuberculosis antibiotic regime was also empirically initiated but also proved ineffective.

An extensive diagnostic panel was repeated [6–8]. Any potential viral or bacterial causes were excluded by laboratory testing (PCR or IgM/IgG serology in serum and/or CSF). Paraneoplastic markers and anti-neuronal antibodies were also negative. Autoimmune etiologies, vasculitis, acute demyelinating pathology, degenerative

processes (e.g. sporadic Creutzfeldt-Jacob disease), or an epileptic cause of the symptoms (e.g. a possible non-convulsive status epilepticus or epileptic discharges with postictal phenotype) were also excluded. SARS-CoV2 PCR was repeatedly negative. Rare causes of severe encephalitis (Japanese encephalitis, Dengue encephalitis, or West-Nile encephalitis) were clinically, radiologically, or epidemiologically also excluded [9].

Repeated CSF diagnostics on days 20 and 33 showed further increase in total protein levels (113 and 142mg/dl), IgG intrathecal production (99 and 315mg/dl), and lactate (5.3 and 6.1 mmol/L), as well as increasing lymphocytosis (40 and 110 leucocytes/ul), indicative of an unknown encephalitis unresponsive to previous treatment efforts. Increased CXCL13 indicated an unspecific intrathecal B cell-related immune activation.

On day 27 we additionally verified the loss of brainstem respiratory center function in our patient. Subsequently, the patient remained dependent on controlled invasive mechanical ventilation thereafter. The MRI brain scan performed on day 28 (Fig. 1-b2) did not correlate with the severity of her clinical status, showing only minimal increases in FLAIR-intensities compared to previous scans, some new punctual or diffuse gadolinium enhancement, and a diffuse increase of T2* signal in basal ganglia probably attributed to normal aging. Eventually, the EEG on day 41 showed a complete absence of electroencephalographic activity, indicating hemispheric death. A further continuation of critical care treatment deemed to be futile, and after discussions with her family, the patient died 42 days after admission.

The family provided informed consent for a diagnostic autopsy. Here, a BoDV-1 infection was revealed both by immunohistopathology and real-time PCR as the cause of the fatal encephalitis. Sequence analysis of the virus genome identified it within cluster 1A, phylogenetic similar to those isolated from the southeast area of Bavaria in other cases. The BoDV-1 antigens and related pathology were diffuse and severe in neocortical, subcortical, cerebellar and neurohypophysial areas (Fig. 2). Retrospectively, these lesions explained the presenting symptoms of the patient, namely cortical and subcortical deficits (aphasic disturbances, hemiparesis, confusion), cerebellar ataxia and the unexplained severe hyponatremia, the latter possibly attributed to the affected neurohypophysis and hypothalamus [10].

In light of the diagnosis, the patient´s family recalled a possible wild-animal attack on the patient´s domestic chickens a few days before the onset of symptoms, as a potential origin of infection with BoDV-1.

Discussion

We report a fatal case of BoDv-1 encephalitis in a 77year-old habitant of southern Germany, presented as rapidly progressive diencephalic and brainstem failure, leading to brain death. After reviewing all reported cases so far, we propose a potential diagnostic algorithm where hyponatremia early in the disease may narrow-down the differential diagnosis.

BoDV-1 infection is a potentially lethal zoonosis in endemic regions with reported spillover infections in horses, alpacas, and sheep [11, 12]. The only definite currently known natural host of BoDV-1 is the bicolored white-toothed shrew (*Crocidura leucodon*), which does not develop any symptoms but excretes the virus via urine and faeces [13]. Despite previous discrepancies regarding its transmission or disease severity in humans, it is now certain – since the first documented cases in 2018 [1, 2] - that BoDV-1 can cause fatal encephalitis in both immune-compromised and healthy humans. The main hypothesis is that infections occur via uptake of contaminated virus-containing particles via the olfactory route [11]. Studies indicate that the virus replicates first in neurons and then in astrocytes, but not microglia [14]. The virus induces an increasing pro-inflammatory immune activation during

BoDV-1 encephalitis[14], either as part of the host´s normal immune reaction or as a dysbalanced pro-inflammatory state, with lymphocytic-mediated (preferably CD8+) degeneration of the brain[15]. Previous single reports on a theoretical BoDV-1 involvement for psychiatric symptoms in non-symptomatic carriers [16, 17] should be interpreted very cautiously, as they were not independently validated, failed in interlaboratory comparisons or could be the result of result of a laboratory contamination [13, 18].

