Case Report

HUMAN BOCAVIRUS, A NEWLY DISCOVERED PARVOVIRUS OF THE RESPIRATORY TRACT

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ABSTRACT

Human Bocavirus is a newly discovered parvovirus. This virus is the fourth most frequently detected virus among symptomatic children with respiratory infection. Human Bocavirus is present worldwide and is a probable cause of symptomatic respiratory infection, although Koch's postulates are not all fulfilled.

In this article, we propose an overview of the main clinical data about this virus, two years after its discovery. In addition, we discuss some hypotheses about its tropism for the lung in young children.

In September 2005, Allander et al. identified a new parvovirus in pooled nasopharyngeal aspirates (NPA) (1). From that time research groups (1-16) detected worldwide the new so-called Human Bocavirus (HBoV) by PCR in their sample collections. The prevalence of HBoV genome detection ranges from 1,5% (4) to 19% (13) among respiratory samples from symptomatic patients. With such a frequency the HBoV represents the fourth most frequently detected virus in respiratory samples (13,15).

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DESCRIPTION OF THE HUMAN BOCAVIRUS AND ITS FAMILY

Human Bocavirus belongs to the genus *Bocavirus in the Parvovirinae* subfamily of the *Parvoviridae* family (better known as "parvovirus"). Thus far, only two other bocaviruses have been described: the Minute Virus of Canines (MVC) which infects dogs (17), and the Bovine Parvovirus (BPV) which infects cattle (18). The name "bocavirus" itself comes from the combination of "bo" (from "bovine") and "ca" (from "canine") (19,20).

Among the *Parvovirinae* subfamily, the only member described in human pathology is the Parvovirus B19. It causes the fifth disease during childhood and transient aplastic crisis in patients with chronic haemolytic anaemia (21). Parvovirus B19 belongs to the Erythrovirus genus of the Parvovirinae subfamily and is divided in several serogroups (22).

Parvoviruses are small viruses of around 20 nm in size, with a 5 kb long single-stranded DNA genome. Several open reading frames (ORF) allow the expression of structural and non-structural proteins. The main feature of parvoviruses is their dependence on the cellular machinery. They need dividing cells in S phase to replicate. Indeed, the small genome of parvoviruses does not contain all the proteins required for its own replication (23).

HBoV genome contains 3 ORFs: an ORF encoding the 2 capsid proteins (VP1 and VP2), another ORF for the non-structural protein NS1, and a third one encoding NP1, a protein of unknown function (1).

At the time of HBoV identification, Allander et al. described 2 strains of the virus (1). Thus far, all studies in which a gene of the virus has been sequenced, have confirmed that HBoV is a highly conserved virus with all the sequences related to these 2 strains. The systematic analysis of the fully sequenced HBoV genome has shown that the NS1 and NP1 genes do not vary among different HBoV isolates. In contrast, some variations in VP1 and VP2 genes sequences have been demonstrated. Therefore, from a pratical point of view, NS1 and NP1 genes should be targeted for HBoV detection in routine clinical laboratories (24).

PATHOGENIC ROLE OF THE HUMAN BOCAVIRUS

HBoV seems to be an infectious agent of the respiratory tract, but the causal link between the presence of HBoV and a respiratory illness remains to be demonstrated. A direct pathogenic role is suggested by several independent reports which show that the HBoV genome is not detected in respiratory samples of healthy subjects (11-14,16,25). Four studies do not show any detection of the HBoV genome among asymptomatic subjects (11,13,14,25) and two other show a proportion of only 1% of asymptomatic individuals in whom HBoV was detected (12,16).

Surprisingly, HboV is found more frequently in association with another respiratory virus. This observation is constant in all studies, ranging from 5% (11) to 83% (16) of co-infection in the HBoV-positive samples. Co-infection with respiratory viruses was rarely described up to a few years ago (26). The contemporary use of the PCR as a virus-detection tool (viral nucleic acid detection rather than infectious virus or antigen detection) modified the previous observations. Several newly identified viruses present a high frequency of co-detected viruses (27-30). To a lesser extent, Respiratory Syncitial Virus, Rhinovirus, human Para-influenza Virus, Influenza Virus and Adenovirus might also co-infect patients (13,16,31). In the presence of HBoV, the rate of co-infection is definitely higher than with other respiratory viruses. In a prospective study, Fry et al. showed that classical respiratory viruses are associated with each other in 0 to 34% of nasopharyngeal aspirates (NPA) from patients with pneumonia, whereas, HBoV co-infection occurs in 83% of the same cohort (16).

To better assess a pathogenic role of HBoV in respiratory infection, Brieu et al. have shown parvovirus-like particles by electronic microscopy in high-titered NPA of HBoV infected children (32).

