

Short communications

Severe Apparent Life-threatening Event (ALTE) in an Infant with SARS-CoV-2 Infection

Running head: A case of ALTE with SARS-CoV-2 Infection

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Summary

The 2019 novel coronavirus (severe acute respiratory syndrome-coronavirus: SARS-CoV-2) has currently caused a global outbreak of infection. In general, children with the coronavirus disease-2019 have been reported to show milder respiratory symptoms as a respiratory infection than adult patients. Here, we describe SARS-CoV-2 infection in an infant who presented with a severe episode of apparent life-threatening event (ALTE). An 8-month-old otherwise healthy infant who was transported to our hospital because of a sudden cardiopulmonary arrest. Approximately one hour before this episode, she was almost fine but in a slightly worse humor than usual. On arrival at our hospital, severe acidosis but no clear sign of inflammatory response was denoted. A chest computed tomography scan showed weak consolidations in the upper right lung as well as atelectasis in the lower left lung. No sign of congenital heart disease or cardiomyopathy was observed in echocardiography, and no significant arrhythmia was observed in the later clinical course. Of note, the specific SARS-CoV-2 RNA was detected in both of her tracheal aspirate and urine sample by real-time RT-PCR. Although further accumulation of the cases is indispensable, our case suggests that SARS-CoV-2 infection may be one of the underlying

factors in the pathophysiology of ALTE.

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The 2019 novel coronavirus (severe acute respiratory syndrome-coronavirus: SARS-CoV-2) has currently caused a global outbreak of infection (1-3). In general, children with the coronavirus disease-2019 (COVID-19) have been reported to show milder respiratory symptoms as a respiratory infection than adult patients (4). Moreover, asymptomatic infection is supposed to be more common in children (5). However, several severe cases have been recently reported in younger children, especially in infants (6). In infants, an apparent life-threatening event (ALTE) is a clinical manifestation defined as follows in an Italian guideline (7): an episode that is frightening to the observer and is characterized by some combination of apnea, color change, marked change in muscle tone, choking or gagging. In infants with ALTE, lower respiratory infection is one of the underlying conditions (7, 8). Here, we have detected SARS-CoV-2 infection in an infant who presented with a severe episode of ALTE.

An 8-month-old girl was transported to our hospital owing to cardiopulmonary arrest. Her mother called ambulance when she noticed that the child was pale, and not breathing at prone position, and exhibiting no response to stimulation. Approximately one hour before this observation, the mother had engaged in face-

to-face interaction with the child when feeding her. At that time, she was almost fine but in a slightly worse humor than usual. She had pulseless electrical activity in the ambulance. She was immediately transferred to our hospital after intratracheal intubation by the emergency physician in the ambulance. Recovery of spontaneous circulation was accomplished after cardiopulmonary resuscitation with intraosseous infusion of adrenaline and sodium bicarbonate. On arrival at our hospital, blood gas analysis using a bone marrow sample revealed severe acidosis (pH 6.525, pCO₂ 94.8 mmHg, BE -27.1 mmol/L). Her medical history showed that she was the only child of healthy non-consanguineous Japanese parents and that her family had no history of febrile seizures, epilepsy, heart disease, or sudden death in childhood. She was vaginally delivered at full-term weighting 3,016 g and no abnormalities were found in the metabolic screening test performed in the neonatal period. She was well developed at a level appropriate for her months of age and had no previous history of any symptoms including respiratory symptom and febrile seizure. Her immunization had been performed on schedule without significant adverse events, and she was inoculated with BCG at 5 months of age.

Her peripheral blood count on admission was as follows; white blood cell

5.39 × 10³ /μL, hemoglobin 10.2 g/dL and thrombocytes 234 × 10³ /μL. Her blood tests revealed no clear sign of inflammatory response; levels of serum C-reactive protein and procalcitonin were < 0.1 mg/dL and 0.03 ng/mL, respectively. Her serum immunoglobulin G level was as low as 114 mg/dL, but her levels of CD3+T-cells, CD19+B-cells, and CD56+NK-cells in peripheral blood were within normal range. Viral antigen tests of her nasopharyngeal aspirates showed negative reaction to respiratory syncytial or influenza virus infections. After recovery of spontaneous circulation, the electrocardiogram showed a mild prolonged QT interval (QTc= 456 ms), but no significant arrhythmia was observed in the later clinical course of infection. Echocardiography indicated normal left ventricular ejection fraction, suggesting that involvement of congenital heart disease or cardiomyopathy was unlikely. A chest computed tomography (CT) scan showed weak consolidations in the upper right lung (Figure 1, A and B) as well as atelectasis in the lower left lung (Figure 1, C). Moreover, a head CT scan showed signs of brain edema with some ambiguous grey-white differentiation and narrow cerebral ventricles but no signs of bleeding (Figure 1, D), suggesting the development of hypoxic encephalopathy. Consequently, systemic hypothermia for brain protection using a ventilator was immediately started.

