Apnoea, dyspnoea and wheezing in primary lower respiratory infections due to human rhinovirus in Japanese infants

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Human rhinovirus (HRV) is generally recognized as a common cold agent, but it can be associated with severe acute respiratory infection and result in illnesses such as pneumonia. Here, we report on manifestations of severe respiratory infection, including apnoea, dyspnoea and wheezing, that might have been due to primary HRV infection, in two Japanese infants. Although both cases had a good outcome, the infants, a 40-day-old male and 2-month-old male, displayed the aforementioned symptoms with life-threatening bronchitis and hyperinflation, and received aggressive respiratory care (intubation or oxygen tent). HRV alone was detected in respiratory specimens. Genetic and phylogenetic analysis of the detected HRV revealed strains that are prevalent in various countries (HRV-A, genotype HRV-96 and HRV-C, genotype HRV-C46). The results suggest that, besides respiratory syncytial virus, primary HRV infection in infants can be associated with severe respiratory symptoms such as apnoea, dyspnoea and wheezing in lower respiratory infections, although these cases may be rare.

**Keywords:** apnoea; dyspnoea; human rhinovirus; wheezing.

**Introduction**

Human rhinovirus (HRV) belongs to the genus *Enterovirus* and family *Picornaviridae*. In general, HRV is a typical agent of mild acute respiratory infection (ARI), such as the common cold. Recent studies suggest that HRV may also be associated with more severe respiratory infections such as bronchitis, bronchiolitis and pneumonia (Turner & Couch, 2007). However, the exact epidemiology and pathogenicity of HRV in infants is not clear. Clearly, apnoea and dyspnoea due to lower respiratory infections in infants can be serious and lead to life-threatening conditions. Here, we report two cases of apnoea, dyspnoea and wheezing in Japanese infants that may have been caused by HRV infection.

**Case report**

**Case 1**

In November 2012, a 40-day-old male (gestational age 38 weeks 2 days; birth weight 2744 g; normal delivery) was admitted to the Department of Pediatrics at our hospital with apnoea and dyspnoea. He was diagnosed with the common cold by a paediatrician and prescribed medication. However, the infant’s respiratory function worsened during the day and he was brought back to the hospital. On admission, he showed apnoea, severe dyspnoea and seizure with very low atrial oxygen saturation (60%).

**Abbreviations:** ARI, acute respiratory infection; HRV, human rhinovirus; RSV, respiratory syncytial virus.
Bilateral coarse crackles and wheezing were heard on chest auscultation. Chest radiography revealed bronchitis and hyperinflation. Laboratory tests showed a white blood cell count of $8.9 \times 10^9$ $\text{l}^{-1}$, serum C-reactive protein level of 2.16 mg $\text{dl}^{-1}$ and serum sodium level of 120 mmol $\text{l}^{-1}$. Venous blood gas tests showed that $pCO_2$ was 56.3 mmHg and the pH was 7.332. Cerebrospinal fluid examination was normal.

We administered oxygen via an oxygen tent ($\text{FiO}_2$: 0.50) and cefotaxime by drip infusion after electrolyte revision. This resulted in gradual improvements of the apnoea and dyspnoea. After 5 days of treatment, the infant’s breathing difficulties and low levels of atrial oxygen saturation were resolved. He was fully recovered on hospital day 8.

**Case 2**

In November 2013, a 2-month-old male (gestational age 39 weeks 5 days; birth weight 3268 g; normal delivery) was admitted to the Department of Pediatrics at our hospital with apnoea and severe dyspnoea. He had developed rhinorrhoea and a cough over 24 hours. His oral intake had gradually decreased and he looked unwell. On admission, the infant had recurrent apnoea and severe dyspnoea, and his arterial oxygen saturation was low (85 % on pulse oximetry). Bilateral coarse crackles and wheezing were heard on chest auscultation. Chest radiography revealed bronchitis and hyperinflation. Laboratory tests showed a white blood cell count of $4.5 \times 10^9$ $\text{l}^{-1}$ and serum C-reactive protein level of 1.21 mg $\text{dl}^{-1}$. Venous blood gas tests showed that his $pCO_2$ was 48.7 mmHg and his pH was 7.324. Cerebrospinal fluid was normal.

The infant was intubated and connected to a respirator for frequent apnoea. In addition, we administrated ampicillin and cefotaxime in a drip infusion after electrolyte revision. After 2 days of treatment, the infant’s apnoea and breathing difficulties resolved and he was extubated, with oxygen gas administration started by nasal cannula ($1 \text{ l min}^{-1}$). Two days later, on hospital day 4, oxygen administration was stopped. The patient recovered without sequelae.

