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Review

Human Bocavirus: Understanding its role as a respiratory pathogen

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A new virus was discovered by molecular techniques in respiratory samples collected from young children with respiratory diseases in Sweden in 2005. The virus, named human bocavirus, is genetically related to the bovine parvovirus and the canine minute virus, both of which belong to the bocavirus genus of the parvoviridae family. Recent studies conducted in different countries have shown that HBoV is found in 1.5 - 19% of children with respiratory diseases. HBoV has been observed to be associated with a broad spectrum of both upper and lower respiratory tract diseases, more frequently related to lower respiratory diseases, one third of which is pneumonia. HBoV infection is of worldwide distribution, and a seasonal distribution with a peak in winter and spring is suspected. There is increasing evidence that HBoV is pathogenic for the human respiratory tract, especially in infants and young children, and HBoV has been detected from patients with gastroenteritis. However, given the frequent co-infection with bacterial or viral pathogens, the exact role played by this virus in human diseases still remains disputable. Further investigations, including population- based studies with controlled subjects, are needed to prove its pathogenic potential and epidemiologic patterns.

Key words: Respiratory virus, human bocavirus, parvovirus; HBoV; respiratory infection, children

INTRODUCTION

Acute respiratory tract infections (ARTI) are among the leading killers of children under 5 years of age, resulting in around 1.9 million of deaths worldwide annually (Williams et al., 2002). Viruses account for the largest number of respiratory infections. The respiratory viruses include rhinoviruses, respiratory syncytial virus (RSV), influenza virus, adenoviruses, parainfluenza viruses, and coronaviruses. However, there are still a certain pro-portion of ARTI patients from whom no specific patho-gens can be detected even using modern laboratory methods (Manning et al., 2006; Allander et al., 2007) . In recent years, using new technology, several "novel" vi-ruses have been discovered in patients with respiratory infections, including the human metapneumovirus and several coronaviruses (SARS, NL63, HKU1) (Fouchier et al., 2005; van der Hoek et al., 2005; Woo et al., 2005). Human bocavirus (HBoV), the second parvovirus poten-tially pathogenic to human after parvovirus B19 (Young et al., 2004), was discovered by molecular technique in res-piratory samples collected from young children with respiratory diseases in Sweden in 2005 (Allander et al., 2005). Since the first description of HBoV as a possible human pathogen of lower respiratory tract infections in children (Allander et al., 2005), HBoV has been detected in at least 19 countries in the five continents of Africa, America, Asia, Europe and Oceania

Sources and selection criteria

We searched Medline, Embase, the Cochrane Collabo-ration and the ISI Web of Knowledge from 2000 onwards by using the key words of "human bocavirus" or "parvo-virus" or "respiratory infections". We searched the same databases before that date, focusing on "bocavirus" only. We selected all the articles on bocavirus from abstracts and hand-searched these for other pertinent publications.

Identification and taxonomy of HBoV

Virus infections impose an enormous disease burden on humanity, but most studies are limited to investigation of already known viruses, whereas the discovery of an un-known virus remains a rare occurrence (Allander et al., 2005; van den Hoogen et al., 2001; Pyrc et al., 2007). Allander et al. (2001) have developed a method of screening for unknown viral sequences based on DNase treatment of specimens, followed by nucleic acid extrac-tion, restriction enzyme digestion, sequence-independent

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Table 1. Frequency of human bocavirus in children with respiratory tract infections in selected countries.

