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Acute Life Threatening Event (ALTE) in an Infant With Human Coronavirus HCoV-229E Infection

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Summary. In this short report we discuss the temporal association between an acute life threatening event (ALTE) and a RT-PCR confirmed coronavirus HCoV-229E infection in a 4 months old otherwise healthy infant. More detailed microbiological investigations of affected children even without apparent signs of a respiratory tract infection may help to clarify the etiology in some patients and extend our understanding of the pathogenesis. PCR-based techniques should be utilized to increase the sensitivity of detection for old and new respiratory viral pathogens in comparable cases. **Pediatr Pulmonol. 2007; 42:393–396.** © 2007 Wiley-Liss, Inc.

Key words: acute life threatening event (ALTE); coronavirus; infants.

INTRODUCTION

Almost 35 years after their first description,[1] human coronaviruses (HCoVs) attained new interest in 2002–2003, when the SARS epidemic was found to be caused by an infection with a new coronavirus.[2,3] Since then, several new HCoVs like NL63[4,5] (also known as HCoV-NH[6,7]) and HKU1[8] have been identified. Of note, HCoV-NL63, HCoV-NL, and HCoV-NH represent closely related group I coronaviruses and thus may represent different strains of the same species of viruses, although this topic is currently under conflicting discussion.[9]

Most HCoVs are respiratory pathogens with worldwide distribution and show a seasonal peak in incidence. Thus, there are periods of high prevalence in a defined community. It is, therefore, always difficult to link these infections to rare clinical syndromes in particular to those of hitherto unknown etiology. For example, Esper et al.[6] recently reported a temporal association between infection with HCoV-NH and Kawasaki disease by means of a case-control study in hospitalized children, with quite strong statistical significance.[2] In the meantime, this observation has been rejected by other investigators.[10–13] We report the first case of an acute life threatening event (ALTE) in an infant with human coronavirus HCoV-229E infection.

CASE REPORT

On March 29th a 4 months old girl was referred to our emergency department. According to the mother's report the child had stopped breathing for approximately 15 sec while falling asleep in supine position. The child then gasped for air and started crying. Having turned around her child into prone position the girl continued to have approximately 15 additional episodes of apnea. Being a full-term infant the child had been delivered by secondary cesarean section due to breech presentation. Birth weight was 3,960 g; APGAR-Scores were 9, 10 and 10. No remarkable event in the patient's medical history was found. The patient had received two series of the regular vaccination schedule according to the national recommendations (STIKO, Robert Koch-Institute, Berlin). During the last few days she had shown symptoms of a minor upper respiratory tract infection.

On admission the patient was in good physical condition, oxygen saturation being 98% on pulse oximetry without supplemental oxygen. Physical examination revealed no abnormal findings. Her white blood cell count showed 6.2×10^9 leukocytes/L, hemoglobin 10.8 g/dl and thrombocytes 473×10^9/L. Serum C-reactive protein concentration and interleukin 6 were normal with <0.1 mg/L (normal: <3) and 5.4 pg/ml (<6.0), respectively.

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Due to the actual lack of symptoms she was admitted to a general pediatric ward. A nasopharyngeal aspirate (NPA) was sampled as routine procedure to exclude an RSV-infection.[14]

During the first 5 hr of hospitalization the patient displayed two severe episodes of apnea-bradycardia with a significant decrease in oxygen saturation. She was, therefore, transferred to the pediatric intensive care unit and a lumbar puncture was performed[15] with unremarkable results. Blood cultures were drawn, which remained sterile. The consultation of a pediatric neurologist did not disclose any general or focal neurological deficit. Electroencephalography and chest X-ray established no abnormalities. Ultrasound examination of the brain and the abdomen revealed no remarkable findings, except a single short episode of gastric reflux.

To exclude gastroesophageal reflux disease a 24-hr esophageal pH monitoring was performed, which yielded no pathological findings. Eventually, the family was provided with a home-monitoring system[16] and both parents received resuscitation training[17] before the patient was released from hospital on April 1st. According to a telephone contact to the parents on October 08, 2006, the patient recovered uneventfully and did not experience additional episodes of apnea-bradycardia syndrome at home, which strongly argues against reflux etiology of the symptoms.

VIROLOGICAL AND MICROBIOLOGICAL RESULTS

The investigated material was a NPA[18] diluted in physiologic sodium chloride. Viral RNA and DNA were extracted as described earlier[19] and RT-PCR for coronaviruses (i.e., HCoV-NL63/NL, SARS, OC43, 229E, HKU-A/B/C),[20,21] human Metapneumovirus,[22] respiratory syncytial virus, Influenza viruses, adenovirus, and bocavirus[23] were performed. Except the RT-PCR for coronaviruses, all PCR and RT-PCR reactions were negative. Direct sequencing of the coronavirus RT-PCR amplificate revealed HCoV-229E RNA in the patient's specimen. To exclude an infection due to *Bordetella pertussis*,[24] *parapertussis* and *bronchiseptica*, as well as an infection due to *Mycoplasma pneumoniae* and Chlamydia spp., real-time PCRs were performed out of the patient's specimen,[25] which all yielded negative results.

DISCUSSION

To our knowledge, this is the first report of an ALTE event in an infant temporally related to HCoV-229E infection, confirmed by PCR-based virological methods. Recently, Bastien et al.[26] published a brief report on HCoV-NL63 infection in Canada. One of these HCoV-NL63-positive patients, a 4 months old male, was post-mortem investigated after sudden infant death. The authors suspected ''smothering by bed linens'' as the primary causality but also documented a chronic laryngotracheo-bronchitis at autopsy.

In the early nineties Sizun et al.[27] prospectively investigated respiratory secretions from hospitalized premature infants and newborns with indirect immunofluorescence for HCoV infection and revealed a high rate of bradycardia, apnea, hypoxemia, and fever in positive cases.[28] In a letter related to this article, Giudicelli et al.[29] speculated about a possible association of HCoV-infection and sudden infant death syndrome. Using indirect immunofluorescence, for HCoV strains 229E and OC43, Gagneur et al.[30] investigated the incidence of HCoV-related nosocomial respiratory tract infection in neonates and children hospitalized in a Pediatric/Neonatal-ICU. Seven samples were positive in 7 out of 64 neonates (incidence of 11%), all for HCoV: HCoV-229E: $N = 5$, HCoV-OC43: $N = 1$ and one with both HCoV-229E and -OC43. Either intubation or nasal positive pressure support initiation was used in 57% of the HCoV-infections. Nonetheless, these happened in premature neonates, who acquired the HCoV-infection in the NICU.

An important obstacle in the management of our case is the missing MRT investigation, which should have been considered (in addition to the consultation of a pediatric neurologist, the sonographic examination and the electroencephalography) by the attending physicians as a standard procedure in the diagnostic workup of children with ALTE.[31] Perhaps, the decision to perform an MRT would have been fostered, if the results of the HCoV testing were interpreted beyond the background of distinct in vitro studies, which confirmed the invasion and a potential persistence of HCoV-229E in cells of the human nervous system, such as oligodendrocytes and possibly neurons.[32–34]

Although our case report does not prove the association between ALTE and HCoV-229E infection, it should be noticed as a remark for further investigation. Viral infection appears to be an uncommon cause of ALTE and of sudden children death syndrome (SIDS),[35] but more detailed microbiological investigations of affected children even without apparent signs of a respiratory tract infection may help to clarify the etiology in some cases and our understanding of the pathogenesis.[36,37] PCR-based techniques should be utilized to increase the sensitivity of detection for old and new respiratory viral pathogens.[38]

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