**Aetiology**

In both patients, detectable defects in immunoglobulin levels or white blood cell compartments were found. In addition, neither infant had a history of respiratory infections after birth, excluding these events in both cases.

To identify the aetiological agents, we collected nasopharyngeal swabs and intratracheal aspirations after obtaining written informed consent from the patients’ guardians. The study protocol was approved by the Ethics Committee on Human Research of the St Luke’s International Hospital (13-R150).

We extracted viral RNA and DNA using the QIAamp MinElute Virus Spin kit (Qiagen) (Miyaji et al., 2013).

Reverse transcription and PCR procedures for the amplification of different viral genomes, including respiratory syncytial virus (RSV), HRV/human enterovirus, human metapneumovirus, human parainfluenza virus types 1–4, influenza virus subtypes A–C, adenovirus and human bocavirus, were conducted as described previously (Miyaji et al., 2013). Positive and negative controls were included in all PCR assays. PCR products were determined by electrophoresis on 3 % agarose gels. Purification of DNA fragments and nucleotide sequence determination procedures were performed as described previously (Miyaji et al., 2013). Evolutionary distances were estimated using Kimura’s two-parameter method and a phylogenetic tree was reconstructed using the neighbour-joining method.

In addition, we attempted to isolate or detect various respiratory bacteria such as *Haemophilus influenzae*, *Legionella pneumophila*, *Neisseria* species and *Bordetella pertussis* using culture methods or an available kit (OSOM Strep A Test; Sekisui Diagnostics) in the case of *Streptococcus* (Abdeldaim et al., 2010; Thurman et al., 2011). We also attempted to detect *Mycoplasma* species using reverse transcription PCR (Thurman et al., 2011).

In our two patients, rhinovirus alone was detected; no pathogenic bacteria were isolated or detected. Phylogenetic analysis showed that the HRV strains detected were located in a cluster: HRV-96 type from Case 1 (AB910764) and HRV-C46 type from Case 2 (AB910765) (Fig. 1). In addition, the strains were closely related to the SHAPHC2685/SH/CHN/10 strain (identity 98.7 %) in Case 1 and the NL2010016666 strain (identity 98.7 %) in Case 2. These viruses were genetically related to other strains detected in some countries (Fig. 1).

The results suggest that the apnoea, dyspnoea and wheezing with bronchitis experienced by the infants in this study may have been caused by prevalent strains of HRV.

**Discussion**

The patients showed severe respiratory symptoms including apnoea, dyspnoea and wheezing due to HRV infection, with no suggestion of a history of ARI. A number of previous cohorts with HRV infection have been described (Bender et al. 2014; Costa et al., 2014; Drysdale et al., 2014). For example, Drysdale et al. (2014) suggested that HRV coinfections with other pathogens, such as RSV, can often be associated with more severe disease. However, there was no evidence of coinfections in either of our cases. Thus, primary infection with HRV alone may have been associated with severe ARI.

HRV-A (HRV-96 type) and HRV-C (HRV-C46 type) were detected in Cases 1 and 2, respectively (Fig. 1). These HRV strains may be common in Japan (Fujitsuka et al., 2011; Kaida et al., 2011) and a recent study suggested that HRV-A and HRV-C are major agents of various respiratory infections such as the common cold, wheezy bronchitis/bronchiolitis...
and pneumonia (Arakawa et al., 2012). In addition, other recent studies have discussed the roles of HRV-A and HRV-C in severe ARI (Xiang et al., 2010; Broberg et al., 2011; Lauinger et al., 2013). For example, Xiang et al. (2010) have suggested that HRV-C may be associated with severe ARI comparable with that of HRV-A infection. Although we report here on only two cases, both HRV-A and HRV-C were associated with severe ARI symptoms of apnoea, dyspnoea and wheezing. Thus, further studies on the role of HRV species in severe ARI may be needed.

The clinical manifestations and chest radiographic findings in our cases did not significantly differ from those seen with ARI caused by other pathogens, such as RSV (Peter & James, 2007). This finding is compatible with that of an earlier report (van Piggelen et al., 2010). Thus, more precise laboratory confirmation may be needed to identify causative pathogens.

In conclusion, primary HRV infection may be associated with serious respiratory symptoms such as apnoea, dyspnoea and wheezing in lower respiratory infections in infants, although these types of cases may be relatively rare.

### Conflicts of interest

The authors have no conflicts of interest to declare.

### Acknowledgements

This work was supported in part by a Grant-in-Aid (H25-Shiko-Ippan-015) for research on emerging and re-emerging infectious diseases, Labour and Welfare Programs, from the Ministry of Health, Labour and Welfare of Japan.

### References