Countries	Target diseases*	No. of subjects	Positives (%)	Coinfections (%)	References
Sweden	LRTI	540	17(3·1)	3 (17·6)	Allander et al., 2005
Australia	ARTI	315	15(4·8)	10(66·7)	Arden et al., 2006
Canada	ARTI	1209	18(1·5)	ND	Bastien et al., 2006
China	ARTI	319	13(4·1)	ND	Zhao et al., 2006
Finland	Acute wheezing	259	49(19)	37(75.5)	Allander et al., 2007
France	ARTI	262	9(3·4)	3(33·3)	Foulongne et al., 2006
Germany	ARTI	835	87(10·3)	34(39·1)	Weissbrich et al., 2006
Iran	ARTI	261	21(8.0)	7(33.3)	Naghipour et al., 2006
Italy	ARD:	200	9(4.5)	4(44.4)	Maggi et al., 2007
Japan	LRTI	318	18(5·7)	ND	Ma et al., 2006
Jordan	ARTI	312	57(18·3)	41(72)	Kaplan et al., 2006
Korea	LRTI	515	58(11·3)	22(37·9)	Choi et al., 2006
Netherland	Febrile	245	4(1.6)	3(75%	Monteny et al., 2007
South Africa	ARTI	341	38(11)	14(37)	Smuts et al., 2006
Spain	ARTI Gastroenteritis	520 527	40(7.7) 48(9.1)	25(62.5) 28(58.3)	Vicente et al., 2007
Switzerland	ARTI	112	5(4·5)	4(80)	Regamey et al., 2007
Thailand	Pneumonia	1178	53(4·5)	ND	Lu et al., 2006
United Kingdom	ARTI	574	47(8·2)[+]	23(43)[+]	Manning et al., 2006
USA	ARTI	1474	82(5·6)	10(12·2)	Kesebir et al., 2006

*LRTI: lower respiratory tract infection; ARTI: acute respiratory tract infection; ARD: acute respiratory disease. [+]A total of 924 samples collected from 574 patients were detected with 53 samples positive, and the co-infection rate was calculated based on positive samples. ND: no data available for co-infection.

independent single primer amplification (SISPA) of the restriction fragments and finally sequencing and subsequent blasting of the amplified products. HBoV was successfully cloned from pooled clinical samples from hospitalized children with lower respiratory tract infection, using this screening method (Allander et al., 2005).

HBoV is most closely related to the minute virus of canines (MVC) and the Bovine Parvovirus (BPV), which have been classified in the genus *Bocavirus* within the family *Parvoviridae* (Tattersall et al., 2005). Like BPV and MCV, HBoV has two major ORFs encoding a nonstructural protein (NS1) and at least two capsid proteins (VP1 and VP2) and a third middle ORF that encodes a product having 47% amino acid identity to NP1 of MCV and BPV. However, HBoV has only 43 and 42% amino acid identity to the nearest neighbours MCV and BPV in both major ORFs, respectively. Therefore, HBoV is designated as a new member of the genus *Bocavirus*, subfamily *Parvovirinae*, family *Parvoviridae* (Allander et al., 2005). Up to now, all the bocaviruses detected in different countries shared a very high sequence similarity, indicating HBoV is a highly conserved virus. However, variations in the HBoV NP1 gene were demonstrated in recent studies (Kaplan et al., 2006; Kesebir et al., 2006) . It was further demonstrated by phylogenetic analysis of complete coding sequences that the NS1 and NP1 genes of HBoV are conserved, whereas VP1 and VP2 show certain variations (Chieochansin et al., 2007).

Clinical features of HBoV infections

Clinical symptoms and disease spectrum of HBoV infections

HBoV infections showed a variety of clinical symptoms. Arnold et al. (2006) reported that the most common symptoms among 54 HBoV-infected children without co-infections were cough (85%), followed by rinorrhea (67%), fever (59%), difficulty in breathing (48%), diarrhea (16%), conjunctivitis (9%) and rash (9%) . All of the 18 HBoV-infected children reported by Ma et al. (2006) suffered from fever, cough and various degrees of respiratory distress, with body temperature ranging from 37.5 to 40.2^{o}C and 50% of the children having temperature above 39^{o}C, while Foulongne et al. (2006) reported that all the children infected with HBoV had mild-to-moderate fevers (37.3 - 38.5^{o}C). Kesebir et al. (2006) reported that wheezing were present in more than 50% of the children infected with HBoV. Arnold et al. (2006) reported that 19% of the patients with cough, described as having "paroxysmal" cough, were also suspected of suffering from prussic. Nausea, sore throat, headache and myalgia were also recorded in HBoV-infected children of older age and adults (Bastien et al., 2006; Naghipour et al., 2007; Weiss

Table 2. Clinical diseases related to HBoV in children in selected countries.