Real time reverse transcription polymerase chain reaction (RT-PCR) analysis of SARS-CoV-2 was performed (9) using the patient's tracheal aspirate (Figure 2, A) by N (P28706 – 28814) and N2 (P29125 – 29263) primers (Figure 2, B). Tracheal aspirate was treated with 0.75% DTT in PBS for 10 min and, subsequently, treated with DNase for 10 min. Viral RNA was extracted using QIAamp viral RNA mini kit (Qiagen). The SARS-CoV-2 RNA was detected using AgPath-ID™ One-Step RT-PCR Reagents (AM1005) (Applied Biosystems) on CobasZ480 (Roche). Nested PCR was performed using the same sample. First PCR was performed using sense (P28185 – 18204) and anti-sense (P29548 – 29567) primers, and second PCR was performed using N2 primer (Figure 2, B). In each PCR, amplification was performed for 40 cycles.

Considering the weak pulmonary consolidations observed in the chest CT scan, we performed real time PCR analysis of SARS-CoV-2 using the patient's tracheal aspirate. Real time RT-PCR analysis revealed positive reactions by both N primer (Ct; 29.1 and 29.8) and N2 primer (Ct; 27.7 and 28.2) (Figure 2, C). To verify the positive reaction in real time RT-PCR, nested RT-PCR was also performed using the same sample, and expected size (158 bp) of second PCR product was observed (Figure 2, D). Positive reaction was also

confirmed in real time RT-PCR analyses using her tracheal aspirate and urine obtained on day 4 (data not shown).

In the presented case report, an 8-month-old infant who exhibited a sudden onset of cardiopulmonary arrest was found to be infected with SARS-CoV-2. We performed RT-PCR analysis of SARS-CoV-2 after observing indications of pulmonary consolidations in her chest CT scan. However, rapid progression of respiratory symptoms due to COVID-19 associated pneumonia is unlikely to have been a direct cause of her cardiopulmonary arrest, since the patient had no symptoms of respiratory infection and except for atelectasis her pulmonary consolidations were extremely weak at time of admission. Previous report shows that 50-58% of the cases classified as ALTE can be associated with co-morbidities such as seizures, metabolic disease, arrhythmias, congenital heart diseases, and infections (7). However, in the present case, these co-morbidities except for SARS-CoV-2 infection was unlikely to be the cause of ALTE based on her medical history and the findings in head CT examination, electrocardiography, and echocardiography. In this context, it should be noted that a case of ALTE with severe apnea attributable to human coronavirus HCoV-229E infection has previously been reported (10). In this previous case report, RT-PCR analysis

successfully detected HCoV-229E in a 4-month old infant who showed repeated episodes of apnea in a short time (10).

Considering these previous reports, although episodes of apnea were not directly observed in the presented case, it may be understandable to consider that any rapidly progressive co-morbidities due to SARS-CoV-2 infection such as apnea may be one of the candidates for the mechanism underlying her cardiopulmonary arrest.

In summary, although further accumulation of the cases is indispensable for drawing a conclusion, our case suggests that SARS-CoV-2 infection may be one of the underlying factors in the pathophysiology of ALTE and sudden infant death syndrome (SIDS).

