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Case Report

Sudden infant death suspected to be due to human bocavirus infection : a case report and literature review

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Abstract

Background : Infants who die due to sudden infant death syndrome are known to have significantly more respiratory infection symptoms before the event than the control group, indicating the involvement of suffocation and cardiopulmonary arrest.

Methods : We present a case of sudden death of a 5-month-old baby who was positive for human bocavirus in his airway secretions. He had respiratory infection symptoms with wheezing before the event. After feeding, the baby was carried on the father's back for 25 minutes. At their destination, the father found the baby showing abnormalities, and the baby died at hospital soon after.

Results : Lung autopsy demonstrated bronchopneumonia and the sample was positive for human bocavirus by real-time multiplex polymerase chain reaction (PCR).

Conclusions : These results suggest that human bocavirus might be a causative pathogen of sudden death with airway obstruction.

Introduction

Human Bocavirus (HBoV) is a type of Bocavirus in the parvovirus subfamily of *Parvoviridae*, which was discovered in Sweden in 2005[1)]. It is widely distributed all over the world and causes respiratory infections mainly in young infants[1-3)]. Sudden infant death syndrome (SIDS) is the sudden death of an apparently healthy baby, and the cause is still unknown[4)]. Here, we report a sudden infant death in which HBoV was detected in the infant's airway secretions.

Case

At the age of 5 months, the male infant presented with a cold for 1 week before the fatal event. On the first day of illness, he had a fever of 38°C and stayed home from daycare, and visited a doctor. He was prescribed antimicrobial agents (Cefditoren pivoxil) under the diagnosis of a common cold. During the next 2 days (third and fourth day of disease), he went to daycare without any symptoms of respiratory distress. On the fifth day of disease, he woke up 6 : 00 am, and drank about 100 mL of fomula at around at 6 : 30 am.

The father carried the baby on his back from 7 : 10 to 7 : 35 am and took him to the daycare by bicycle. The infant was crying from 7 : 10 to 7 : 20 am. As he arrived at the daycare and lowered the baby from his back, the father noticed that the infant's appearance was

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strange and consulted the daycare teacher. The daycare teacher placed her ear near the infant's nose and noticed he was not breathing at around 7 : 35 am and called for emergency help. The infant was taken to hospital at 8 : 11 am. At that time, he was not breathing and had no pulse.

His pH was 6.3, pCO2 was 174.2. He was tracheally intubated and given adrenaline three times but there was no reaction and death was confirmed at 8 : 34 am. The baby had no remarkable family or past histories. There was no historical episode of muscle weakness until the event. There was no particular problem with his birth or developmental history.

The baby had no malformation trauma, nor lymph-node enlargement. Ecchymoses and petechiae were not observed. His white blood cell count was 14,700/μL (neutrophils : 7% ; lymphocytes : 88% ; eosinophils : 1% ; basophils : 0.0% ; and monocytes 4%) and hemoglobin level was 11 g/dL. His platelet count was 554 × 10^3/μL, and c-reactive protein level was 0.79 mg/dL. The aspartate aminotransferase, alanine aminotransferase, and gamma-glutamyl transpeptidase levels were 132 (normal range : 13-30) IU/L, 71 (normal range : 10-42) IU/L, and 15 (normal range : 9-64) IU/L, respectively. His total bilirubin level was 0.1 (normal range : 0.4-1.5) mg/dL, and alkaline phosphatase was 687 U/L. Kidney function tests were normal. Data obtained at the hospital at the time of admission is shown (Table 1).

Twenty-four hours after confirmation of death, the infant was transferred to our hospital where the pathological autopsy was performed upon requestby police.

