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Detection of Human Bocavirus in Respiratory Tract Specimens

Solunum Yolu Örneklerinde İnsan Bocavirüs Tespiti

Yeliz Tanrıverdi Çaycı, Elif Ateş, Demet Gür Vural, Kemal Bilgin, Asuman Birinci

Ondokuz Mayıs University, Faculty of Medicine, Department of Medical Microbiology, Samsun, Türkiye

ORCID ID: Yeliz Tanrıverdi Çaycı: https://orcid.org/0000-0002-9251-1953, Elif Ateş: https://orcid.org/0009-0002-4270-4850
Demet Gür Vural: https://orcid.org/0000-0003-2974-6589, Kemal Bilgin: https://orcid.org/0000-0002-8892-2223,
Asuman Birinci: https://orcid.org/0000-0002-8653-4710

***Sorumlu Yazar / Corresponding Author:** Yeliz Tanrıverdi Çaycı, **e-posta / e-mail:** yeliztanriverdi@gmail.com

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Abstract

Aim The aim of this study was to retrospectively examine the patients who presented with the complaints of respiratory tract infection and were found to have Human bocavirus (HBoV) in the samples studied with the respiratory tract pathogens panel.

Material and Method We retrospectively analyzed patients of all age groups who were diagnosed with HBoV by PCR in the respiratory tract pathogens panel between January 2021 and November 2022.

Results Between January 2021 and November 2022, 36 patients with HBoV DNA detected by PCR in nasopharyngeal swab samples taken from a total of 989 patients were examined. Of 989 patients, 557 were male and 432 were female (male/female 1.28). The median age of HBoV positive patients was 2.3. According to age groups, 1-2 age years-old showed the highest prevalence. In patients with positive HBoV DNA, the most common symptom was cough (77.7%) and catarrh (69.4%). HBoV was detected alone in 15 (41.7%) patients and together with other viruses in 21 (58.3%) patients in total. Rhinovirus/Enterovirus was found to be the most common co-pathogen.

Conclusion Patients positive for HBoV exhibited few respiratory symptoms as a result of single or co-pathogenicity, confirming its role in respiratory diseases. However, it is difficult to say that HBoV is the primary responsible pathogen in respiratory tract infections.

Keywords *Acute respiratory infection, children, human bocavirus, respiratory tract pathogens.*

Özet

Amaç *Solunum yolu enfeksiyonu şikâyetiyle gelen ve solunum yolu patojenleri paneli ile çalışılan örneklerde Human bocavirus (HBoV) saptanan hastaların retrospektif olarak incelenmesi*

Gereç ve Yöntem *Ocak 2021-Kasım 2022 tarihleri arasında solunum yolu patojenleri panelinde PCR yöntemi ile HBoV saptanan tüm yaş grubundaki hastaları geriye dönük olarak inceledik.*

Bulgular *Ocak 2021-Kasım 2022 tarihleri arasında toplam 989 hastadan alınan nazofaringeal sürüntü örneklerinde PCR ile HBoV DNA saptanan 36 hasta incelendi. Toplamda 989 hastanın 557'si erkek, 432'si kadındı (erkek/kadın1,28). HBoV pozitif hastaların medyan yaşı 2,3 idi. Yaş gruplarına göre 1-2 yaş en yüksek prevalansı göstermiştir. HBoV DNA'sı pozitif olan hastalarda en yüksek semptom öksürük (%77,7) ve nezle (%69,4) idi. HBoV 15 (%41,7) hastada tek başına, 21 (%58,3) hastada diğer virüslerle birlikte saptandı. Rhinovirus/enterovirus en yaygın ko-patojen olarak bulundu.*

Sonuç *HBoV için pozitif olan hastalar, tek veya ko-patojenitenin bir sonucu olarak, solunum yolu hastalıklarındaki rolünü doğrulayan birkaç solunum semptomu sergiledi. Bununla birlikte solunum yolu enfeksiyonlarında HBoV 'nin birincil sorumlu patojen olduğunu söylemek güçtür.*

Anahtar Kelimeler *Akut solunum yolu enfeksiyonu, çocuklar, human bocavirus, solunum yolu patojenleri.*

INTRODUCTION

Acute respiratory tract infections are among the most important causes of childhood mortality and morbidity. Although influenza viruses, parainfluenza viruses, respiratory syncytial virus (RSV), picornaviruses (rhinovirus or enteroviruses), adenoviruses and coronoviruses are the most common viruses causing respiratory tract infections, pathogenic microorganisms cannot be identified in some of these infections.[1,2] With the development of molecular methods, new viruses such as Human bocavirus (HBoV), Human metapneumovirus (HMPV), Human coronaviruses (HCoV-NL63, HCoV-HKU1, HCoV-OC43, HCoV-229E) have also been detected in respiratory tract specimens. The worldwide estimate of the total prevalence of HBoV in respiratory tract infections is 6.3%. The presence of co-pathogen rate in people with respiratory tract infection and HBoV positivity is between 8.3-100%.[3,4]

