Journal of Clinical Virology 43 (2008) 391–395

Contents lists available at ScienceDirect

Journal of Clinical Virology

journal homepage: www.elsevier.com/locate/jcv

Clinical and epidemiological aspects of human bocavirus infection

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ARTICLE INFO

Article history:
Received 28 May 2008
Accepted 14 August 2008

Keywords:
Human bocavirus
Respiratory Disease
Gastroenteritis

ABSTRACT

Human bocavirus was recently described as a novel member of the *Parvoviridae* to infect humans. Based on accumulating clinical and epidemiological data the virus is currently being associated with respiratory infections in young children and infants and is furthermore discussed as causative agent of gastrointestinal illness.

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1. Introduction

Acute respiratory tract infections (ARTIs) caused by viruses represent a major cause of hospitalization and morbidity in young children and infants worldwide. Pathogens associated with this clinical condition include the respiratory syncytial virus (RSV), human adenovirus, human metapneumovirus and coronaviruses NL63 and HKU1.[1] Although a constantly growing number of pathogens is being associated with ARTIs, a high percentage of infections still remain uncharacterized and their causative agents unknown.

In 2005 Allander et al. described a previously uncharacterized virus in pools of human nasopharyngeal aspirates obtained from children suffering from diseases of the respiratory tract.[2] Comprehensive sequence and phylogenetic analyses revealed a close relation of the new virus with the bovine parvovirus (BPV) and the canine minute virus (CnMV), both members of the *Bocavirus* genus of the *Parvoviridae* family. It was therefore provisionally named human bocavirus (HBoV).

Parvoviruses represent a large family of small, non-enveloped viruses characterized by linear single-stranded DNA-genomes and an exceptional structural simplicity. Besides HBoV two additional parvoviruses, parvovirus B19 (B19V) and PARV4 including its second genotype termed PARV5, are currently known or discussed to infect humans.[3–5] For almost three decades B19V has represented the only member of the virus family to cause illness in humans, e.g. the self-limiting childhood disease *Erythema infectiosum*.[6] Additionally, B19V infections during pregnancy are known to frequently result in intrauterine infections of the fetus, occasionally leading to miscarriage or *Hydrops fetalis*.[7] While the clinical relevance of PARV4 remains unclear up to date, evidence for an influence of HBoV infections in the manifestation of respiratory and gastric symptoms is accumulating.

2. Material and methods

2.1. Detection of HBoV-specific antibodies by ELISA

For detection of HBoV VP2-specific IgG and IgM, 100 ng of purified HBoV VP2 virus-like particles (VP2–VLP) were generated as previously described[8] and coated onto Nunc-Immuno™ MediSorp™ plates (Nunc GmbH, Wiesbaden, Germany) in coating buffer (0.2 M Na_2CO_3, 0.2 M $NaHCO_3$, pH 9.5) overnight at 4 °C. The plates were subsequently washed six times with washing buffer (PBS, 0.05% Tween 20) and blocked with dilution buffer (PBS, 2% Tween 20, 3% FCS) for 1 h at 37 °C. After incubation with respective serum samples for 2 h at 37 °C, the plates were washed and rabbit anti-human IgG- or IgM-specific HRP-coupled secondary antibodies were added for 1 h at 37 °C (1:6000 and 1:1000 in dilution buffer, respectively; both Dako Deutschland GmbH, Hamburg, Germany). Development was performed using the BD OptEIA™ Substrate (BD Biosciences, Heidelberg, Germany) according to the manufacturer's instructions.

As an international IgG standard for HBoV is not yet available, serially diluted sera of a healthy adult male (age: 28 years) and of a boy (age: 22 months) both exhibiting strong HBoV-specific IgG-

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doi:10.1016/j.jcv.2008.08.009

and IgM-responses, respectively, were introduced for internal reference and used for the calculation of HBoV-specific antibody titers in all performed experiments. Sera with background optical densities were considered negative and used for the determination of respective IgG/IgM cut-off values, which were additionally confirmed by Western blot analysis.

2.2. Reviewed literature

All reports listed in the PubMed-database of the National Library of Medicine (Rockville Pike, MD, USA) until May 2008 have been considered and evaluated in this review.

3. Diagnosis of HBoV infections

Up to date, no cell culture systems for the *in vitro* replication of HBoV have been described. Therefore, diagnosis of HBoV infection has so far mainly been based on the detection of viral genomes present in human respiratory, serum, stool, and urine samples using different PCR techniques employing numerous sets of primers specific for the viral genes NP1,[2,9–12] NS1[12–15] and VP1/2.[11,12,16–18]

Recent reports describe the detection of HBoV-specific antibodies directed against the viral capsid proteins VP1 and/or VP2 in serum samples using ELISA,[19,20] Western blot,[21] and immunofluorescence assays.[22] Up to date, no cross-reactions of HBoV- and B19V-specific humoral and/or cellular immune responses have been described.

