Journal of Clinical Virology 74 (2016) 45–49

Contents lists available at ScienceDirect

Journal of Clinical Virology

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

Review

Human bocavirus in stool: A true pathogen or an innocent bystander?

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ARTICLE INFO

Article history:
Received 23 September 2015
Received in revised form
18 November 2015
Accepted 22 November 2015

Keywords:
Bocavirus
HBoV
Stool
Gastroenteritis
Virulence

ABSTRACT

Human bocavirus (HBoV) is a parvovirus that was discovered only a decade ago and currently includes four genotypes. HBoV-1 is predominantly found in the respiratory tract, whereas HBoV-2, HBoV-3, and HBoV-4 are mainly detected in stool. HBoV-1 is known to be associated with respiratory tract infections. In stool, the prevalence of HBoV (1–4) is similar between patients with gastro-intestinal symptoms and healthy controls in most studies. Furthermore, often other viruses are concurrently present. Both findings suggest that HBoV in stool is an innocent bystander rather than a true pathogen. Nevertheless, several gaps in knowledge on the role of HBoV in stool remain to be addressed. All studies were performed in primarily immunocompetent patients. The role of HBoV in immunocompromised patients remains unknown.

Contents

1. Introduction

Acute gastroenteritis is a prevailing disease with a higher rate and an increased severity of illness found in young children [1,2]. Viral pathogens are important contributors to the burden of this disease, of which norovirus and rotavirus are most common [3,4]. Despite increasing and better detection methods for bacteria, parasites, and viruses, up to 40% of gastroenteritis cases remain of unknown etiology [5]. This has led to the continuous search for an association with other pathogens in the past decade. When a new virus is discovered in patients with acute gastroenteritis, the inevitable question arises whether the virus is a true cause or only a marker of disease.

The human bocavirus (HBoV) is a recently discovered virus, which is named after its first known hosts (i.e., bovine and canine). HBoV belongs to the family of *Parvoviridae* and the subfamily of *Parvovirinae*. This parvovirus is a small single stranded DNA virus with a diameter of 18–26 nanometers and contains a non-enveloped icosahedral capsid. The pathogenesis of HBoV is poorly characterized, because until now no well-established in vitro or animal models are available to study this virus [6]. In contrast to other parvoviruses such as parvovirus B19, HBoV does not seem to integrate into the genome of infected human cells [6,7].

In 2005 the HBoV type 1 was identified in nasopharyngeal specimens of children with respiratory tract infections [8]. It has been suggested that HBoV-1 can persist for longer periods of time in respiratory tract mucosa, although the exact mechanism remains

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http://dx.doi.org/10.1016/j.jcv.2015.11.027
1386-6532/

unknown. Several studies support an association of HBoV-1 with respiratory infections in children with pneumonia, acute wheezing, asthma or bronchiolitis [6]. Some of these studies have, aside virus detection in the nasopharynx, confirmed the diagnosis of HBoV infection by serology or polymerase chain reaction (PCR) in serum [6]. Nevertheless, HBoV is often found in the presence of other well-defined pathogens in respiratory specimens and concerns remain about its primary role as a causative agent in individuals with respiratory disease. The significance of this virus in respiratory disease still remains to be fully elucidated.

In recent years additional genotypes, besides HBoV-1, have been identified: HBoV-2, HBoV-3, and HBoV-4 [9–11]. These latter types are primarily detected in stool. However, the role of HBoV in gastrointestinal (GI) infections is unclear.

Until now, there is considerable variation among microbiological laboratories to include PCR-based testing for HBoV in viral GI diagnostics. The aim of this review is to address whether HBoV present in stool could be considered as an independent risk factor for acute gastroenteritis. An answer to this question can provide guidance to clinical microbiologists and laboratories to decide whether or not to include HBoV as part of their diagnostic algorithm for gastroenteritis.

2. Methods

For the aim of this review we performed a literature search in PubMed and EMBASE using the following search criteria (last performed on 25th April 2015): (boca OR bocavirus OR hbov OR hbov-1 OR hbov-2 OR hbov-3 OR hbov-4) AND (gastroenteritis OR diarrhea OR diarrhoea OR vomiting OR gastro-intestinal OR intestinal OR "gastrointestinal disease"). We selected clinical studies that included subjects with GI symptoms and in whom the presence of HBoV was tested in stool.

First, we determined the prevalence rates of HBoV found in the different studies and divided the studies into those with and without a comparator group. Subsequently, we focused in detail on those studies that had included both symptomatic patients and a control group of asymptomatic subjects to allow a meaningful interpretation of the virulence of HBoV.

