DOI:10.1111/irv.12059
www.influenzajournal.com

Short Article

Fatal respiratory distress syndrome due to coronavirus infection in a child with severe combined immunodeficiency

Aleksandra Szczawinska-Poplonyk,[a] Katarzyna Jonczyk-Potoczna,[b] Anna Breborowicz,[a] Alicja Bartkowska-Sniatkowska,[c] Magdalena Figlerowicz[d]

[a,*]Department of Pediatric Pneumonology, Allergology and Clinical Immunology, Poznan University of Medical Sciences. [b]Department of Pediatric Radiology, Poznan University of Medical Sciences. [c]Department of Pediatric Anesthesiology and Intensive Care, Poznan University of Medical Sciences. [d]Department of Pediatric Neurology and Infectious Diseases, Poznan University of Medical Sciences, Poznan, Poland.
Correspondence: Aleksandra Szczawinska-Poplonyk, Department of Pediatric Pneumonology, Allergology and Clinical Immunology, Poznan University of Medical Sciences, Szpitalna Street 27/33, 60-572 Poznan, Poland. E-mail: ola@malwa.com.pl; klinikapad@xmail.sk5.am.poznan.pl

Accepted 13 October 2012. Published Online 30 November 2012.

Coronaviruses have been demonstrated to contribute substantially to respiratory tract infections among the child population. Though infected children commonly present mild upper airway symptoms, in high-risk patients with underlying conditions, particularly in immunocompromised children these pathogens may lead to severe lung infection and extrapulmonary disorders. In this paper, we provide the first report of the case of a 15-month-old child with severe combined immunodeficiency and coronavirus HKU1-related pneumonia with fatal respiratory distress syndrome.

Keywords Coronavirus, severe combined immunodeficiency, pneumonia, children.

Please cite this paper as: Szczawinska-Poplonyk *et al.* (2013) Fatal respiratory distress syndrome due to coronavirus infection in a child with severe combined immunodeficiency. Influenza and Other Respiratory Viruses 7(5), 634–636.

Introduction

Severe combined immunodeficiency (SCID) is a genetically and clinically heterogeneous group of the most severe primary immunodeficiencies, characterized by the absence of functional T lymphocytes resulting in profound impairment of the cellular and humoral adaptive immunity. Depending on the genetic defect, B lymphocytes and natural killer (NK) cells may be present or absent and this feature constitutes the basis for the classical division into T-B + SCID and T-B−SCID, with further subdivisions into NK+ and NK− disorders.[1] Respiratory tract infection is a common manifestation in children in question and may be present within the neonatal period or in early infancy. Opportunistic pathogens may lead to rapidly progressive, fatal interstitial pneumonitis accompanied by hyperinflation resulting from small airway obstruction or to persistent bronchiolitic presentation. Apart from pyogenic bacteria, such as *Pseudomonas aeruginosa*, *Stenotrophomonas* spp, *Burkholderia* spp, as well as Mycobacteria and fungi, in particular *Pneumocystis jiroveci*, respiratory viruses like respiratory syncytial virus (RSV), adenovirus, parainfluenza virus, human metapneumovirus (hMPV) and other viruses – cytomegalovirus (CMV), varicella–zoster virus (VZV), and Epstein–Barr virus (EBV) are associated with severe pneumonia in SCID children.[2] Human coronaviruses (HCoV) HCoV-229E and HCoV-OC43 and related new strains HCoV-NL63 and HCoV-HKU1, identified after the epidemic outbreak of severe acquired respiratory syndrome (SARS) coronavirus, are likely to be common respiratory viruses in otherwise healthy children and were not implicated in severe lung infections in immunocompromised patients thus far.[3] In this report we present the case of a child with delayed-onset SCID and fatal respiratory coronavirus infection.

**The institution to which the work should be attributed.*

Case presentation

A 15-month-old girl was referred to the University Hospital due to persistent fever and interstitial pneumonitis for the purposes of diagnosis and treatment.