A diagnosis of BoDV-1 encephalitis can now be defined based on recently proposed criteria [19]. Along with that, we propose a diagnostic algorithm that may increase the suspicion of the disease (Figure 3). About 40 BoDV-1 cases have been reported so far (Table 1). A cohort of MRI cases includes 19 patients, 9 out of which were reported elsewhere [9]. Two cohorts with autopsy-data report six [20] and eight [21] cases, one of which was included in a previous report [19]. Our case is new reported one ("case 41", see table below) not included in any previous cohort. Surprisingly, MRI brain scans of our patient did not show the severity of brain pathology, even at later time-points ("MRI-clinical dissociation"). This is uncommon as BoDV1 cases usually -but not always- show extensive MRI-lesions in brain [9, 22]. EEG reflected the clinical severity, with spontaneous burst-suppression and eventual suppressed (practically isoelectric) brain activity, equal to brain death. In light of the final autopsy result, the disease course fitted to a diffuse rapidly progressive cortical and subcortical involvement focused on the diencephalon (thalamus, hypothalamus, and neurohypophysis) and brainstem.

Our patient's symptoms started as a common viral infection, evolved rapidly into a severe encephalitic syndrome of unknown etiology, and progressed to diffuse diencephalic and brainstem failure with eventual brain death. Such an “encephalitis of unknown etiology” may account for as much as 37% of all encephalitis-cases admitted to a hospital, 9% of which are fatal [5]. The presence of unexplained hyponatremia early in the course of such cases may narrow down the differential diagnostic panel because hyponatremia is associated with few causes of encephalitis: the limbic anti-LG1 encephalitis [23], human herpesvirus 6 (HHV-6) [24], herpes simplex virus type 1 (HSV-1) [25], tick-borne encephalitis (TBE) [26], as well tuberculous meningitis [27]. These entities induce a posterior pituitary/hypothalamic lesion explaining the occurrence of hyponatremia. We here suggest that BoDV-1 should be also included in the list of viral encephalitis potentially causing hyponatremia (Figure 3). Niller et al. reported the presence of hyponatremia or diabetes insipidus in 4 out of 8 patients in their BoDV-1 cohort [21]. Eventually, as proposed by our diagnostic algorithm in Figure 3, the presence of hyponatremia in severe basal brain encephalitis should alert clinicians to include BoDV-1 serum- and CSF- tests early in the diagnostic workup, using newly available serological panels [28].

Unfortunately, no effective treatment regiment is available so far. Treatment approaches remain experimental, based on various hypotheses. A report of "anti-viral" efficacy of amantadine in psychiatric patients with subclinical BoDV-1 infection [29] should be critically questioned for reasons discussed above [13, 18]. Single (*in vitro* or *in vivo*) experimental studies testing antiviral compounds (ribavirin [30, 31] or favipiravir (T-705) [32]), cocktails of small interfering RNAs (siRNAs) [33] or combinations of those, have not clinically proven effective at the moment. Indeed, favipiravir or ribavirin administration in individual BoDV-1 cases was ineffective [2, 22, 34], maybe due to a delayed administration. Alternatively, as BoDV-1 induces a severe pro-inflammatory state [20], a combination of antiviral and anti-inflammatory could theoretically be beneficial. This hypothesis was, though, not supported by our treatment efforts (combination of acyclovir and methylprednisolone).

Conclusion

We report a new case of fatal BoDV-1 encephalitis, with early, severe, otherwise unexplained, hyponatremia and development of a rapidly progressing diencephalic and brainstem dysfunction. Our case highlights the early electrolytic disturbances as a key feature for prompt suspicion and diagnosis. **We propose the following learning points**:

- - A (rapidly) progressive severe encephalitis with a) otherwise unexplained hyponatremia and b) signs of fast basal/brainstem failure, should set the suspicion of BoDV-1, especially in endemic regions of central Europe. Serum and CSF BoDV-1 diagnostic panels recently became available.
- - Limbic anti-LG1 encephalitis, HHV-6, HSV-1, and TBE, as well as streptococcus pneumonia and tuberculous meningitis should be included in the differential diagnosis of such cases.
- - Contact with wild animals (shrews, mice, squirrels, chicken, fox, alpacas, horses, sheep, or others) in the history can support the suspicion but is not a prerequisite.
- - Currently, there is no effective therapy regimen for human BoDV-1 encephalitis available. Ribavirin and favipiravir have been applied as experimental therapy approaches, though yet without success; this may be due to delayed administration or unclear dosing and treatment duration.
- - Studies indicate that the BoDV-1-induced, lymphocytic-mediated, brain degeneration may contribute significantly to tissue destruction and fatal outcomes in animals and in humans.

Abbreviations

BoDV-1
Borna Virus-1
CSF
cerebrospinal fluid
BiPAP
Bilevel Positive Air Pressure
CT
computer tomography
MRI
magnetic resonance imaging
BBB
blood-brain barrier

Declarations

Ethics approval and consent to participate: Not applicable

Consent for publication: Written informed consent for publication of their clinical details and clinical images was obtained from the relatives of the patient. A copy of the consent form is available for review by the Editor of this journal

Availability of data and materials: The datasets generated during and analyzed during the current study are not publicly available due to patient confidentiality, but are available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests

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Authors' contributions: AL and LS treated, collected, analyzed, interpreted the patient data and/or wrote the manuscript; RG and SS treated the patient and critically reviewed the manuscript; VR and JC performed the brain autopsy and histological examination; KJ and VH critically supervised the manuscript. All authors read and approved the final manuscript.