CLINICAL PRESENTATION OF THE HUMAN BOCAVIRUS INFECTION

The precise clinical presentation of HBoV infection remains controversial. The typical presentation seems to be a syndrome of lower respiratory tract infection (LRTI) with fever and respiratory distress (like in bronchiolitis and pneumonia). In addition, few studies showed evidence of upper respiratory tract symptoms, such as rhinorrhea, cough and throat pain (6-8,11,33). Moreover, wheezing seems now to stand out as a frequent condition (7,8,13,15,16,34). Indeed, among children suffering of acute wheezing, 14 to 19% were positive for HBoV in their NPA (7,8,13,34). This occurence has not been verified in adults with acute asthma exacerbation (14,35).

The presence of diarrhoea can also be observed in some patients with respiratory samples positive for HBoV (7,8,11,36). Futhermore, HBoV was detected in 0,8 to 9,1% of diarrheal feces, independently of any respiratory syndrome (33,36,37); more than 50% of these HBoV-positive fecal samples showed co-infection with another intestinal pathogen (33,36). A gastro-intestinal picture has also been described in calves and dogs infected with BPV and MVC, the two other bocaviruses (17,38-40). Pozo et al. detected HBoV in urine and stools of two patients hospitalized for LRTI with HBoV in their NPA. This may merely reflect the excretion of the virus through digestive and urinary tracts, but may also explain other manifestations of HBoV-associated disease.

HBoV has also been detected in serum samples from symptomatic patients with HBoV-positive respiratory samples and even in HBoV-negative respiratory samples. As the Parvovirus B19 and other bocaviruses (39,41), HBoV seems to cause systemic infection (13,16).

The virus has also been detected in the serum after clinical recovery. From 2 weeks up to 5 months after the acute event of respiratory infection, HBoV can still

be detected in NPA (15) and even in the serum (13). This information evokes a possible persistence of the HBoV.

CHARACTERISTICS OF THE TARGET-POPULATION OF THE HUMAN BOCAVIRUS

All studies, except one (4), showed a strong proportion of HBoV in the samples from children aged from 6 months to 2 years. A recent study on the seroepidemiology of HBoV confirms this observation. 71,1% of a Japanese population aged from 0 month to 41 years were seropositive for antibodies against the VP-1 protein of HBoV. The seropositive rate was the lowest in the age group of 6 to 8 months (5%) and rapidly increases in the age group of 2-3 years (83%) (42). This tropism for young children opens a number of questions. Indeed, in the Bocavirus genus, MVC and BPV infect preferably young animals. A link seems to exist between Bocavirus and the first period of life in the mammalian development. One explanation could be that parvovirus targets cells in division, more abundant during the development of young mammals.

Interestingly, lung development lasts until the age of 18 years (43). Although initiated at the end of the foetal life, the process of alveolisation takes place essentially from the birth to the age of two years. During this period, epithelial cells rapidly proliferate. The virus might thus infect and replicate in lung tissues. Alveolar cells but also fibroblasts and endothelial cells proliferate intensively during this period. The percentage of proliferating alveolar type II cells reaches 6%, while this type of cells usually replicates very slowly in adulthood (43).

Still, the presence of HBoV in the respiratory tract is not restricted to young children. One case-report (44) describes a 28 year old woman with a strong suspicion of atypical pneumonia due to HBoV, and distinct cohorts (1,3,4,6,7,12,14,16) show positive samples for HBoV in adults or children older than 5 years. At this period of life, the cellular division in lung is rare but lesions caused by pulmonary toxins or infections can stimulate the proliferation of alveolar type II cells (45). HBoV might take advantage of the increase of cell division following cellular damages induced by other viruses. This hypothesis is supported by the high rate of co-infection with HBoV(16).

Immuno-deficient patients are usually preferentially targeted by virus infection. Unfortunately, the immunological status of HBoV-positive patients is only specified in a few studies (14,46,47). The case of a child with acute lymphoblastic leukaemia infected with HBoV was described in depth by Koskenvuo et al. (47). This patient presented successive HBoV infections, simultaneously with his anti-cancer treatment. Instead of multiple infections, this clinical presentation evokes reactivations of a persistent virus. Moreover, Allander et al. have shown two levels in the titer of HBoV detected in their samples; a high level, perhaps related to an acute phase of the disease, and a low level, perhaps related to a persistence phase (13). To assess the hypothesis that HBoV can persist and reactivate in immunodepressed patients, Manning et al have tested bone marrow, brain and lymphoid tissue at autopsy of immunodepressed subjects, and found no HBoV genome in any of these three organs (48). The response might have been different if others organs, like lung and intestine, had been examined.

Very few cases were described in neonates who seem to be protected from the virus (5,11). The presence of passively transferred antibodies from the mother against the virus could explain such low rate of infection (2). Indeed, in the seroepidemiological study, 90,5% of the age group 0 to 3 months were seropositive for HBoV (42).

POTENTIAL CELLULAR TROPISM OF HBOV BY COMPARISON WITH OTHER PARVOVIRUSES

Beside the high level of cell division, additional cell specific factors are necessary for virus targeting (45).