She was the first child of young, non-consanguineous parents, born from the first pregnancy which was terminated in the 39th week of gestation using Cesarian section surgery because of condylomata acuminata due to human papilloma

© 2012 John Wiley & Sons Ltd

virus (HPV) infection in the mother. In early infancy, mild eczema on the child's face, in the perioral and periorbital areas was observed. By the end of the first year of life the child **had thrived** and had not suffered from any severe infections. She received live BCG vaccine, tetanus and diphtheria toxoids, inactivated pertussis, inactivated poliomyelitis, recombinant hepatitis B and conjugated pneumococcal as well as Haemophilus influenzae B vaccines without adverse reactions after the immunizations.

On admission the child demonstrated paroxysmal nonproductive cough and clinical signs of respiratory insufficiency along with injected oral pharyngeal mucosa and dry erythematous lips. Fine papular skin eruption affecting the face was observed. Neither peripheral lymph nodes nor internal organs of the abdominal cavity were palpable. During hospitalization, lymphopenia, anemia, and thrombocytosis (the peak platelet count was $778 \times 10^9/l$) as well as increased levels of inflammatory markers and coagulopathy were found in laboratory tests. Dilation of the right coronary artery was revealed in echocardiography, giving rise to the suspicion of Kawasaki disease and the instituting of treatment with aspirin and immunoglobulins. Despite intensive pharmacotherapy with antibiotics, trimethoprime/sulfamethoxazole, acyclovir and antifungal agents, rapid deterioration of the child's clinical state and the exacerbation of respiratory insufficiency accompanied by progression in radiological features of the respiratory distress syndrome (RDS) occured. On a chest X-ray, massive alveolar and interstitial infiltrations with bilaterally decreased aeration of the lung fields and blurred borders of the diaphragm and the heart shape (as shown on Figure 1) were discernible. Differential diagnostics that included examinations of the tracheal aspirate samples aimed at infectious agents were carried out. Infections with viruses – RSV A and B, parainfluenza viruses 1,2, and 3, influenza A including H1N1 subtype and B, adenoviruses, CMV, EBV, MPV, rhinovirus, human immunodeficiency virus (HIV), with bacteria, such as *Streptococcus pneumoniae, Haemophilus influenzae, Legionella, Bordetella pertussis, Mycoplasma pneumoniae, Chlamydophila pneumoniae*, as well as with fungi – *Candida* spp. and *P. jiroveci* were excluded based on negative PCR examinations, whereas the human coronavirus HKU1 – RNA proved positive. Peripheral blood lymphocyte flow cytometric immunophenotyping revealed a total lack of expression of antigens characteristic for CD4 and CD8 T-cell subsets as well as NK cells along with the presence of functionally immature transitional and naïve B cells. This SCID phenotype was subsequently confirmed by bone marrow flow cytometric evaluation. However, the presence of few NK cells was revealed, indicating for T-B + NK + SCID.

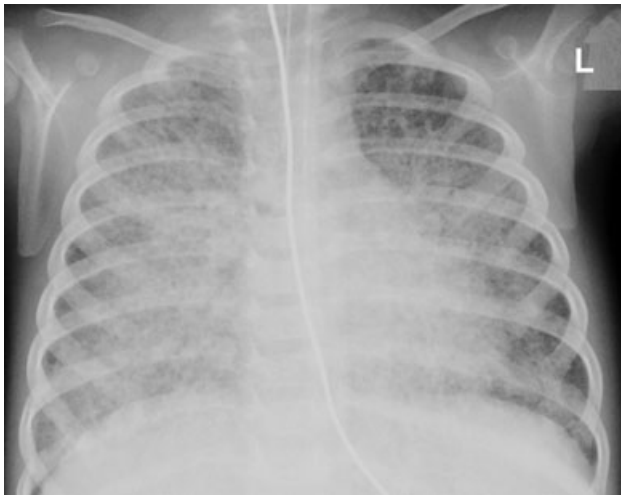

Figure 1. The chest X-ray of a 15-month-old child with severe combined immunodeficiency and respiratory distress syndrome due to coronavirus HKU1 infection. Note the massive alveolar and interstitial infiltrations, with bilaterally decreased aeration of the lung fields and blurred borders of the diaphragm and the heart shape.

