Human bocavirus 1 respiratory tract reactivations or reinfections in two adults, contributing to neurological deficits and death

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CASE REPORT
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Abstract
Human bocavirus 1 (HBoV1) of the family Parvoviridae causes mild to life-threatening respiratory tract infections in young children, but, due to widespread immunity, it is uncommon in adults. HBoV1 reinfections or reactivations leading to casualties are rare, but might be underdiagnosed. We report two young adults, one previously healthy and one immunosuppressed, with rare diagnostic patterns of HBoV1 respiratory tract infection. Both patients exhibited very high loads of HBoV1 DNA in respiratory samples. The immunosuppressed patient was also HBoV1 DNA-positive in blood, stool and a colon biopsy, but exhibited prior HBoV1-specific high-avidity IgG and weak IgM positivity 9 months before the respiratory symptoms. Likewise, the previously healthy patient exhibited HBoV1 IgG of high avidity and very weak IgM in serum, pointing to prior immunity, but with a seroconversion in cerebrospinal fluid. This patient also showed strong HBoV2 cross-reactivity. The molecular and serological results, together with their ages, suggest that both patients exhibited unusual reinfection or reactivation of HBoV1, contributing to neurological deficits and death.

INTRODUCTION
Human bocaviruses (HBoV) are small non-enveloped single-stranded DNA viruses in the genus Bocaparvovirus of the family Parvoviridae. HBoV1 was discovered in paediatric respiratory secretions in 2005 [1] and later shown to cause mild to life-threatening respiratory illness and infrequently also central nervous system (CNS) infections in young children with encephalitis [2, 3]. Three other human bocaviruses, HBoV2–4, infect the gastrointestinal tract more often than the respiratory tract [3, 4]. The specific seroprevalence of HBoV1–4 in 6-year-old children in Finland was already 80, 50, 10 and 0% and in adults in PR China 67, 50, 40 and 1.4%, respectively [5, 6]. The common clinical symptoms of HBoV1 infection are cough, rhinitis and fever, similar to those of other respiratory viruses. Additionally, pneumonia, asthma exacerbations, dyspnoea and bronchiolitis have frequently been diagnosed in hospital-based studies [3]. Encephalitis, myocarditis and hepatitis have also been reported in children infected with HBoV2–3 [2, 3]. However, HBoV1 infections in adults are infrequent and documented endogenous or exogenous reinfections are rare [7–10]. In this study we report two fatal cases of adults with reactivations or reinfections of HBoV1 with respiratory tract illness and neurological deficits.

THE PATIENTS
Case I was a young adult, living in a medium-sized town in Germany, who had an allogeneic T-cell-depleted hematopoietic stem cell transplantation (alloHSCT) for an inborn haemoglobinopathy 1 year before hospitalization for a respiratory tract infection (RTI). Four months prior to the RTI, while being severely immunocompromised due to failure to regenerate T cells, the patient experienced an acute and subsequent moderate chronic graft-versus-host disease (GvHD) of the gut, leading to a transient reactivation of human
herpesvirus (HHV) 6 and BK polyomavirus (BKV). Starting 3 weeks after the onset of RTI, the patient developed severe neurological symptoms, including microvascular damage. The patient died 4 weeks later due to histologically confirmed severe acute grade 4 intestinal GvHD caused by reduction of immunosuppression intended to control the worsened viral RTI. Blood, pharyngeal wash, bronchial secretion, cerebrospinal fluid (CSF), colon, stool and serum samples were collected on different dates, as detailed in Table 1, for HBoV1 quantitative polymerase chain reaction (qPCR) and enzyme immunoassays (EIAs). The patient did not receive blood during this follow-up.

Case II was a previously healthy adult in the early 30s, with a non-significant medical history, who had an acute upper RTI. Two weeks later, the condition of the patient worsened with severe neurological deficits, affecting the cognitive state, leading to a coma a week later. Increased CSF white blood cell count and changes to brain MRI suggested encephalitis; despite antibiotics, antiviral therapy and plasma exchange for assumed autoimmune encephalitis, the patient died approximately 5 weeks later, without regaining consciousness. Tracheal secretion, CSF and serum samples were collected on the dates detailed in Table 1 for PCRs and EIAs.