In order to adequately assess the impact of a virus it is important to consider both the prevalence of the virus itself as well as the prevalence of other pathogens. Therefore, in the second stage we took into account the reported rates of co-pathogens. A high prevalence of co-infections may suggest that HBoV is only an innocent bystander, whereas a low prevalence of co-pathogens (i.e., mono-infection with HBoV) may indicate a more pathogenic role of this virus.

3. Results

The search in PubMed and EMBASE resulted in 144 and 276 hits, respectively. After screening on title, abstract and in some cases full-text article, nine clinical studies remained that included both cases (patients with gastroenteritis) and controls (patients without gastroenteritis).

Table 1 provides an overview of these studies that determined the presence of HBoV in stool in patients with gastroenteritis and controls. HBoV genotypes 1, 2 and 3 were determined in the majority of the included studies, but genotype 4 was only determined in four studies. Among the different genotypes HBoV-2 was the most prevalent type found in stool [5,9,11,12], followed by HBoV-1. HBoV-3 has been reported in smaller frequencies, and HBoV-4 was detected in only one study [11]. The prevalence of HBoV varied from 0% to 26%. The highest prevalence of 26% was reported in China [5], in a study population that included 632 hospitalized children with diarrhea. In the same study a prevalence of 15% was found in 162 healthy controls, which is significantly different from the prevalence in cases. The healthy controls were not matched on age, sex or other characteristics to the cases. The majority of HBoV positive children were 12 months of age or less. This high prevalence was caused by a rise of HBoV-2 positive cases in the second half of the study period. Overall, HBoV-2 was detected in 20% of symptomatic patients, whereas lower prevalence rates were found for HBoV-1, HBoV-3 and HBoV-4: 4%, 1% and 0%, respectively. HBoV-2 was also the most prevalent type (12%) in the control group, followed by HBoV-1 (2%). The peak of HBoV detection was from winter to spring. Notably, in a previous report by the same authors, no significant difference in prevalence was found between cases and controls for the same study population and inclusion criteria but covering shorter inclusion period. In that report, the prevalence was only 3.5% in both groups [13]. In a case-control study that comprised an Australian cluster of children, a significant difference in the prevalence of HBoV-2 was found in patients with GI symptoms (17.2%) compared to age-matched healthy volunteers (8.1%) [9]. Prevalence was based on the presence of HBoV-2 in all the samples taken within the first three days after the first sample. However, only one sample was collected from each control, whereas a second sample was collected in more than half of the cases. Prevalence was not different between cases and controls when only the first sample was considered in the comparison. For HBoV-3 no difference in prevalence was observed between cases (2.7%) and controls (2.2%). No seasonality patterns of either HBoV type were found. Finally, the third and last report showing a positive association between HBoV and acute gastroenteritis was a case control study in Iranian children. The definition of the control group and the HBoV types that were determined, were unfortunately not clearly stated, and many other relevant information details were lacking as well [14]. The remaining six out of nine included studies did not support an association. In the largest study published to date a trend toward a lower prevalence of HBoV was found in 2256 community-acquired gastroenteritis cases (including all ages from <1 to >70 years) compared to age-matched 2124 asymptomatic controls in the United Kingdom [12]. The viral loads between cases and controls were comparable. The prevalence of HBoV was highest in children under five years of age and declined with increasing age. A peak incidence of HBoV was observed between April and June. A third of the HBoV positives were typed. HBoV-1 was primarily found in controls, whereas HBoV-2 was predominantly detected in cases. In the United States a similar trend was found in an active population-based surveillance [15]. This study showed a lower prevalence of HBoV in children under five years of age presenting with acute gastroenteritis to hospitals, emergency departments and primary care clinics (1.4%) compared to age-matched healthy controls (2.4%). HBoV was detected predominantly from December through June in both patients and healthy controls. In an international study among adults in the United States and travelers/resident expatriates in Nepal an overall prevalence rate of 5% was found, but without a significant difference between cases and controls [11]. Also a case-control study could not confirm an association in Finnish children under 15 years of age [16]. Prevalence rates of 5.6%, 3.3% and 0.9% were found in cases with acute gastroenteritis for HBoV-1, 2 and 3, respectively. Most positive cases were detected from November to June. In a Thai study much lower prevalence rates of 0.9% and 0% were found in symptomatic children and healthy children, respectively [17].

Six out of the nine studies determined the concurrent presence of other viruses Table 1 [5,12,13,15–17]. All six studies detected concurrent viruses with prevalence rates varying between 20 and 81% in stool of patients with a positive HBoV. Rotavirus was the most frequent detected co-pathogen, followed by norovirus [5,13,15,16].