There were no heart or coronary artery abnormalities, nor any malformation of the large blood vessels. He had tracheal reddening, which suggested bronchitis. There was a small amount of mucus in the upper respiratory tract and secretions in the trachea (Fig. 1). There were no abnormal findings in the liver, gallbladder, pancreas, spleen, or kidney. Hematoxylin-eosin staining followed by microscopic analysis showed acidophilic changes (ischemic changes) in the cerebrum and midbrain, which were considered to be secondary changes after sudden death. The heart showed eosinophilic changes in the left and right ventricular muscles, which were also considered to be secondary changes. The lungs showed strong congestion and edema, which are widely observed in cases of sudden death and suffocation death. Inflammatory cell infiltration was clearly observed around the trachea and alveoli, and some bronchial tubes showed wall thickening, which suggests the presence of chronic inflammation, such as bronchial asthma. Although there was little destruction of the bronchial wall and tissue destruction of the surrounding parenchyma, congestion and pulmonary edema-like changes were observed, as shown in Fig. 2.

We investigated frozen specimens (brain, intestinal lymph nodes, and airway secretions) by multivirus real-time PCR for 178 types of RNA / DNA viruses, and only the airway secretions were found to be positive for HBoV (Table 2)[5]. The following day, paraffin sections of the upper lung, lower lung, cerebellum, right ventricle, ventricular septum, liver, spleen, and right kidney were ana-

Table 1 Laboratory findings on admission

	Unit
WBC	14.7×10^3/μL
RBC	4.32×10^6/μL
Hb	11 g/dL
Ht	38.6%
MCV	89.4 fL
MCH	25.5 pg
MCHC	28.5%
Plt	55.4×10^4/μL
pH	6.38
pCO2	174.2 mmHg
HCO3	10.1 mEq/L
BE	— 32.4 mEq/L
Na	141.7 mEq/L
K	8.01 mEq/L
Cl	106 mEq/L
Glu	164 mg/dL

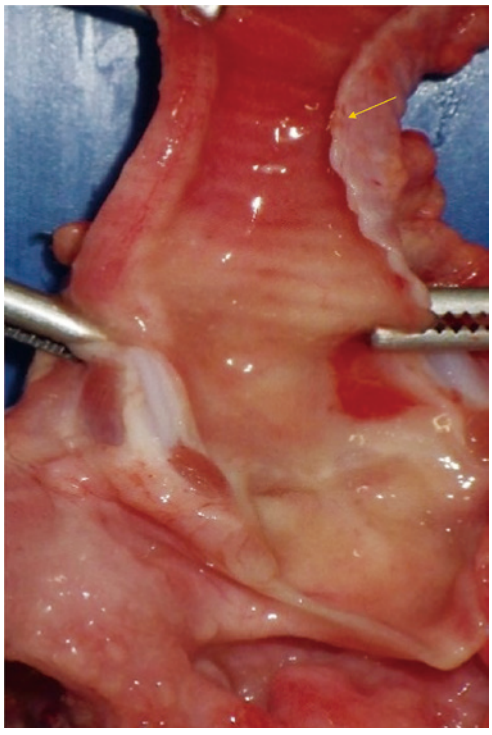

Fig. 1 Bronchus
Redness of the tracheal mucosa is observed. (presumed bronchitis)

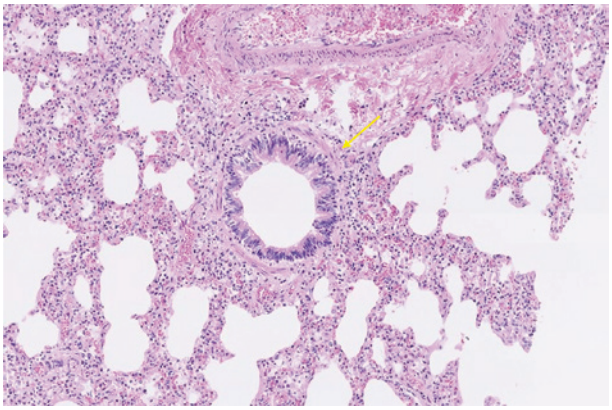

Fig. 2 Pathology of the bronchial wall and tissue
There was little destruction of the bronchial wall and tissue destruction of the surrounding parenchyma. Congestion and pulmonary edema-like changes were observed. (hematoxylin and eosin stain) (×100)

lyzed but were negative for viruses.