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References

1. Korn K, Coras R, Bobinger T, Herzog SM, Lucking H, Stohr R, et al. Fatal Encephalitis Associated with Borna Disease Virus 1. N Engl J Med. 2018;379 14:1375-7; doi: 10.1056/NEJMc1800724.
2. Schlottau K, Forth L, Angstwurm K, Hoper D, Zecher D, Liesche F, et al. Fatal Encephalitic Borna Disease Virus 1 in Solid-Organ Transplant Recipients. N Engl J Med. 2018;379 14:1377-9; doi: 10.1056/NEJMc1803115.
3. Venkatesan A. Epidemiology and outcomes of acute encephalitis. Curr Opin Neurol. 2015;28 3:277-82; doi: 10.1097/WCO.0000000000000199.
4. Schmidt A, Buhler R, Muhlemann K, Hess CW, Tauber MG. Long-term outcome of acute encephalitis of unknown aetiology in adults. Clin Microbiol Infect. 2011;17 4:621-6; doi: 10.1111/j.1469-0691.2010.03276.x.
5. Granerod J, Ambrose HE, Davies NW, Clewley JP, Walsh AL, Morgan D, et al. Causes of encephalitis and differences in their clinical presentations in England: a multicentre, population-based prospective study. Lancet Infect Dis. 2010;10 12:835-44; doi: 10.1016/S1473-3099(10)70222-X.
6. Venkatesan A, Tunkel AR, Bloch KC, Lauring AS, Sejvar J, Bitnun A, et al. Case definitions, diagnostic algorithms, and priorities in encephalitis: consensus statement of the international encephalitis consortium. Clin Infect Dis. 2013;57 8:1114-28; doi: 10.1093/cid/cit458.
7. Bhimraj A, Hasbun R. Diagnostic approach and update on encephalitis. Curr Opin Infect Dis. 2022;35 3:231-7; doi: 10.1097/QCO.0000000000000832.
8. Richie MB, Josephson SA. A Practical Approach to Meningitis and Encephalitis. Semin Neurol. 2015;35 6:611-20; doi: 10.1055/s-0035-1564686.
9. Finck T, Liesche-Starnecker F, Probst M, Bette S, Ruf V, Wendl C, et al. Bornavirus Encephalitis Shows a Characteristic Magnetic Resonance Phenotype in Humans. Ann Neurol. 2020;88 4:723-35; doi: 10.1002/ana.25873.
10. Santos Fontanez SE, De Jesus O. Neurohypophysis. In: StatPearls. Treasure Island (FL); 2022.
11. Kupke A, Becker S, Wewetzer K, Ahlemeyer B, Eickmann M, Herden C. Intranasal Borna Disease Virus (BoDV-1) Infection: Insights into Initial Steps and Potential Contagiosity. Int J Mol Sci. 2019;20 6; doi: 10.3390/ijms20061318.
12. Schulze V, Grosse R, Furstenau J, Forth LF, Ebinger A, Richter MT, et al. Borna disease outbreak with high mortality in an alpaca herd in a previously unreported endemic area in Germany. Transbound Emerg Dis. 2020; doi: 10.1111/tbed.13556.
13. Hornig M, Briese T, Lipkin WI. Borna disease virus. J Neurovirol. 2003;9 2:259-73; doi: 10.1080/13550280390194064.