HBoV belongs to the Parvoviridae family, the Parvovirinae subfamily, and the Bocavirus genus. HBoV is a non-enveloped DNA virus with an icosahedral capsid, a 5.5 kb linear and single-stranded genome. In addition, HBoV subdivided into 4 genotypes. HBoV1 is predominantly found in the respiratory tract and often in association with another pathogenic viruses.[5,6] HBoV1 has been associated with upper respiratory tract infections and lower respiratory tract infections, wheezing, bronchiolitis, and pneumonia. HBoV2-4 is mainly found in stool samples from patients with gastroenteritis.[6-8]

In this study, our aim is to determine the frequency of HBoV in patients of all age groups admitted to the hospital with respiratory tract infection complaints and to describe the clinical features of infected patients.

MATERIALS and METHODS

Nasopharyngeal swab samples were taken from 989 patients who applied to Ondokuz Mayıs University Hospital with complaints of respiratory tract infections such as fever, cough, wheezing, dyspnea and nasal congestion between January 2021 and November 2022 and developed one or more of these symptoms. Swab samples were taken throughout the year, but especially in November, December, January, February, due to more severe symptoms. These swab samples were studied using Multiplex Real Time PCR to determine the causative pathogen. Qiastat-Dx (Qiagen, Germany) Respiratory SARS-CoV-2 Panel, which can detect 22 pathogens (SARS-CoV-2, influenza A, influenza A subtype H1N1/2009, influenza A subtype H1, influenza A subtype H3, influenza B, coronavirus 229E, coronavirus HKU1, coronavirus NL63, coronavirus OC43, parainfluenza virus 1, parainfluenza virus 2, parainfluenza virus 3, parainfluenza virus 4, RSV A/B, HMPV A/B, adenovirus, HBoV, rhinovirus/ enterovirus, Mycoplasma pneumoniae, Legionella pneumophilia and Bordetella pertussis), was used for PCR. The Qiastat-Dx Respiratory SARS-CoV-2 Panel cannot differentiate between rhinovirus/enterovirus. The swab samples taken were added to the transport medium (Universal Transport Medium, UTM), delivered to the laboratory within one hour, and most of the samples were studied within two hours. For the test, 300 µl of was taken from the transport medium and placed in the main port of the Qiastat-Dx Respiratory SARS-CoV-2 Panel Cartridge. No different buffer solution was used during the transfer of the sample to the device. The test was started by placing the Qiastat-Dx Respiratory SARS-CoV-2 Panel Cartridge into the QIAstat-Dx Analyzer 1.0. Extraction, amplification and analysis of nucleic acids in the sample detection was performed automatically by the QIAstat-Dx Analyzer 1.0.

The Qiastat-Dx Respiratory SARS-CoV-2 Panel detects HBoV DNA and however a universal primer was used for HBoV1-4, it was not possible to distinguish between different subtypes of HBoV, which is a limitation of our study.

Statistical Analysis

Comparative statistical analyzes were used in HBoV positive and negative patient groups. Categorical variables were expressed as age and percentage of numbers, and

continuous variables as median and range. All data analyzes were performed using SPSS+ statistics calculation program version 21.

RESULTS

The study included 986 patients whose nasopharyngeal swab samples were sent to the microbiology laboratory to be studied with a respiratory panel between January 2021 and November 2022. The age distrution of the patienst was 0-87 years. Of 989 patients, 557 were male and 432 were female (male/female 1.28). In total, 36 (3.6%) of 989 patients were found to be positive for HBoV DNA positive, and 26 (72.2%) of them were male. The presence of complaints such as cough, wheezing, dyspnea, fever, nasal congestion, catarrh and their diagnosis were bronchiolitis, and bronchopneumonia were investigatig through hospital information system. Table 1. showed details of the patients. Considering the age groups, one-two years -olds showed the highest prevalence.

Table 1. Characteristics of the patients

Variable	Category	Frequency	Male/ Positive	Female/ Positive	Total positive HBoV
Age	0-1 year	211	121/4	90/1	5
	1-2 years	92	52/7	40/4	11
	2-3 years	71	40/6	31/2	8
	3-4 years	60	35/2	25/1	3
	4-5 years	54	32/2	22/0	2
	5-18 years	350	204/5	146/1	6
	>18 years	151	73/0	78/1	1
Total		989	557/26	432/10	36

The median age of HBoV positive patients was 2.3 years-old. Cough was the most common symptom and followed by catarrh in patients who was positive for HBoV (Table 2).

