Human Bocavirus in Febrile Children Consulting a GP Service in the Netherlands

Miriam Monteny*, MD, Hubert G.M. Niesters†, PhD, Henriëtte A. Moll‡, PhD,

Marjolein Y. Berger*, PhD

* Department of General Practice, Erasmus MC, Rotterdam, The Netherlands

† Department of Virology, Erasmus MC, Rotterdam, The Netherlands

‡ Department of Pediatrics, Erasmus MC-Sophia, Rotterdam, The Netherlands

Correspondence:

Marjolein Berger, general practitioner, MD

Erasmus MC

Department of General Practice

Room Ff 332

PO Box 2040, 3000 CA Rotterdam, The Netherlands

Tel. +31 10 408 7631, fax. +31 10 408 9491

Email: **m.berger@erasmusmc.nl**

Word count: 800

Keywords

Parvoviridae Infections

Human BOCA virus

Child

Fever

Communicable diseases, Emerging

Family Practice

Abstract

Human bocavirus (HBoV) was detected in nasopharyngeal swabs of 1.6% (95% CI 0.4% to 3.9%) of 257 febrile children presented to a GP center. Symptoms of respiratory tract infection, gastrointestinal symptoms and skin rash were reported. Our results suggest HBoV as a pathogen causing mild disease in non-hospitalized febrile children.

Text

Human bocavirus (HBoV) is a recently discovered virus of the family *Parvoviridae*, genus *Bocavirus*, and appears to be a widespread causative agent of respiratory tract infections (RTI) in children. In selected groups of children with RTI, detection rates varied between 2.8% and 11.3% (1-9). However, the exact prevalence and pathogenic impact of this virus remain to be established.

During a prospective cohort study evaluating the prognosis of fever at a general practice out-of-hours service (GP service) in Rotterdam, nasopharyngeal swabs were collected from febrile children and tested for respiratory viruses including HBoV. We report the incidence and clinical features of HBoV in these children.

Between June 1st 2005 and January 16th 2006, all children aged 3 months to 6 years contacting the GP service with fever as reason for encounter, reported by parents and not further defined, were eligible for inclusion. Children were excluded in case the parents could not communicate in Dutch (n =77) and in case a child had already been included within the last two weeks (n =11). A research nurse visited the child at home within 24 hours after inclusion. The child was physically examined and a nasopharyngeal swab and blood sample for CRP measurement was collected. The parents subsequently registered symptoms in a diary during 7 days. The Central Committee on Research Involving Human Subjects (CCMO), The Netherlands, approved this study.

Nucleic acids were isolated on a MagnaPure isolation station (Roche Applied Science, Penzberg, Germany) and subsequently analyzed by real time assays. Detection of HBoV was performed using a primers set and a FAM labeled TaqMan probe directed against sequences of the NP1 gene. Sequences are available through the corresponding author.

Routinely was tested for influenza virus types A and B, parainfluenza virus types 1-4, RSV types A and B, adenovirus, coronavirus (OC43, 229E and NL63) and rhinovirus.

Nasopharyngeal swabs were collected from 257 children (81% of 319 enrolled children). The overall virus detection rate was 52.9% (most frequently adenovirus (11%), RSV-A (10.5%), parainfluenza virus type 1 (8.5%) and rhinovirus (8%)). Five children were included twice, none of them was HBoV-positive. The PCR for HBoV was positive in four children (1.6%), all boys. The characteristics of these children are shown in the table.

All 4 children reported rhinorrhea and cough. Patient 1 reported abdominal pain, diarrhea (more than twice daily, with mucus), dyspnea and a skin rash along with respiratory symptoms. All symptoms lasted for more than a week. At physical examination the children were not or slightly ill. Patient 1 had a skin rash and palpable cervical lymph nodes. Patient 4 had palpable lymph nodes and red tonsils.

Patient 1 was prescribed antibiotics for otitis media and patient 4 for tonsillitis, as diagnosed by the GP on the clinical presentation, without bacteriological confirmation. During one-week follow-up none of the patients had any further consultations.

Our finding that HBoV may cause RTI is in accordance with the literature (1-6). Our findings support those of others in suggesting a role for HBoV in systemic infection, causing gastrointestinal symptoms and skin rash (6,8).

Our detection rate, in general practice, is lower than the reported rates in former studies of children with RTI (3-10%) (1-8). Co-infection of HBoV and other viruses was found among three children out of four (table). In other studies co-infection was found in 17.6% to 55.6% (mainly adenovirus, RSV and HMPV) (1,2,5,7-9). The other detected

viruses could have caused the symptoms of patients 2-4. However, HBoV was the only detected virus in one child with respiratory symptoms, gastrointestinal symptoms and rash, and might therefore be the pathogen. Considering the high amount of HBoV in patient 3, symptoms are likely caused by HBoV as well in this case.