14. Rauch J, Steffen JF, Muntau B, Gisbrecht J, Portner K, Herden C, et al. Human Borna disease virus 1 encephalitis shows marked pro-inflammatory biomarker and tissue immunoactivation during the course of disease. Emerg Microbes Infect. 2022;11 1:1843-56; doi: 10.1080/22221751.2022.2098831.
15. Bilzer T, Stitz L. Brain cell lesions in Borna disease are mediated by T cells. Arch Virol Suppl. 1993;7:153-8; doi: 10.1007/978-3-7091-9300-6_12.
16. Zhang L, Xu MM, Zeng L, Liu S, Liu X, Wang X, et al. Evidence for Borna disease virus infection in neuropsychiatric patients in three western China provinces. Eur J Clin Microbiol Infect Dis. 2014;33 4:621-7; doi: 10.1007/s10096-013-1996-4.
17. Sauder C, Muller A, Cubitt B, Mayer J, Steinmetz J, Trabert W, et al. Detection of Borna disease virus (BDV) antibodies and BDV RNA in psychiatric patients: evidence for high sequence conservation of human blood-derived BDV RNA. J Virol. 1996;70 11:7713-24; doi: 10.1128/JVI.70.11.7713-7724.1996.
18. Lipkin WI, Briese T, Hornig M. Borna disease virus - fact and fantasy. Virus Res. 2011;162 1-2:162-72; doi: 10.1016/j.virusres.2011.09.036.
19. Eisermann P, Rubbenstroth D, Cadar D, Thome-Bolduan C, Eggert P, Schlaphof A, et al. Active Case Finding of Current Bornavirus Infections in Human Encephalitis Cases of Unknown Etiology, Germany, 2018-2020. Emerg Infect Dis. 2021;27 5:1371-9; doi: 10.3201/eid2705.204490.
20. Liesche F, Ruf V, Zoubaa S, Kaletka G, Rosati M, Rubbenstroth D, et al. The neuropathology of fatal encephalomyelitis in human Borna virus infection. Acta Neuropathol. 2019;138 4:653-65; doi: 10.1007/s00401-019-02047-3.
21. Niller HH, Angstwurm K, Rubbenstroth D, Schlottau K, Ebinger A, Giese S, et al. Zoonotic spillover infections with Borna disease virus 1 leading to fatal human encephalitis, 1999-2019: an epidemiological investigation. Lancet Infect Dis. 2020;20 4:467-77; doi: 10.1016/S1473-3099(19)30546-8.
22. Liesche-Starnecker F, Schifferer M, Schlegel J, Vollmuth Y, Rubbenstroth D, Delbridge C, et al. Hemorrhagic lesion with detection of infected endothelial cells in human bornavirus encephalitis. Acta Neuropathol. 2022;144 2:377-9; doi: 10.1007/s00401-022-02442-3.
23. Huang X, Fan C, Gao L, Li L, Ye J, Shen H. Clinical Features, Immunotherapy, and Outcomes of Anti-Leucine-Rich Glioma-Inactivated-1 Encephalitis. J Neuropsychiatry Clin Neurosci. 2022;34 2:141-8; doi: 10.1176/appi.neuropsych.20120303.
24. Victoria NC, Phan TL, Agarwal KA. A Systematic Review of Sodium Disorders in HHV-6 Encephalitis. Biol Blood Marrow Transplant. 2020;26 5:1034-9; doi: 10.1016/j.bbmt.2020.01.023.
25. Basaran S, Yavuz SS, Bali EA, Cagatay A, Oncul O, Ozsut H, et al. Hyponatremia Is Predictive of HSV-1 Encephalitis among Patients with Viral Encephalitis. Tohoku J Exp Med. 2019;247 3:189-95; doi: 10.1620/tjem.247.189.
26. Czupryna P, Moniuszko A, Garkowski A, Pancewicz S, Zajkowska J. Comparison of hyponatremia and SIADH frequency in patients with tick borne encephalitis and meningitis of other origin. Scand J Clin Lab Invest. 2016;76 2:159-64; doi: 10.3109/00365513.2015.1129669.
27. Lim AKH, Paramaswaran S, Jellie LJ, Junckerstorff RK. A Cross-Sectional Study of Hyponatremia Associated with Acute Central Nervous System Infections. J Clin Med. 2019;8 11; doi: 10.3390/jcm8111801.
28. Neumann B, Angstwurm K, Linker RA, Knoll G, Eidenschink L, Rubbenstroth D, et al. Antibodies against viral nucleo-, phospho-, and X protein contribute to serological diagnosis of fatal Borna disease virus 1 infections. Cell Rep Med. 2022;3 1:100499; doi: 10.1016/j.xcrm.2021.100499.

29. Dietrich DE, Bode L, Spannhuth CW, Hecker H, Ludwig H, Emrich HM. Antiviral treatment perspective against Borna disease virus 1 infection in major depression: a double-blind placebo-controlled randomized clinical trial. BMC Pharmacol Toxicol. 2020;21 1:12; doi: 10.1186/s40360-020-0391-x.
30. Lee BJ, Matsunaga H, Ikuta K, Tomonaga K. Ribavirin inhibits Borna disease virus proliferation and fatal neurological diseases in neonatally infected gerbils. Antiviral Res. 2008;80 3:380-4; doi: 10.1016/j.antiviral.2008.08.001.
31. Jordan I, Briese T, Averett DR, Lipkin WI. Inhibition of Borna disease virus replication by ribavirin. J Virol. 1999;73 9:7903-6; doi: 10.1128/JVI.73.9.7903-7906.1999.
32. Tokunaga T, Yamamoto Y, Sakai M, Tomonaga K, Honda T. Antiviral activity of favipiravir (T-705) against mammalian and avian bornaviruses. Antiviral Res. 2017;143:237-45; doi: 10.1016/j.antiviral.2017.04.018.
33. Teng D, Obika S, Ueda K, Honda T. A Small Interfering RNA Cocktail Targeting the Nucleoprotein and Large Protein Genes Suppresses Borna Disease Virus Infection. Front Microbiol. 2019;10:2781; doi: 10.3389/fmicb.2019.02781.
34. Meier H, Bauer C, Finkenzeller W, Nentwich J, Stadt M, Steininger P, et al. [Bornavirus encephalitis as a differential diagnosis to seronegative autoimmune encephalitis]. Nervenarzt. 2022; doi: 10.1007/s00115-021-01259-x.
35. Frank C, Wickel J, Bramer D, Matschke J, Ibe R, Gazivoda C, et al. Human Borna disease virus 1 (BoDV-1) encephalitis cases in the north and east of Germany. Emerg Microbes Infect. 2022;11 1:6-13; doi: 10.1080/22221751.2021.2007737.
36. Bourgade K, Thouard A, Abravanel F, Hebral AL, Del Bello A, Viguier A, et al. Fatal encephalitis and Borna Disease Virus-1 seropositivity in two kidney-transplant patients living in the same nonendemic area. Transpl Infect Dis. 2021;23 6:e13734; doi: 10.1111/tid.13734.
37. Tappe D, Portner K, Frank C, Wilking H, Ebinger A, Herden C, et al. Investigation of fatal human Borna disease virus 1 encephalitis outside the previously known area for human cases, Brandenburg, Germany - a case report. BMC Infect Dis. 2021;21 1:787; doi: 10.1186/s12879-021-06439-3.
38. Coras R, Korn K, Kuerten S, Huttner HB, Ensser A. Severe bornavirus-encephalitis presenting as Guillain-Barre-syndrome. Acta Neuropathol. 2019;137 6:1017-9; doi: 10.1007/s00401-019-02005-z.