### Table 1. Serological and PCR results for HBoV1 in the two patients

| Case | Sample type (dilution) | Sampling day post-alloHSCT / hospitalization | HBoV1 IgG UB/B (abs)* | HBoV2 IgG UB/B (abs)* | HBoV1/HBoV2 IgM UB, (abs)* | HBoV1/HBoV2 IgG avidity (%)* | HBoV1 DNA, qPCR (copies ml−1)† | Other viruses detected |
|------|------------------------|------------------------------------------|-----------------------|-----------------------|----------------------------|--------------------------------|---------------------------------|------------------------|
| 1    | Serum (1:200)          | +115                                     | 1.949/0.471           | 1.514/0.040           | 0.186/0.050                | 39.4/ND                       | Negative                        | None                   |
|      |                        | +399                                     | 1.837/0.608           | 1.292/0.042           | 0.148/0.012                | 49.8/ND                       | ND                              | None                   |
|      |                        | +405                                     | 1.816/0.541           | 1.262/0.034           | 0.136/0.015                | 39.4/ND                       | None                            | None†                  |
|      |                        | +412                                     | 3.443/1.637           | 2.612/0.144           | 0.107/0.012                | 50.6/ND                       | 300                             | None                   |
|      | CSF (1:10)             | +399                                     | 0.107/ND              | ND                    | ND                         | 0.084/ND                      | ND                              | Negative               |
|      | Whole blood            | +270                                     | ND                    | ND                    | ND                         | ND                            | ND                              | ND                     |
|      |                        | +361                                     | ND                    | ND                    | ND                         | ND                            | 100                             | None                   |
|      | Pharyngeal wash        | +407                                     | ND                    | ND                    | ND                         | ND                            | 3.0E+03, 1.6E+03‡              | None||                 |
|      | Bronchial secretion    | +415                                     | ND                    | ND                    | ND                         | ND                            | 5.0E+08, 2.1E+09§              | None||                 |
|      | Colon                  | +412                                     | ND                    | ND                    | ND                         | ND                            | 3.0E+04¶                        | HHV6, BKV               |
|      | Stool                  | +412                                     | ND                    | ND                    | ND                         | ND                            | 3.10E+5                         | None                   |
| 2    | Serum (1:200)          | Day 2                                    | 0.699/0.097           | 1.190/0.213           | 0.156/0.028                | 58.0/69.3**                   | Negative                        | None                   |
|      |                        | Day 8                                    | 1.456/0.098           | 1.824/0.110           | 0.266/0.083                | 59.4/55.4**                   | Negative                        | None                   |
|      | CSF (1:10)             | Day 2                                    | 0.119/0.013           | 0.238/0.013           | 0.144/0.022                | ND                            | Negative                        | None††                 |
|      |                        | Day 9                                    | 0.452/0.014           | 0.526/0.031           | 0.179/0.049                | ND                            | Negative                        | None                   |
|      | Tracheal secretion     | Day 4                                    | ND                    | ND                    | ND                         | ND                            | 6.0E+08, 9.8E+09§              | RV‡‡                   |

*The HBoV1 cutoffs for positive IgG and IgM and low IgG avidity were 0.150, 0.130, and 15%, respectively; unblocked (UB) and/or heterotypic blocking (B) showed (while homotypic VLPs blocked all reactivities, not shown).
†PCR results from University of Regensburg, unless otherwise stated.
‡Negative for adenovirus, HSV1, HSV2, VZV, CMV, HHV6, HHV7, BKV, JCV, measles virus, TBEV, bornavirus and Toxoplasma gondii nucleic acids.
§PCR results from University of Helsinki.
||Negative for HSV1, HSV2, VZV, CMV, EBV, influenza virus A and B, parainfluenza virus 1–4, seasonal coronaviruses, metapneumovirus A and B, RSV A and B, measles virus, adeno virus, enterovirus, rhinovirus and parechovirus nucleic acids.
¶copies/1 million cells.
**Serial dilution starting with 1 : 50 in competition enzyme immunoassays [14].
††Negative for HSV1, 2, VZV, CMV, EBV, HHV6, WNV, enterovirus, rhinovirus, influenza virus A and B, measles virus, mumps virus and bornavirus nucleic acids and for cell culture.
‡‡Negative for influenza virus A and B, parainfluenza virus 1–4, seasonal coronaviruses, metapneumovirus A and B, RSV A and B, adeno virus, enterovirus and parechovirus nucleic acids. AlloHSCT, allogenic haematopoietic stem cell transplantation; Abs, absorbance; ND, not done; CSF, cerebrospinal fluid; HHV6, human herpesvirus 6; BKV, BK polyomavirus; RV, rhinovirus.
The human experimentation guidelines of the University Hospital of Regensburg were followed in the conduct of this research and all investigations of these two fatal cases were performed within routine medical care.