Diagnosis	Canada†	China¶	France‡	Germany†	Japan¶	Korea†	USA†
URTD*	21(36)#	3 (23)	4(15)	13(33)	1(6)		13(24)
LRTD**	36(62)	10(77)	15 (58)	24(60)	16(89)	29(81)	27(50)
Bronchitis		2(15)		7(18)	3(17)		
WB***		1(8)		5(13)	6(33)		
Bronchiolitis	23(40)	5(39)	12(46)	2(5)	1(6)	9(25)	14(26)
Pneumonia	13(22)	2(15)	3(12)	10(25)	6(33)	20(56)	13(24)
Asthma			7(27)		1(6)	4(11)	13(24)
Febrile seizures				3(8)			
Croup	1(2)					3(8)	
Other							1(2)
Total	58(100)	13(100)	26(100)	40(100)	18(100)	36(100)	54(100)

† HBoV infected patients without co-infection; ¶ HBoV infected patients with no record of co-infection; ‡ HBoV infected patients with co-infection; *URTD: upper respiratory tract disease; **LRTD: lower respiratory tract disease; ***WB: Wheezing bronchitis; # Number of patients with percent in parenthesis

brich et al., 2006).

In the first report of HBoV, the virus DNA was detected in 3.1% of 540 Swedish children with lower respiratory tract disease (Allander et al., 2005) . Based on the data available, it seems that there is no obvious association between HBoV infection and a distinct clinical manifestation. Instead, its association with a broad spectrum of both upper and lower respiratory tract diseases (URTD and LRTD) was observed, being more frequently related to lower respiratory diseases.

Table 2 summarizes the clinical diagnosis of HBoV infections reported in selected countries (Bastien et al., 2006; Zhao et al., 2006; Foulongne et al., 2006; Weissbrich et al., 2006; Ma et al., 2006; Choi et al., 2006; Arnold et al., 2006). Of the URTDs, rhinitis, otitis media, tonsillitis, pharyngitis, laryngotracheitis and apnoic spells were observed. Out of the LRTDs caused by HBoV, more than one third received a clinical diagnosis of pneumonia, followed by bronchiolitis, bronchitis and wheezing bronchitis. In addition to URTDs and LRTDs, asthma, acute respiratory distress and croup were also recorded in patients with HBoV infections.

Diarrhea is also a common symptom in some children infected with HBoV. Arnold et al. (2006) reported 16% of the children infected with HBoV without co-infection had diarrhea. Kesebir et al. (2006) reported that 5 of the 20 only-HBoV infected children had diarrhea and 3 of these children were ultimately diagnosed as having "viral gastroenteritis". Maggi et al. (2007) detected HBoV from stools of a 6-month- old child with bronchopneumonia and diarrhea. Recently, Vicente et al. (2007) reported that HBoV was detected in 9.1% of children under 3 years of age with gastroenteritis, with or without respiratory symptoms, in Spain, and a much lower prevalence rate (0.8%) of HBoV in children with gastroenteritis was reported in Korea (Lee et al., 2007).

Laboratory and radiography findings

Based on the limited laboratory data available for HBoV infections, the WBC count in patients with HBoV infections was 3000 - 31000 cells/mm^3, with a median count of 13300 cells/mm^3, and the median neutrophil, band, lymphocyte and monocytes percentage were 40, 10, 39 and 10%, respectively, without notable abnormal findings in routine chemistry panels (Foulongne et al., 2006; Arnold et al., 2006).

The findings of chest X-ray varied in different reports. In the first description of HBoV, Allander et al. (2005) recorded pathological chest X-ray of interstitial bilateral infiltrates in 86% (6/7) of cases. Arnold et al. (2006) reported that 66% of the 48 HBoV-infected patients without co-infection had pathological findings, with 10% showing a focal infiltrate and 56% having findings consistent with bronchiolitis or other presumed viral lower respiratory tract involvement. Bastien et al. (2007) reported that 84.4% of the 45 patients, who were positive for HBoV but negative for influenza viruses, parainfluenza virus, adenovirus and respiratory syncitial virus, showed pathological radiography of atelectasis (35.6%), hyperinflation (24.4%), perihilar thickening (22.2%), patchy consolidation (17.8%), lobar consolidation (11.1%), peribronchial thickening (6.67%) and pleural effusion (2.2%). Ma et al. (2005) reported that the pathological radiography of HBoV infection included peribronchial, monolateral and bilateral infiltration and hyperinflation, but only 44.4% (8/18) of the patients showed such pathological damage on radiography.