Table 2. Frequency of symptoms among HBoV-positive children

Symptom	Frequency
Cough	28
Catarrh	25
Dyspnea	16
Nasal congestion	15
Wheeze	15
Fever	14
Vomiting	2

In addition, according to clinical data, 11 (30.5%) of 36 patients were diagnosed with pneumonia and nine (25.0%) were diagnosed with bronchiolitis. While only HBoV was detected in 15 of 36 (41.7%) patients, other factors were detected together with HBoV in 21 (58.3%) patients. The most common co-pathogens were with rhinovirus/enterovirus, SARS-CoV-2 and RSV (Figure 1.).

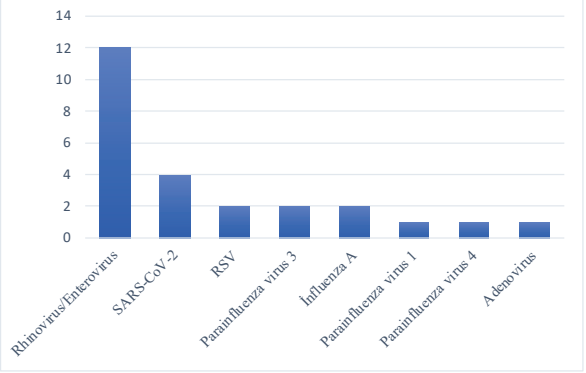

Figure 1. Viruses determined with HBoV.

Five rhinovirus/enterovirus, four SARS-CoV-2, one parainfluenza virus 3, one parainfluenza virus 4, one influenza A were found in eight pneumonıa cases in which HBoV was detected as a co-pathogen. Three rhinovirus/enterovirus and one influenza A were detected in four bronchiolitis cases with HBoV as co-pathogen. No co-pathogenicity of HBoV with bacteria or fungi was seen. When the distribution of HBoV positivity was examined by months, the highest positivity was seen in October, and the least in May and Jun (Figure 2.).

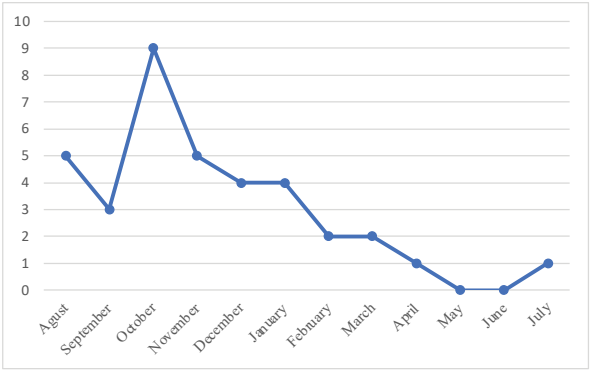

Figure 2. Distribution of HBoV positivity by months

DISCUSSION

HBoV, first identified in respiratory samples of Swedish children with lower respiratory tract infections, is increasingly associated with acute respiratory tract infection of unknown etiology, especially in young children. HBoV is detected more frequently in young children (<2 years) compared to older children and adults.[7,9,10]

Respiratory diseases such as colds, asthma, wheezing, bronchiolitis, pneumonia have been reported in many studies in connection with HBoV. It is not possible to clinically distinguish respiratory tract infections caused by different viruses or even bacteria such as rhinovirus, RSV, influenza virus and HBoV. In a recent study, respiratory tract infection symptoms seen in HBoV positive children in nasopharyngeal swap were most commonly cough (79%) followed by fever (67%) runny nose (66%).11-13 In a study by Joseph et al.[14] in Nigeria, they reported that the most common symptoms in children with HBoV were cough (100%), catarrh (100%) and nasal congestion (59.2%). In our study, cough (77.7%), catarrh (69.4%) and dyspnea (44.4%) were observed most frequently. In a study by Petrarca et al.[15], 34 (56.6%) of 60 HBoV positive patients had bronchiolitis and three (5%) had pneumonia; reported that HBoV alone was detected in 13 (38.2%) patients with bronchiolitis and in all patients with pneumonia. In our study, we found that 14 of 36 HBoV positive patients (38.8%) had pneumonia, nine (25%) had bronchiolitis, and five of nine patients with bronchiolitis and six of 14 patients with pneumonia had HBoV as a single pathogen. For HBoV positive patients, a more detailed anamnesis and examination will be useful to define clinical symptoms of HBoV and to better recognize HBoV.