HBoV mainly targets the lung of children. In order to better understand such tropism, we reviewed the literature concerning the tropism of other parvoviruses: MVC, BPV, Aleutian Mink Disease Parvovirus (ADV) and Parvovirus B19.

MVC infects only dogs. Pups inoculated at birth with MVC through the oro-nasal route develop an interstitial pneumonia. Using immunofluorescence staining, Carmichael et al. showed that the virus is mainly located in the alveolar epithelium, as well as in the bronchial epithelium and in the extra-cellular area surrounding the alveoli (41). Note that there are differences between experimental infections and cases in the field. Indeed,

pulmonary lesions were less described in "wild" cases (40,49,50).

BPV provokes principally diarrhea in calves (38,39). However, BPV has been shown to be able to infect lung and tracheal cells, in vitro(51). Sialic acid seems to have a role in the attachment of the virus to the target cell (52). No data are currently available about a potential role of this parvovirus in respiratory disease in calves.

ADV causes an acute interstitial pneumonia in newborn mink kits, which often develop a fatal respiratory distress syndrome (53). The pathology is characterized by hypertrophy and hyperplasia of alveolar type II epithelial cells, and the occurrence of intra-nuclear viral inclusions in these cells. Using in situ hybridation (ISH), Viuff et al. showed that ADV replicates to a high level in 2% of the total lung cells. The morphology and distribution of the infected cells resemble alveolar type II cells, as demonstrated by double ISH with specific markers. ADV-positive cells rarely concern another cell type (54).

Concerning Parvovirus B19, the other parvovirus able to infect humans, few data are currently available about its potential tropism for the lung (55,56). The cellular receptor of Parvovirus B19 has been already identified as the P antigen present on red blood cell line.

REMAINING QUESTIONS ABOUT THE HUMAN BOCAVIRUS

While Koch's postulates remain the standard for establishing a causal link between a pathogen and a disease, recent reviews on emerging viruses suggest that a causal relationship can also be supported by accumulation of evidences (11,57): 1. The presence of the organism in diseased tissues, 2. The development of a specific immunity, 3. The consistent association of the organism with a particular disease or group of diseases.

Is Human Bocavirus a cause of respiratory disease following these criteria?

1. The detection of HBoV in lung has not yet been realised and would be only interesting if at the same time the infected cell type is determined. The presence of parvovirus-like particles was described only once in high-titered respiratory samples. 2. The presence of anti-HBoV specific antibodies in the serum has been recently determined, showing a seroprevalence of 71% in a Japanese population from 0 to 41 years. 3. Despite the frequent detection of HBoV in the population over time and on all continents, no formal proof of the pathogenic role has been obtained until now.

The puzzling question of mixed infections should be solved in some way. One way out would be to quantify the co-infecting virus genomes. This may more clearly indicate the predominant and perhaps causal virus. Furthermore the co-infecting virus could trigger cellular division, giving HBoV target cells in S phase, necessary for its own replication.

HBoV has primarily been found in respiratory samples. Afterwards HBoV has also been detected in stools, urine and serum. The exact virus target thus remains elusive, and may be even more complex as the site of acute viral replication could differ from a potential site of persistence. Other techniques than PCR have to be used to determine tissue and cells tropism of HBoV. Due to the present lack of antibody tests, of a cellular model or animal model, *in situ* hybridisation could be a way to consider.

The first infection of HBoV occurs very early in life, as shown in the sero-epidemiological data and by the high rate of detection of HBoV genome in children. However, the characteristics of the target-population should better be clarified concerning the adults or the immune deficient population.

Many other questions remain unsolved concerning the meaning of viral genome detection in humans. But, because of its strong presence in the community, the Human Bocavirus will probably remain a subject of interest in the medical and research fields for the years to come.

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ABSTRACT

Le Bocavirus Humain est un nouveau membre des parvovirus, découvert récemment. Ce virus est le quatrième virus le plus fréquemment détecté dans les échantillons respiratoires d'enfants symptomatiques.

Le Bocavirus Humain est présent sur tous les continents et cause très probablement une infection respiratoire symptomatique, bien que les postulats de Koch ne soient pas tous remplis.

Dans cet article, nous résumons les principales informations cliniques sur ce virus, deux ans après sa découverte, et discutons certaines hypothèses à propos de son tropisme pour le poumon chez les jeunes enfants.

ABSTRACT

Het humaan Bocavirus is een recent ontdekt parvovirus. Het is het vierde meest frequente virus in respiratoire monsters bij symptomatische kinderen. Het humaan Bocavirus wordt wereldwijd teruggevonden en is heel waarschijnlijk de oorzaak van symptomatische respiratoire infecties, hoewel de postulaten van Koch niet alle vervuld zijn.

In dit artikel willen wij een overzicht geven van de belangrijkste klinische informatie over dit virus twee jaar na zijn ontdekking. Wij bespreken tevens enkele hypothesen in verband met zijn bijzonder tropisme voor de long bij jonge kinderen.

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