Epidemiology of HBoV infections

In the two years since the first identification of HBoV, the virus has been detected in Asia (Choi et al., 2006; Lu et

al., 2007; Ma et al., 2006; Qu et al., 2006), Europe (Allander et al., 2005; Foulongne et al., 2006; Weissbrich et al., 2006; Maggi et al., 2007; Regamey et al., 2007; Manning et al., 2006), the Americas (Bastien et al., 2006; Arnold et al., 2006), Africa (Smuts et al., 2006), Middle East (Kaplan et al., 2006; Naghipour et al., 2007), and Australia (Sloots et al., 2006; Arden et al., 2006), indicating a worldwide distribution of HBoV infections.

The age distribution of HBoV-infected humans ranged from 10 days to 60 years (Bastien et al., 2006; Manning et al., 2006), but HBoV was primarily detected in young children aged 6 months to 3 years. Arnold et al. (2006) reported that 63% of patients with HBoV infection were aged 12 months. It is indicated that a peak detection of HBoV was among children of 6 to 24 months of age. In the report by Zhao et al. (2006) in China, there was no detection of HBoV infections among children younger than 5 months. Similarly, in Korea, a sharp increase of HBoV infection was observed among children older than 3 months (Chung et al., 2006). Maternal antibodies may play a role in protection of infants younger than 6 months from HBoV infections. A recent seroepidemiology study showed the lowest seropositive rate for HBoV antibody in the age group of 6 to 8 months and a gradual increase with age (Endo et al., 2007), which provides further evidence that young children aged 6 to 24 months are the most sensitive population to HBoV infection.

The available data indicated a male to female (M:F) predominance sex distribution of HBoV infections, but the M:F ratio varied among different studies. The M:F ratios were 1.5 to 1.9:1 in Canada, France and Germany (Bastien et al., 2006; Foulongne et al., 2006; Weiss rich et al., 2006), and 2.5 to 2.8:1 in Sweden, Japan and Korea (Allander et al., 2005; Chung et al., 2006; Ma et al., 2006), while the M:F ratio was only 1.04:1 in Jordan (Kaplan et al., 2006). More males than females require hospitalization for respiratory tract disease and may thus be one explanation for the male predominance of HBoV infection. Whether HBoV infection *per se* is more frequent in males than in females needs further investigation from population-based studies. Globally, infections with HBoV could be found year-round, but the seasonal patterns varied in different coun- tries, where seasonality was demonstrated. Most of HBoV infections occurred in the winter and early spring months in France (Foulongne et al., 2006), Germany (Weissbrich et al., 2006), Sweden (Allander et al., 2005) and USA (Arnold et al., 2006), whereas most of the cases in Korea occurred in late spring and early summer months (Choi et al., 2006), and no apparent seasonal prevalence was observed in Canada (Bastien et al., 2006). More population-based data are needed to understand the seasonal patterns of HBoV infection.

Etiological consideration of HBoV as a human pathogen

The assumption in the initial description of HBoV, that this virus might be an etiologic agent of respiratory tract disease, was based on the fact that HBoV infections were found significantly more often in samples negative for other respiratory viruses (Allander et al., 2005). In a second report, HBoV was detected in 5.6% of respiratory samples in Australian children and adults (Sloots et al., 2006) . In a third study in Japan, HBoV DNA was found in 5.7% of respiratory specimens of children with lower respiratory tract disease (Ma et al., 2006). An even higher prevalence rate (>10%) of HBoV infection was also reported in patients with respiratory infection in Germany (Weissbrich et al., 2006), Jordan (Kaplan et al., 2006), Korea (Choi et al., 2006) and Finland (Allander et al., 2007) . Recently, HBoV was reported being detected in 9.1% of children with gastroenteritis (Vicente et al., 2007). The high frequency of HBoV detection in the feces of children with gastroenteritis and the absence of other intestinal pathogens suggests that HBoV is an enteric, as well as a respiratory pathogen.