Table 1

Table 1. Reported cases of Borna Virus encephalitis, along with the presence of brainstem and/or hyponatremia since its initial report in 2018 [35] and up to December 2022 (w: weeks, d: days, m: months)

No of cases	Fatality (time)	year	Symptoms, signs, MRI	Hyponatremia	Main localization	Ref.
1	1 (7w)	2022	flu-like symptoms, progressive confusion and speech disorders, coma. MRI: increased FLAIR signal bilateral in basal nuclei, the insular and hippocampal region; subinsular hemorrhage	Not reported	basal nuclei, the insular and hippocampal region	[22]
2	2 (10w, 16d)	2022	Fever, flu-like symptoms, headaches, dysphagia, vigilance decline, epileptic seizures, temperature regulation disorders, dyspnea, loss of brainstem reflexes, coma. MRI: increased FLAIR signal bilateral in cortex, basal ganglia and hippocampus.	Not reported	Frontotemporal, basal ganglia, thalamus, insula, limbic system	[34]
1	1 (30d)	2022	Confusion, dizziness, vomiting, memory impairment, BBB disruption, respiratory deterioration, coma, and brainstem involvement. MRI: no pathology	Not reported	Frontal cortex, optic, and peripheral nerves	[28]
3	2 (5w; unknown)	2022	Fever, dysphasia, ataxia and progressive vigilance decline, epileptic seizures, loss of brainstem reflexes, and coma (terminal). MRI: Widespread increased FLAIR signal, thalami, basal ganglia	Not reported	Cortexes, brainstem, whole brain	[35]
2	2 (5m.; 3m)	2021	Cognitive deterioration, apathy, brainstem involvement, respiratory deterioration, coma. MRI: no data reported	Not reported	Diffuse, brainstem, radiculitis	[36]
1	1 (4w)	2021	nausea, psychomotor slowing, apathy, temporary sensory aphasia, ataxia and dyspnea, paraplegia, and coma. MRI: normal at all timepoints	Not reported	All brain areas, from the cortex to brainstem	[37]

3	3 (3-4w, also reported in [21] and [20])	2018-2022	Fever, headache, encephalitis, coma/epileptic seizures/confusion. MRI: no data reported in the manuscript	Not reported	In 2/3 no autopsies	[19]
19	9 out of 19 cases were previously included in other case studies.	<2020	(MRI study) On day 1: 53% MRIs with lesions. On end-scan lesions typical in the caudate nucleus, striatum, insula, limbic system, and brainstem -> spreading to frontal/ temporal parenchyma and brainstem	Not reported	Multiple brain areas	[9]
8	8 (1 co-reported in [19]) (death within 16-57d after admission)	1999-2019	Headache, fever, confusion, ataxia, progressive confusion, epileptic seizures, focal deficits, coma, brainstem deficits/death. MRI: initially normal (up to day 9) -> then, lesions "typical" for BoDV-1 in 7/8 patients	Hyponatremia in 4/8	Multiple brain areas (panencephalitis)	[21]
6	6 (autopsies, 1 co-reported in [19]) (death within 2-14w)	2019	Flu-like symptoms, headache/fever, GBS (1 case), hemiparesis (1 case) -> focal deficits, epileptic seizure, confusion -> coma, brainstem deficits MRI: diffuse indicative of encephalitis	Not reported	Cortical and subcortical hemispheric areas, brainstem, cerebellum	[20]
3	2 (transplant donors: 96 and 99d post-onset)	2018	GBS-like, encephalitis (2/3) Facial palsy, anomia, cognitive deficits, optic neuritis (1/3). MRI: atrophy, diffuse FLAIR signal intensities (encephalitis)	Not reported	Cerebellum, cerebral cortex	[2]
1	1 (1m)	2018	Fever, headache, confusion, myoclonus, gait instability, continuous fever, brainstem deterioration. MRI: meningitis, brain edema on day 20.	Not reported	Joest–Degen inclusion bodies, diffuse	[1]
1	1 (5m)	2019	GBS polyradiculitis	Not reported	Brain biopsy	[38]

with cytoalbuminic dissociation, EEG pathologic. Fever, coma within 14ds.