Intensive therapy and mechanical ventilation conducted in the Department of Pediatric Anesthesiology and Intensive Care did not contribute to either clinical or radiological improvement and the child died because of multiorgan failure.

Discussion

Analysis of the available data concerning the effects of non-SARS human coronaviruses (HCoV) in children suggests that their clinical relevance in children is substantial, particularly in the hospital settings, even though the incidence of HCoV airway infections are generally less frequent than with other viruses which have an established role in respiratory disease, such as RSV and influenza.[4] However, detailed epidemiological data on the prevalence of HCoV infections in children are discordant, ranging from 2·5% of NL63 strain in young children with bronchiolitis reported by Ebihara *et al.*[5] to 18% in the study by Vabret *et al.*[6] in different age groups of the child population. Moreover, seroconversion with regard to HCoV-229E and above-mentioned HCoV-NL63 in young children was much higher and was estimated to 42·9–50% and 75%, respectively.[7] The characteristics of clinical manifestation of coronavirus respiratory tract infection are predominantly reliant on case reports, and in otherwise, healthy children are comparable with bronchitis, bronchiolitis, and pneumonia due to other viral infections. The epidemiological study by Kuypers *et al.*[8] indicated that a considerable proportion of coronavirus-infected children had underlying chronic central nervous system, cardiovascular, pulmonary, allergic, and renal or hepatic conditions and diseases. These authors also paid attention to immunocompromised pediatric patients with acute lymphocytic leukemia and organ transplant recipients as a high-risk group for the development of severe lung dis-

© 2012 John Wiley & Sons Ltd

ease. However, it is worth noting that coronavirus respiratory infections have not been described in children with genetically determined immunodeficiencies thus far and this is the first report of a documented HCoV-HKU1-related pneumonia with the RDS in a child with SCID. It is also interesting to note that the preliminary clinical diagnosis in this patient was Kawasaki disease, what is consistent with the hypothesis by Esper *et al.*[9] regarding the association between Kawasaki disease with HCoV infection, supported by identification of the 'New Heaven' coronavirus (HCoV-NH) in 72·7% of respiratory specimen from affected children.

Concluding remarks

The identification of HCoV-HKU1 provides a novel insight into the epidemiology and clinical implications of coronavirus infections in severely immunocompromised children and indicates for consideration of this pathogen-related etiology of respiratory infection in SCID. Further, epidemiological studies are necessary to define the impact of HCoV on lung disease in children with immunodeficiencies.

Acknowledgement

The assistance of Dr Husam Samara from the Department of Immunology for the flow cytometric immunophenotyping of peripheral blood and bone marrow leukocytes is acknowledged.

Competing interests

The authors have no competing interests.

References

1 Van der Burg M, Gennery A. The expanding clinical and immunological spectrum of severe combined immunodeficiency. Eur J Pediatr 2011; 170:561–571.
2 Eslamy HK, Newman B. Pneumonia in normal and immunocompromised children: an overview and update. Radiol Clin North Am 2011; 49:895–920.
3 Kahn JS. The widening scope of coronaviruses. Curr Opin Pediatr 2006; 18:42–47.
4 Principi N, Bosis S, Esposito S. Effects of coronavirus infections in children. Emerg Infect Dis 2010; 16:183–188.
5 Ebihara T, Endo R, Ma X, Ishiguro N, Kikuta H. Detection of human coronavirus NL63 in young children with bronchiolitis. J Med Virol 2005; 75:463–465.
6 Vabret A, Mourez T, Dina J *et al.* Human coronavirus NL63, France. Emerg Infect Dis 2005; 11:1225–1229.
7 Shao X, Guo X, Esper F, Weibel C, Kahn J. Seroepidemiology of group 1 human coronaviruses in children. J Clin Virol 2007; 40:207–213.
8 Kuypers J, Martin ET, Heugel J, Wright N, Morrow R, Englund JA. Clinical disease in children associated with newly described coronavirus subtypes. Pediatrics 2007; 119:e70–e76.
9 Esper F, Shapiro ED, Weibel C, Ferguson D, Landry ML, Kahn JS. Association between a novel human coronavirus and Kawasaki disease. J Infect Dis 2005; 191:499–502.

© 2012 John Wiley & Sons Ltd