However, whether or not HBoV is really a human pathogen remains to be further investigated. Firstly, a large proportion of cases with evidence of co-infection were demonstrated in different investigations (Table 1). In an Australian study (Arden et al., 2006), HBoV was detected with other potential respiratory pathogens in 66.7% of patients, and even higher co-infection rates were recorded in Jordan (Kaplan et al., 2006), Finland (Allander et al., 2007) and Switzerland (Regamey et al., 2006). In Spain, the co-infection of HBoV with other pathogens was 62.5% for respiratory infections and 58.3% for gastroenteritis (Vicente et al., 2007). In Hong Kong, co-detection with other pathogens occurred in 33% and 56% of nasopharyngeal aspirates and fecal samples from patients < 18 years old (Lau et al., 2007). In the studies in Canada (Bastien et al., 2006), China (Zhao et al., 2006) and Japan (Ma et al., 2006), where no co-infections were recorded, exclusion of specimens positive for other respiratory viruses made it impossible to analyse the co-infection rates. There was no report of detection of other respiratory viruses in the study in Thailand (Liu et al., 2006) . Secondly, it appeared that most of the investigations up to the present time were hospital-based retrospective studies, and the prevalence of HBoV infections in healthy populations remains unclear. Thirdly, HBoV has not been propagated in cell culture, and there is no animal model thus far (Weissbrich et al., 2006). Therefore, more evidence is required to establish etiological association between HBoV and respiratory or intestinal tract infections.

Recent studies have cast new light on the pathogenicity of HBoV. Maggi et al. (2007) reported that HBoV was detected in 4.5% of children with respiratory diseases, while all the healthy infants were negative for HBoV. In another hospital-based controlled retrospective study, the positive rate for HBoV was 5.2% in children with respiretory infection and no HBoV was detected in asympomatic children (Kesebir et al., 2006). In a controlled stu-

dy using hospitalized patients with pneumonia, identified through active population-based surveillance, Fry et al. (2007) demonstrated that the risk of HBoV infection was 4 times higher among patients with pneumonia than among control patients, providing the first clear association between HBoV infection and pneumonia requiring hospitalization. Allander et al. (2007) reported that HBoV was found significantly more frequently among children with acute wheezing than among asymptomatic children and it was more prevalent among children with symptoms of an otherwise unexplained etiology than among those in which other viruses were detected. They further demonstrated that the presence of HBoV at high-but not at low-viral load is associated with previously unexplained acute wheezing, suggesting an etiological role of HBoV at high viral load and a possible asymptomatic shedding role at low viral load. Nevertheless, the comparison between symptomatic and asymptomatic individuals should not be exaggerated, because the control subjects were not randomly selected and not age-, sex- and time-controlled in most of the controlled studies. The high prevalence of co-infection may result in a higher prevalence among symptomatic patients than among control subjects and the different respiratory secretion of symptomatic and asymptomatic subjects may also affect the detection of HBoV.

On the basis of these considerations, although HBoV has been detected widely in patients with respiratory tract infections, it is possible that HBoV is an aggravating factor of respiratory diseases, an innocent bystander just detected by chance, or a persisting virus that is reactivated by the inflammatory process (Weissbrich et al., 2006). However, there is increasing evidence for HBoV pathogen genicity from controlled studies (Maggi et al., 2007; Kesebir et al., 2006; Fry et al., 2007; Allander et al., 2007), and the detection of HBoV from serum (Allander et al., 2007), which suggests that HBoV is a systemic infection, provides further evidence for its pathogenicity. More investigations are needed to fulfill the epidemiological criteria of the disease causation or molecular diagnostic criteria for causality proposed by Fredricks and Rel-man (1996), to establish the etiologic association of HBoV with respiratory tract diseases or other human diseases.

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