4. HBoV epidemiology

4.1. Prevalence of HBoV-DNA

HBoV-DNA has been frequently detected worldwide in respiratory,[2,9–11,13–16,18,23–66] serum,[30,43] fecal,[17,30,33,35,38,67,68] and urine samples[38] obtained from infants mainly around 2 years of age. The prevalence of HBoV-DNA has been described to vary considerably between 2.7–19% in children suffering from ARTIs and 0.8–9.1% in patients with gastroenteritis.[17,25,35,43] However, since the majority of currently published studies have been performed retrospectively, these variations in viral prevalence may be explained by differences in the study populations and patient characteristics. In infected infants, viral loads have been described to range between <500 to 10^{10} and $<10^3$ to 5.9×10^5 genome copies in nasopharyngeal aspirates and fecal samples, respectively.[25,37,43,52] In serum, we have detected viral loads of up to 1.2×10^6/ml.[69]

Only limited data is available on the prevalence of HBoV viremia in asymptomatic individuals, since most of the studies have focused on children with distinct clinical symptoms of infectious diseases. In a first study a total of 96 healthy controls were included for diagnostic analysis of HBoV, yet no viral DNA was observed in respiratory samples from these individuals.[16] Furthermore, we were unable to detect HBoV-DNA in sera collected from 298 healthy adult blood donors. However, a recent publication describes the detection of viral genomes in 5% of respiratory samples obtained from asymptomatic children.[24]

While most studies have detected the virus during the winter season,[2,28,33,38,46,70] single reports describe increased numbers of viral infections in spring or summer.[9,31,40] No information is currently available on the routes of viral transmission. However, since HBoV can be frequently detected in respiratory and fecal samples, a transmission of the virus via aerosols or direct contact has to be presumed. Thereby, the contagiousness of virus-containing body secretions might be potentiated by the exceptional stability of parvoviral virions and might facilitate increased frequencies of nosocomial infections.

4.2. Prevalence of HBoV-specific antibodies and cellular immune reactions

Up to date, only a limited number of studies have been focused on the analysis of HBoV-specific adaptive immune responses in healthy individuals and infants suffering from ARTIs, mainly due to the initial lack of recombinant viral antigens and standardized diagnostic methodologies.

In the first report published on HBoV seroprevalence Endo and co-workers describe ubiquitous IgG-responses against the viral capsid protein VP1 in up to 100% of children aged $\geq$2 years with respiratory infections.[22] The overall seroprevalence of HBoV-specific IgG in the Japanese population aged between 0 months and 41 years was 71.1%, while seronegative patients were observed most frequently in infants with 6–12 months of age.

In a subsequent study the prevalence of HBoV-specific antibodies in Finnish infants suffering from ARTIs was assessed using Western blot.[21] In children determined positive for HBoV-DNA, IgG- and IgM-antibodies against the viral VP2 protein were observed in 73% and 49% of analyzed samples, respectively. The mean age of these children was 2.1 years. The overall prevalence of HBoV-specific IgG and IgM in children without detectable viral genomes in nasopharyngeal samples was 35% and 13%, respectively. Antibodies against the aminoterminal domain of the viral VP1 protein, termed VP1-unique region, were detected rarely: only 7% (IgG) and 2% (IgM) of the patients showed positive results. In contrast to the data provided by Endo and colleagues and by our group (see below), the prevalence of HBoV-specific IgG was shown to decline from 52% in 1–2 year old infants to 29% in children aged over 5 years in the Finnish study.[21] Furthermore, maternal VP2-specific IgG were not observed in children <6 months of age despite a seemingly high seroprevalence of HBoV in adults. This finding may be due to the maturation of IgG-specificity in the time period of up to 6 months following an acute infection, during which antibodies against linear epitopes get replaced by those preferentially recognizing conformational antigen structures. This process has been well documented for B19V-specific humoral immune responses,[71] and therefore it may be assumed that similar changes in IgG affinity take place during HBoV infections.

More recently, we and others have established ELISA assays based on the use of recombinant HBoV VP2–VLP for the detection of HBoV-specific antibodies in human serum samples.[19,20] Herein, our group observed the prevalence of IgG_1 subclass antibodies against HBoV VP2–VLP to rise from 24% in children with 7–9 months of age to 98.3% adult blood donors (mean age: 42 years).

In addition to humoral immune reactions the presence of HBoV-specific T-cells in healthy adults supports a high prevalence of HBoV-specific immunity in adults. Thereby, frequent interferon-gamma (IFN-γ) mediated $CD4^+$ T helper cell reactions were observed against HBoV capsid proteins.[8] Similar data have been previously described for B19V-specific cellular immune responses.[72–75]

5. Clinical associations

HBoV infections are frequently linked to high rates of co-infections with viral and bacterial pathogens of the respiratory and/or gastrointestinal system. Together with the fact that most of the studies have been performed retrospectively and long-term follow-up studies with detailed clinical characterization of

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