The presence of bacteria and fungi were analyzed comprehensively by multi-microbial real-time PCR[6], and 3 types, namely, *Streptococcus salivaris*, *Streptococcus pneumoniae*, and *Neisseria meningitidis* were detected from the frozen tissues (airway secretions) and paraffin sections (Table 2), which were all normal bacterial flora.

In Table 3, the severe cases caused by HBoV that have been published to date are shown. The first case was a fatality caused by multiple organ failure and encephalopathy[7]. In the other 2 cases, the subjects were under 1 year of age and had respiratory symptoms. Furthermore, they were both premature infants and the only virus detected was HBoV[8][9]. In Japan, three patients at risk for the respiratory system have been reported[10].

Discussion

Infants who die due to sudden infant death syndrome (SIDS) are known to have significantly more respiratory infection symptoms before the event than the control group. Many investigations focusing on the association between SIDS and viral infections have been reported since the 1970s. In 1978, Scott et al. reported that the lung tissue of 19 subjects (18.2%) out of the 104 cases of cot death were positive for a virus, and the viruses identified were respiratory syncytial virus, adenovirus, parainfluenza, rhinovirus, enterovirus (Coxsackie and Echovirus), and those of the herpes group[11]. In a recent study using genetic methods, 18 subjects (4%) out of 546 who

Table 2 Results of multi-virus and multi-microbial real-time PCR (positive results only)

Target	Brain	Intestinal lymph node	Tracheal secretion
Human bocavirus	Undetectable (UD)	Undetectable (UD)	5.67E+01
Beta-actin	8.16E+04	1.65E+05	8.16E+04

Target	Brain	Intestinal lymph node	Tracheal secretion
Streptococcus salivaris	Undetectable (UD)	Undetectable (UD)	2.24E+04
Streptococcus pneumoniae	Undetectable (UD)	Undetectable (UD)	2.00E+04
Neisseria meningitidis	Undetectable (UD)	Undetectable (UD)	1.50E+04
Moraxella catarrhalis	Undetectable (UD)	Undetectable (UD)	Undetectable (UD)
Haemophilus influenzae	Undetectable (UD)	Undetectable (UD)	Undetectable (UD)
Fusobacterium nucleatum	Undetectable (UD)	Undetectable (UD)	Undetectable (UD)
Beta-actin	1.02E+05	1.21E+05	5.80E+04

Table 3 Reported severe cases with infection of Human bocavirus

Year	Age and Gender	Country	Symptoms	Author
2008	unknown	Japan	multiple organ failure, encephalopathy	Hirabayashi M et al.[6]
2008	4-month-old girl	Spain	respiratory distress Low birth weight (24w, 705 g)	C. Calvo et al.[7]
2015	5-month-old girl	Turkey	high fever and stridor Low birth weight (27w, 1,180 g)	Nihan Ziyade1, et al.[8]
2019	1-year-old boy	Japan	Chronic lung disease	H. Kobayashi, et al.
2019	3-month-old girl	Japan	Hypophosphatasia	H. Kobayashi, et al.
2019	2-year-old girl	Japan	double-outlet right ventricle with high pulmonary blood flow as a respiratory risk	H. Kobayashi, et al.
2019	5-month-old boy	Japan	cough and stridor	our case