MRI: normal on admission

Figures

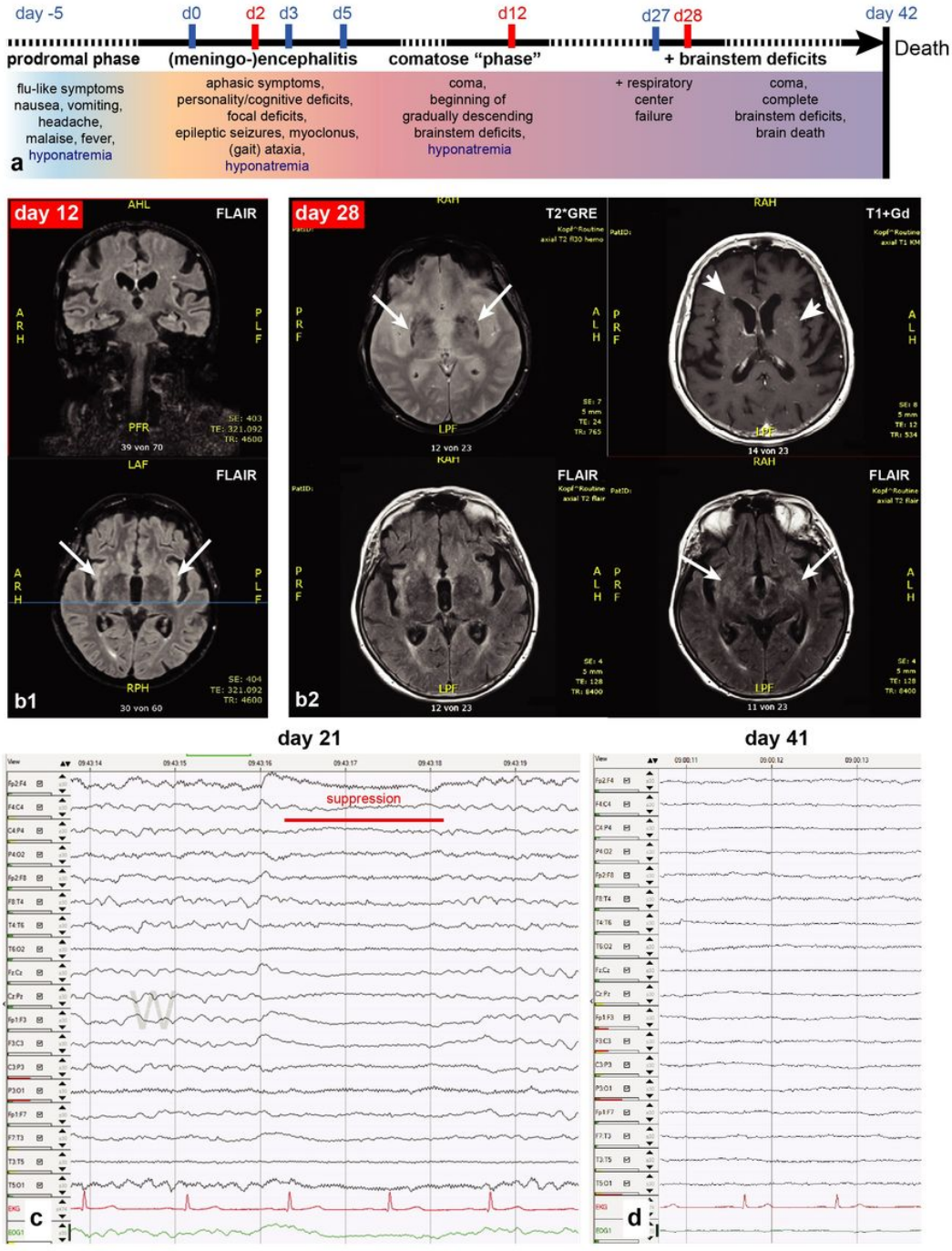

Figure 1

(a) Clinical course of the patient, shown as a black axis line (blue marks fonts indicate critical timepoints, see text; red marks and fonts indicate MRIs); a "typical" BoDV-1 disease course is shown as a color-gradient below the black axis-line, based on the reported cases (see Table). (b1) The brain MRI on day 12 was mainly unremarkable, except for mild FLAIR signal enhancement in both insular cortexes (arrows). (b2) The MRI scan on day 28 showed age-related hemorrhagic alterations in basal ganglia (T2*GRE: arrows), diffuse and punctual Gadolinium enhancement (T1+Gd: BBB-leakage, arrowheads), and mild extension of FLAIR pathological signal (FLAIR: arrows). (c) EEG on day 21 shows spontaneous electrical suppression (red line) between theta-delta diffuse slowing, while the patient was clinically comatose. (d) On day 41 there is a complete suppression of the EEG-activity.