In the study conducted by Ljubin-Sternak et al.16 in two different hospitals in Croatia, 957 respiratory tract samples taken from children aged 0-18 years who applied with the complaint of respiratory tract infection between May 2017 and March 2021 were examined. They reported that HBoV was detected in 73 (7.6%) of 957 children, 13 (17.8%) of them were found to be a single pathogen, and 60 (82.2%) were associated with one or more respiratory tract viruses. It was also stated that the most common accompanying virus was rhinovirus (35.8%). They also reported that the male: female ratio of HBoV positive patients was 41:32 (1.28:1) and the median age of HBoV positive patients was 1.36. They found that the highest rate (61.6%) according to age groups belonged to the 1-2.99 age group. In the study conducted by Madi et al.[17] in respiratory samples of 5941 patients with respiratory tract infection symptoms, HBoV was detected in 111/5941 (1.9%) samples. They stated that 59 (53.2%) of HBoV positive patients were male, 52 (46.8%) were female, and the median age was 1 year. While HBoV alone was detected in 48 (43.%) of 111 HBoV positive patients, it was found together with another virus in the remaining 63 (56.8%); reported that the most common association was with RSV (10.8%) and rhinovirus (9.9%). In the study conducted by Uyar et al.[18] with 95 patients, they detected HBoV in three (3.1%) people and it was reported that one of these three people was a single pathogen. Similar to these studies, in our study, the copatogenicity rate was found to be higher than the single detection of HBoV; rhinovirus/enterovirus (57.1%) was foundto be the most common virus accompanying HBoV. The male: female ratio of HBoV positive patients was 2.6. Similar to most studies, we observed more positivity in males. In our study, the HBoV positivity rate was found 3.6% for the whole age group and 4.17% for those under the age of[18]. In

addition, the median age ratio (2.3) was found to be higher in our study than these studies. The differences in HBoV positivity can be explained by the different study patterns and the age of the study group. While these studies covered the younger age group, this study was carried out on patients of all age groups.

Any seasonal distribution for HBoV is controversial as it varies by geographic region. Some studies reported that HBoV infections occurred with a high prevalence in winter and spring, some studies showed a higher prevalence in late spring and early summer, and some studies reported that no significant seasonal activity was observed.[15,19,20] In our study, it was seen that the distribution of HBoV intensifies in autumn. The differences with the seasonal distribution of HBoV are likely due to the different populations involved in the studies and different geographic regions.

It is difficult to prove the clinical significance and pathogenicity of HBoV due to its high co-pathogen ratio and to say that HBoV is the primary factor in infected patients. It can be said that HBoV is a factor that exacerbates respiratory diseases.[6,19] Although many studies have confirmed the severity of infection with HBoV positivity, some studies have not found a clear association between HBoV infection and different clinical manifestations.9 However, the frequency of HBoV detection in symptomatic patients is higher than in healthy controls.[21]

Studies have shown that the presence of HBoV continues for up to six months in nasopharyngeal samples taken from healthy asymptomatic children.[22] Therefore, newly acquired infection is not the only cause of HBoV DNA detection in the respiratory tract. It should also be considered that HBoV may remain latent in the respiratory tract. A positive PCR result for HBoV should be interpreted together with clinical symptoms.[9,22]

The first infection of HBoV occurs very early in life, as seen in epidemiological studies. There are few systematic studies involving adults, but studies show a very low prevalence of viruses in the respiratory tract of adults by PCR. More research is needed in adults and immunosuppressed individuals.[23,24]

Our retrospective study had some limitations; there were no healthy controls in the study and viral load could not be determined in the nasalopharyngeal specimens. Patients positive for HBoV exhibited few respiratory symptoms as a result of single or co-pathogenicity, confirming its role in respiratory diseases. However, it is difficult to say that HBoV is the primary responsible pathogen in respiratory tract infections. Although there is increasing evidence for the role of HBoV in respiratory infections, more studies are needed to fully understand the relationship between its pathogenicity and infection severity.

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None to declare.

Ethical Approval

Ethics Committee Approval: The study was approved by the Medical Ethics Committee of Ondokuz Mayıs University. (B.30.2.ODM.0.20.08/776-169)

Declaration of Helsinki

The study was conducted in accordance with the Declaration of Helsinki and followed the ethical standards of the country of origin. (B.30.2.ODM.0.20.08/776-169)

Peer-review

Externally and internally peer-reviewed.

Authorship Contributions

Concept: Y.T.C., Design: Y.T.C., Data Collection: Y.T.C., E.A. Analysis or Interpretation: Y.T.C., E.A., Literature Search: Y.T.C., E.A., Writing: Y.T.C., E.A.

Conflicts of Interest

The authors have none to declare

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