**HUMAN BOCAVIRUS DIAGNOSTIC METHODS**

Both in-house HBoV1-4 multiplex and HBoV1 singleplex qPCRs were performed targeting the nonstructural protein 1 (NS1) and nucleoprotein 1 (NP1) regions of HBoV1, respectively [11, 12]. Similarly, HBoV1-, 2- and 3-specific immunoglobulin (Ig)M and IgG were measured, by EIAs with biotinylated virus-like particles (VLPs) as antigen, in serum and CSF samples of both patients, as described previously [5]. Since antibody cross-reactivity among HBoVs is common, competition EIAs were used to block any possible cross-reacting heterotypic HBoV2 and HBoV3 IgG [5]. Further, we timed the infections by denaturing EIAs measuring HBoV1 and HBoV2 IgG avidity, which, based on slow B-cell maturation, separates acute infection from prior immunity, as described elsewhere [13, 14].

**RESULTS**

In case I, CSF was negative for HBoV1 DNA and antibodies, but serum, whole blood, pharyngeal wash, bronchial secretion, stool and a colon biopsy were all HBoV1 qPCR-positive, with as many as 2.1 E+09 copies ml⁻¹ in the bronchial secretion, suggesting acute HBoV1 infection (Table 1). However, the sequential serum samples were already HBoV1 IgG-positive and weakly IgM-positive 9 months before the RTI episode, followed by a decline in IgM and a sudden twofold increase in IgG (titres 1:1600 to 1:3200) by the time of the RTI. Moreover, all serum samples disclosed IgG of high avidity, confirming past infection [13]. No other pathogens were found in any sample types, except for the transient reactivations of BKV and HHV-6 in blood 4 months before RTI, but their DNA had disappeared before the next blood sampling 3 months later, although persisting in the colon (Table 1).

For case II, the tracheal secretion was strongly PCR-positive for HBoV1 (but not HBoV2–3) DNA with 9.8 E+09 copies ml⁻¹, but the sera and CSF were HBoV1 DNA-negative (Table 1). In extended laboratory testing, no other infectious agents or autoantibodies (including autoimmune encephalitis antibodies) were found, except rhinovirus RNA in the tracheal secretion (Table 1). The patient exhibited both HBoV1 and HBoV2 IgG in unblocked EIA, with a titre of 1:800 rising twofold to 1:1600 within a week, but with considerable cross-reactivity and cross-blocking between HBoV1 and HBoV2 IgG (Table 1). Both HBoV1 and 2 showed high IgG avidity in competition EIA. However, the serum was barely positive for HBoV1 IgM and negative for HBoV2 IgM (Table 1). A seroconversion in HBoV1 IgG to 1:40, with weak to borderline IgM, was observed in the paired CSF samples, suggesting intrathecal IgG production.

**DISCUSSION**

HBoV1 is one of the most common respiratory viruses among children, causing mild to life-threatening RTIs, and it has been found worldwide by PCR in respiratory tract samples of 2–30% of young children with upper or lower respiratory tract illness [2, 3]. HBoV1 is, however, infrequent in adults in whom airway persistence is less common than in children. [15–17]. There are case reports of four elderly men, three immunocompetent ones in Germany and one immunosuppressed one in the UK, with HBoV1-induced pneumonia [9, 18, 19]. One of the immunocompetent men also showed neurological symptoms of unknown aetiology and loss of consciousness but survived, while the immunosuppressed man, who was seronegative, died [9, 19]. All four patients exhibited HBoV1 DNA in both serum and respiratory samples. There are furthermore reports of HBoV1 CNS infections in children with encephalitis diagnosed with PCR in CSF [2, 3, 20–23]. In one CSF sample, parvovirus particles were also detectable by electron microscopy [20]. Of note, HBoV1 DNA has also been reported as sole detections in the CSF of two adults (aged 46 and 66 years) from Sri Lanka, both with encephalitis [22]. The severity of symptoms in the HBoV1-positive patients did not differ from those with encephalitis of other aetiologies (dengue-, adeno- or echoviruses), and all recovered.

In general, positive PCR assays of airway samples of children are not considered to be reliable as sole indicators of acute HBoV1 infection because HBoV1 DNA may persist with waning loads in the airways for months [2, 3, 7]. In severe infections, detection of high viral load, mRNA, antigen, viraemia, IgM, seroconversion of IgG and low IgG avidity is therefore a better option for a clinically more truthful diagnosis [2, 3, 14, 24, 25].

In both our adult cases we observed extremely high loads of HBoV1 DNA in the airways, and in the first patient also viraemia, both suggesting acute HBoV1 infections. The very low IgM results, prior immunity and high IgG avidity, together with the patient ages, however, point more to exogenous or endogenous reinnfections of HBoV1, rather than acute primary infections. Such adult reinfections are not often reported, especially with a fatal outcome. In Jula et al. the previously healthy grandmother of an HBoV1-infected boy had low-load viraemia and an increase in pre-existing HBoV1 (and HBoV2) IgG of high avidity, with no IgM, indicating reinfection [8]. Despite the prior antibodies, she developed symptoms, even though mild in the form of rhinitis. In addition, one 29-year-old immunocompetent male with chronic pharyngitis and cough exhibited HBoV1 DNA as sole pathogen, in both serum and BAL, for over 5 months [10]. He was also seropositive with high IgG avidity and negative IgM during the whole observation period, indicating prior immunity.