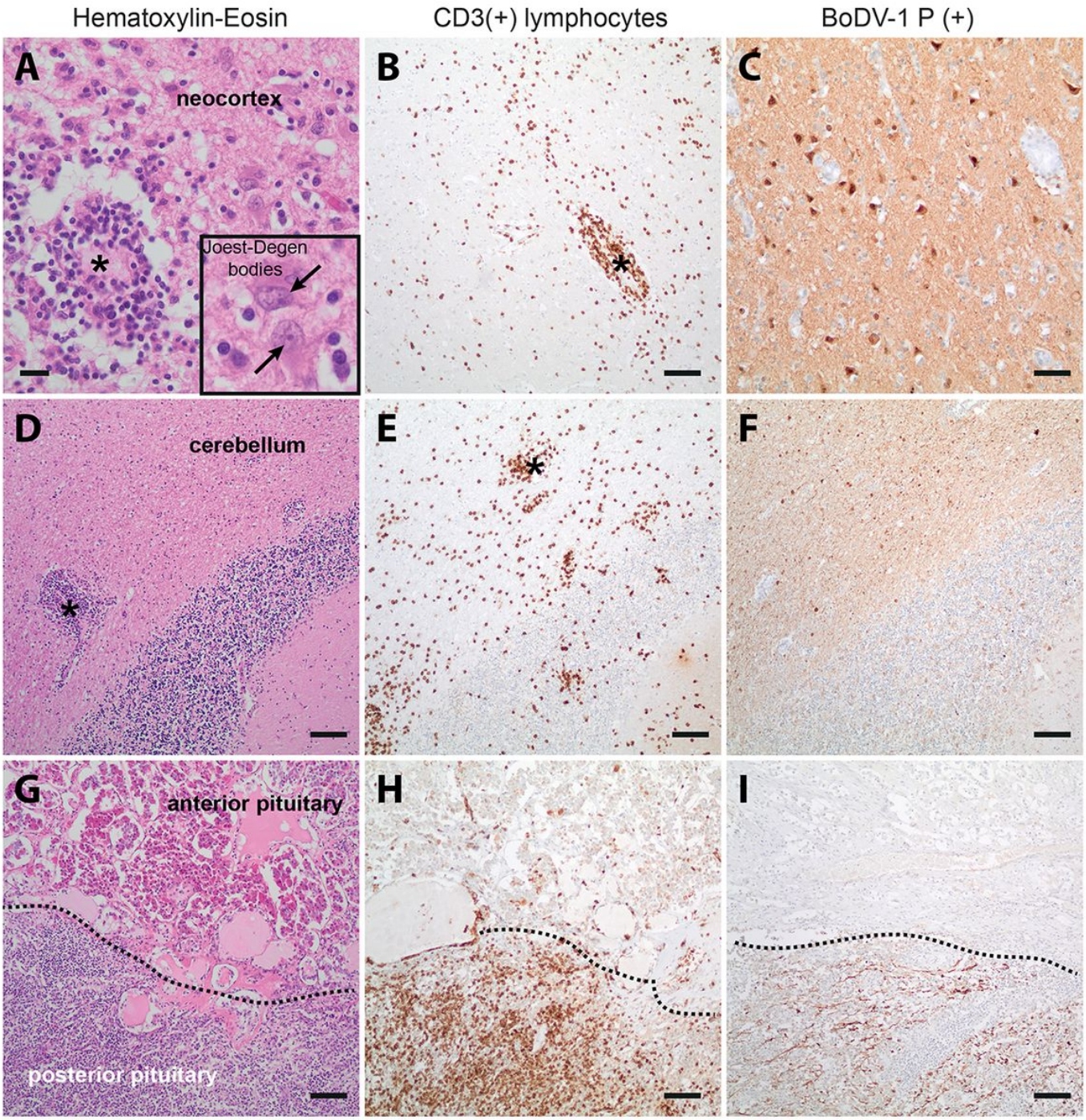

Figure 2

Brain pathology of our Borna-Virus case in neocortical (A-C), cerebellar (D-F), and pituitary (G-I) areas. Hematoxylin-Eosin or CD3 (for T lymphocytes) and Borna-Virus-Type-1 immunohistochemistry are illustrated here. Prominent perivascular as well as diffuse lymphocytic infiltration was found in all neocortical areas (Fig. 2A, B, asterisks at indicative infiltrations). This was accompanied by marked reactive astrogliosis with bizarrely enlarged reactive astrocytes, some of them with eosinophilic intranuclear inclusions (Fig. 2A-inset, arrows point at Joest-Degen bodies). Borna disease virus 1 (BoDV-1) immunohistochemistry revealed strong positivity in neurons as well as the surrounding neuropil (Fig. 2C). Distinct inflammatory infiltration was also seen in the cerebellum (Fig. 2D, E, indicative asterisks), though reactive changes were less pronounced. BoDV-1 signal was primarily visible in the white matter (Fig. 2F). The adenohypophysis (Fig. 2G, H, I, lower half) demonstrated massive lymphocytic infiltration (Fig. 2 G, H) and presence of viral BoDV-1 antigens (Fig. 2I), in contrast to a relative absence of inflammatory infiltrates in the adenohypophysis (Fig. 2G, H, I upper half). Cumulatively, the pathology indicated a non-purulent, lymphocytic sclerosing panencephalomyelitis with detection of BoDV-1-typical eosinophilic, spherical intranuclear Joest-Degen inclusion bodies, in accordance with previous neuropathology studies [20]. Scale bars: 20 μm (A), 50 μm (C), 100 μm (B, D-I).