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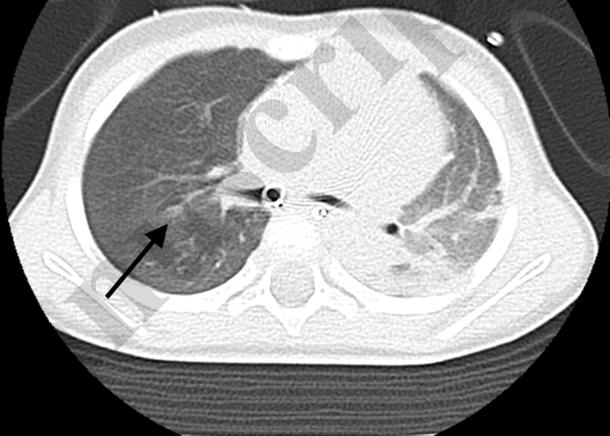
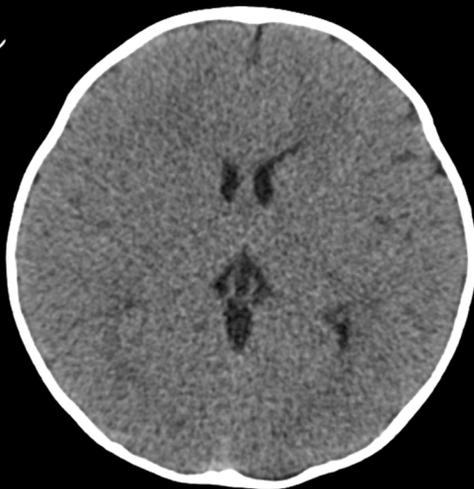
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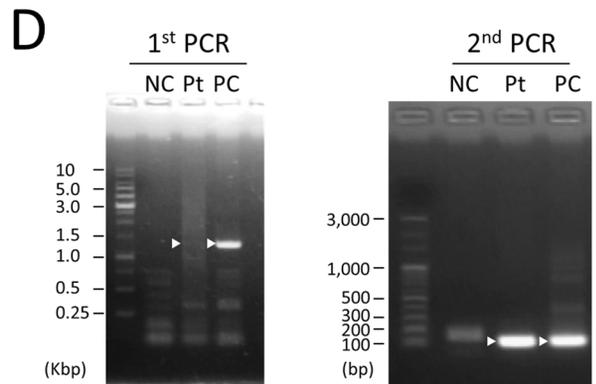
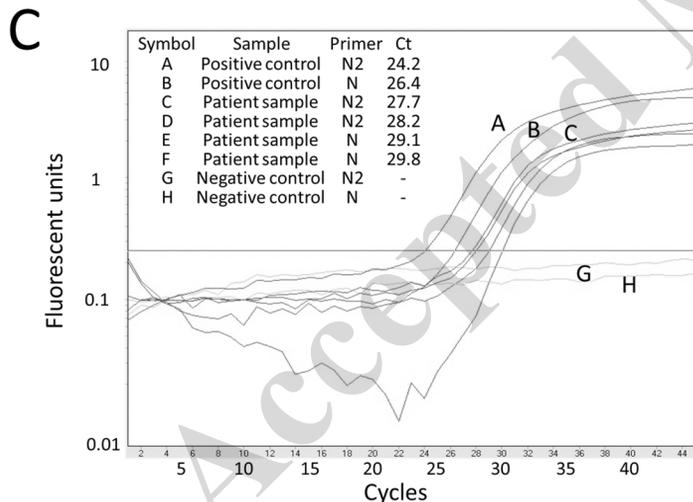
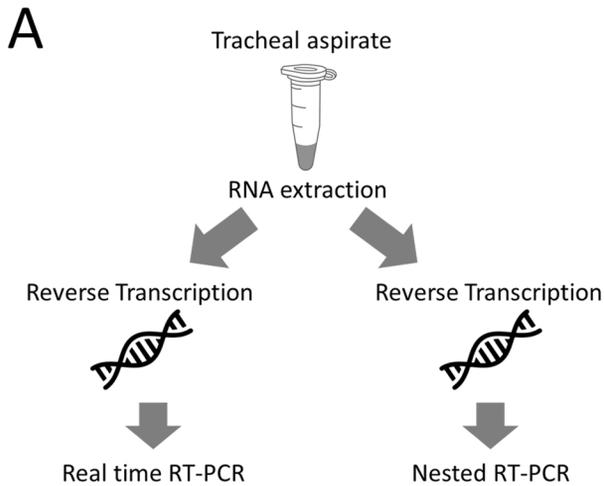
Figure Legends

Figure 1. Chest (**A**, **B** and **C**) and head (**D**) computed tomography scans of the patient on admission. **A** and **B**, Arrows indicate weak consolidations in the upper right lung. **C**, Circle indicates atelectasis in the lower left lung.

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Figure 2. RT-PCR analysis of SARS-CoV-2. **A**, Schematic representation of RT-PCR analysis. **B**, Primers and probes for RT-PCR analyses. Numbers indicate nucleotide sequence of viral RNA (GenBank MN908947.3). Arrows indicate primers for real time and nested RT-PCR and boxes indicate probes for real time RT-PCR. Initial ATG and stop codon of nucleocapsid phosphoprotein are highlighted. **C**, Amplification curves of real time RT-PCR analysis using a tracheal aspirate on admission. **D**, Nested RT-PCR analysis using a tracheal aspirate on admission. Left panel indicates first PCR, while right panel indicates second PCR. Arrowheads indicate specific PCR samples.

A**B****C****D**



NC; Negative control (DDW)
 Pt; Patient sample (Presented case)
 PC; Positive control (SARS-CoV-2+Patient sample)