We report two young adults with RTI and neurological deficits, one immunosuppressed after alloHSCT and the other previously healthy, with acute HBoV1 reinfections or reactivations contributing to their deaths. However, due to the broad immunodeficiency in the first patient, reactivation of
HHV6 and BKV was co-detected in blood, complicating the interpretation of the role of HBoV1 in the disease severity, not excluding synergy of the viruses and GvHD. However, these viruses had disappeared from blood long before the RTI, whereas HBoV1 was still present. Since the CSF was HBoV1-negative, we could not directly link the neurological symptoms with HBoV1 infection; they could also have been caused by a systemic inflammation due to the underlying haemoglobinopathy. Interestingly, this patient had received an alloHSCT 1 year before her RTI, indicating that the current humoral immune status could have come from the bone marrow donor [26] and from residual circulating HBoV1-specific memory B and plasma cells generated before alloHSCT, while the lack of T cells after alloHSCT may prevent a de novo response from naïve B cells. Even in normal immune reconstitution, the recovery of the immune system can take 6 to 12 months. Kainulainen et al. reported a chronic HBoV1 infection in a 7-month-old child with severe T-cell deficiency [27]. This child also had high viral loads in respiratory samples and stool and exhibited borderline IgM and declining IgG, but recovered.

The second patient, who was immunocompetent, also had high loads of HBoV1 DNA in the airways, pointing to an acute HBoV1 infection. However, the weak-to-borderline IgM and lack of viraemia, in combination with high IgG avidity, indicated prior immunity. In addition, HBoV1 IgG seroconversion and a low IgM were observed in CSF, concurring with the neurological signs; nevertheless, viral DNA was not detected in CSF. This paradoxical finding could be due to non-optimal timing of the two samplings, to low viral loads, or leakage through the blood–brain barrier. Not enough samples were left for albumin measurements. The patient did exhibit an even higher IgG absorbance for HBoV2 than for HBoV1, showing cross-blocking in competitive EIA, which could suggest an HBoV2 infection. Nevertheless, even though the IgM response was very weak, it was specific for HBoV1, while no HBoV2 (or HBoV3) IgM was detected. Likewise, all PCRs performed by two different laboratories clearly indicated that the current infection was due to HBoV1, not HBoV2.

Interestingly, such problematic cross-blocking of HBoV1 and 2 IgG can be due to a long-known immunological phenomenon called original antigenic sin (OAS), where a prior infection of an unrelated virus, possibly affecting the brain and had an important role in the cause of death. Even if the trachea was also rhinovirus RNA-positive, the CSF samples were negative. Rhinoviruses, despite belonging to the genus Enterovirus, are furthermore not considered to be neurotropic [31].

In conclusion, we report two young adults, one immunocompromised and the other constitutionally healthy, with HBoV1 RTIs, contributing to neurological deficiency and death. Both patients had extremely high viral loads (close to 10^6 copies ml^-1) of HBoV1 in their airway samples and a non-diagnostic increase in IgG titre with low IgM, while one of them had also viraemia and the other seroconversion in CSF, all pointing to an acute HBoV1 infection. Nevertheless, the high IgG avidity and prior immunity revealed that these infections were not from acute primary infections, but instead from reactivations or reinfections. Our two cases should prompt clinicians and researchers to investigate whether HBoV1-induced RTI, with or without CNS symptoms, after reactivation or reinfection among adults actually occurs more frequently than previously thought.

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Author contributions
R.R.T.: investigation, methodology, analysis, Writing of original draft and review and editing. A.P.: conceptualization, methodology, project administration, writing – review and editing. M.E.: resources, patient care, writing – review and editing. M.S.V.: conceptualization, funding acquisition, writing – review and editing. D.W.: resources, patient care, writing – review and editing. K.A.: resources, patient care, writing – review and editing. M.E.: resources, patient care, writing – review and editing.

Conflicts of interest
The authors declare that there are no conflicts of interest.

Ethical statement
The human experimentation guidelines of the University Hospital of Regensburg were followed in the conduct of this research and all investigations of these two fatal cases were performed within routine medical care. Since it is not possible to obtain publication permission from next of kin, we were required to leave out age and gender so that these patients could not be identified.

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