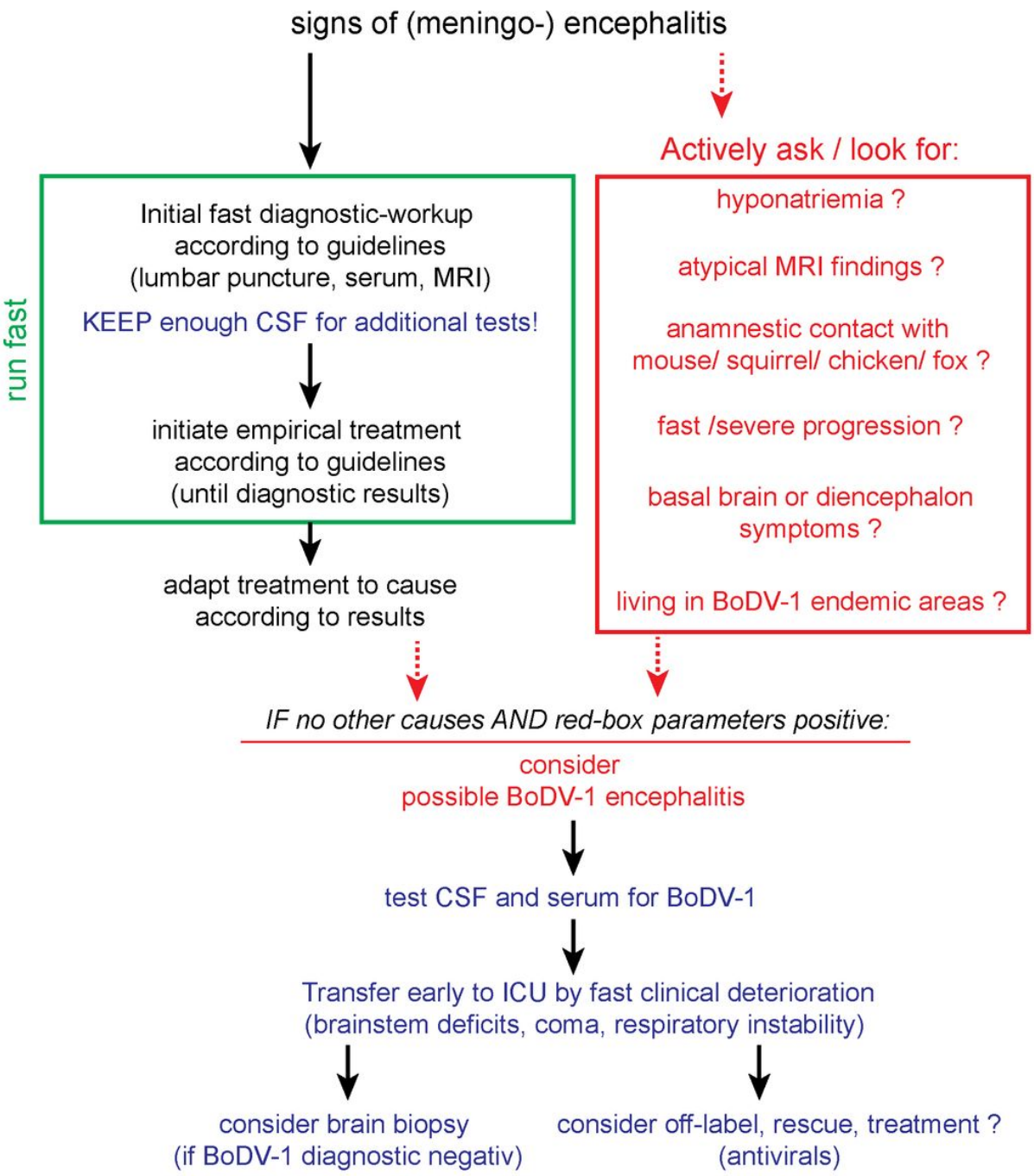

Figure 3

Proposed diagnostic algorithm and "diagnostic keys" (in red box) for BoDV-1 encephalitis. Although an antiviral treatment may be, off-label, considered, it is shown ineffective in the few cases used so far (see Discussion). All initial diagnostic steps should preferably be performed fast, within 1-2 days after admission (green and red boxes).