died of SIDS were positive for a virus. The study identified 5 cases of enterovirus, 4 cases of RS, 3 cases of the herpes group, and 1 case each of adenovirus, influenza, and HIV and reported that one-third of cases were caused by viral infection but others were caused by bacterial infection or unknown causes[12]. Others also reported similar viruses as the cause of SIDS[13][14]. Recently, human parechovirus type 3 was identified, and has been reported to be the cause of some cases of sudden death[15]. Here, we encountered an infant who died suddenly with bronchopneumonia, who was positive for HBoV. This virus was isolated in 2005 in Sweden from children with lower respiratory tract infections[1]. The virus is classified into types 1-4, and type 1 HBoV causes respiratory infections. The clinical symptoms are fever, cough, nasal discharge, hyperpnea, wheeze, and dyspnea. The course is usually mild upper respiratory inflammation, but in some cases it becomes severe[16]. There have also been reports of bronchial asthma attacks. In respiratory infections with nonasthmatic wheezing below the age of 2 years, it is second in frequency only to human metapneumovirus[17]. HBoV was isolated from a infant with severe plastic bronchitis[18].

In Japan, it has been reported that approximately 2.9% of children with community-acquired pneumonia are found to have HBoV[19]. Another study showed that HBoV was detected in 9.9% of respiratory tract infections in children under 14 years of age (the fourth most common : RSV > rhinovirus > adenovirus > HBoV). Three quarters of the children have mixed infections with other pathogens. Cases detected HBoV alone are more likely to develop asthma after pneumonia, and more often from December to January[18]. The clinical disease of such patients was pneumonia with infiltration and less bronchiolitis on X-ray[20].

In this study we encountered a case of sudden infant death in which HBoV was detected in the infant's airway secretions, and we made 2 hypotheses regarding the reason for the infant's death as it did not apply to SIDS. The first hypothesis was that HBoV causes a respiratory disorder and the resulting asphyxiation leads to death. Alternatively, HBoV is occasionally a passenger virus, and there is the possibility that another cause exists, because of the absence of pathological changes. Mackay et al. reported that persistent virus shedding for over a month was observed in patients who died of SIDS who had significant underlying diseases[21]. However, the possible causes of the sudden death of our patient are thought to be upper airway obstruction, limitation of thoracic expansion, and insufficient temperature control owing to viral infection. We similarly reported 4 patients with sudden death accompanied with several viral infections[22].

In conclusion, we emphasize that HBoV infections must be taken into consideration when clinicians encounter a baby with sudden death or in a life-threatening condition with a respiratory infection, particularly with wheezing.

Finally, the multiple PCR assay is recommended as a useful method to understand the etiology of sudden infant deaths in both clinical and forensic autopsies. Virus detection can be performed from 25 μL of DNA and RNA solutions extracted from each sample (also from paraffin sections). A quantitative line is created on the same plate, and the amount of each virus and bacterium can be roughly measured.

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Informed consent

There is no conflict with any employment. The patient's family agreed to this publication and informed consent was obtained.

Ethical approval

This article does not contain any experiments involving human participants or animals performed by any of the authors.

Disclosure

The authors declare no conflict of interest.

Author contribution

SM and MY designed the study ; GY, YK, and HK performed the experiments, and collected and analyzed the data ; MY wrote the manuscript ; HK provided technical support and conceptual advice. All authors read and approved the final manuscript.

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ヒトボカウイルス感染による乳幼児の突然死と文献レビュー

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【要旨】 背景：乳幼児突然死症候群（SIDS）で死亡した乳児は、発症前に有意に多くの呼吸器感染症症状を呈することが知られており、窒息や心肺停止が関与していることが示唆されている。

方法：気道分泌物中にヒトボカウイルス陽性を示した生後 5 ヶ月の乳児突然死の 1 例を示す。発症前に喘鳴を伴う呼吸器症状を呈していた。授乳後、乳児は父親の背中に 25 分程度背負われていたが、保育園に到着後に呼吸をしていないことに気付き救急要請し、搬送先の病院で死亡した。

結果：肺の剖検で気管支炎が示唆され、Polymerase Chain Reaction（PCR）でヒトボカウイルス陽性が確認された。

結論：ヒトボカウイルスが気道閉塞を伴う突然死の原因ウイルスの 1 つである可能性が示唆された。

〈キーワード〉 SIDS、気管支肺炎、multivirus real-time PCR、ヒトボカウイルス