The severity of disease in our study population was limited since all children presented with mild disease and no child was hospitalized. However, all children reported a prolonged course of fever, more than 7 days or recurrent within a week. This is in contrast with the mean duration of fever of 2.6 days in the study of Arnold et al, which was based in hospital setting (6). None of the HBoV-positive children was diagnosed with bronchiolitis, pneumonia or bronchitis, as in previous studies. None of the four children in our study was born pre-term, compared to 19-44% of HBoV-positive children in previous studies (5,6). Neither did they have a positive history for asthma or other underlying diseases, as did up to 50% of the children in previous studies (1,6).

In conclusion, HBoV was detected in nasopharyngeal swabs of 1.6% of 257 children younger than 6 years, presented with fever in general practice. Our results suggest that HBoV might cause mild disease with respiratory and gastrointestinal symptoms and skin rash. Further research to clarify the prevalence and pathogenicity of this new virus in the general population should not be restricted to susceptible or hospitalized patients alone.

This study was supported by the Dutch Organization for Health Research and Development (ZonMw), Program Common Diseases.

Acknowledgments

We thank Dr Ann Vossen of the Department of Virology, Erasmus MC for the analysis of the swabs (present address Department of Virology, University Medical Center Leiden).

First author's biographical sketch

Miriam Monteny is a PhD-student at the Department of General Practice of the Erasmus MC Rotterdam. She is a medical doctor and has a degree in Biomedical Sciences. Her primary research interests include infectious diseases in children in general practice and emergency medicine.

References

1. Allander T, Tammi MT, Eriksson M, Bjerkner A, Tiveljung-Lindell A, Andersson B. Cloning of a human parvovirus by molecular screening of respiratory tract samples. Proc Natl Acad Sci U S A. 2005;102(36):12891-6.

2. Sloots TP, McErlean P, Speicher DJ, Arden KE, Nissen MD, Mackay IM. Evidence of human coronavirus HKU1 and human bocavirus in Australian children. J Clin Virol. 2006;35(1):99-102.

3. Ma X, Endo R, Ishiguro N, Ebihara T, Ishiko H, Ariga T et al. Detection of human bocavirus in Japanese children with lower respiratory tract infections. J Clin Microbiol. 2006;44(3):1132-4.

4. Bastien N, Brandt K, Dust K, Ward D, Li Y. Human Bocavirus infection, Canada. Emerg Infect Dis. 2006;12(5):848-50.

5. Foulongne V, Rodiere M, Segondy M. Human Bocavirus in children. Emerg Infect Dis. 2006;12(5):862-3.

6. Arnold JC, Singh KK, Spector SA, Sawyer MH. Human bocavirus: prevalence and clinical spectrum at a children's hospital. Clin Infect Dis. 2006;43(3):283-8.

7. Weissbrich B, Neske F, Schubert J, Tollmann F, Blath K, Blessing K et al. Frequent detection of bocavirus DNA in German children with respiratory tract infections. BMC Infect Dis. 2006 Jul 11;6:109.

8. Chung JY, Han TH, Kim CK, Kim SW. Bocavirus infection in hospitalized children, South Korea. Emerg Infect Dis. 2006 Aug;12(8):1254-6.

9. Choi EH, Lee HJ, Kim SJ, Eun BW, Kim NH, Lee JA et al. The association of newly identified respiratory viruses with lower respiratory tract infections in Korean

children, 2000-2005. Clin Infect Dis. 2006 Sep 1;43(5):585-92.

Table

Patient	*Age (yr)*	*Month collected*	*Symptoms*	*Body temperature (℃)*	*CRP (mg/L)*	*Positive PCR (log copies/mL)*
1	2.3	November 2005	Earache Rhinorrhea Cough Sore throat Abdominal pain Diarrhea Skin rash Dyspnea Increased breathing rate	36.2	9	Bocavirus (4.20)
2	1.9	November 2005	Rhinorrhea Cough Sore throat Vomiting Increased breathing rate	38.8	26	Rhinovirus (7.57) RSV B (5.51) Bocavirus (2.88)
3	1.3	December 2005	Earache Rhinorrhea Cough Headache Vomiting Skin rash Increased breathing rate	38.6	26	Bocavirus (6.72) Para-influenzavirus 4 (4.11) Adenovirus (2.00)
4	1.0	January 2006	Earache Rhinorrhea Cough Sore throat Abdominal pain Diarrhea Vomiting	37.7	88	Adenovirus (6.90) Bocavirus (2.88)