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Case Report

Severe SARS-CoV-2 and Respiratory Syncytial Virus Coinfection in Two Children

Andreana Angelova[1,2,3], Mariya Atanasova[1,3,4], Kostadin Ketev[5,6], Zeyra Halil[6], Ivanka Paskaleva[6,7], Gergana Lengerova[1,2,3], Teodora Dimcheva[8], Neli Korsun[9], Mariana Murdjeva[1,2,3]

[1] *Department of Microbiology and Immunology, Faculty of Pharmacy, Medical University of Plovdiv, Plovdiv, Bulgaria*

[2] *Laboratory of Microbiology, St George University Hospital, Plovdiv, Bulgaria*

[3] *Research Institute, Medical University of Plovdiv, Plovdiv, Bulgaria*

[4] *Laboratory of Virology, St George University Hospital, Plovdiv, Bulgaria*

[5] *Medical Simulation Training Center at the Research Institute of Medical University of Plovdiv, Plovdiv, Bulgaria*

[6] *Department of Pediatrics, St George University Hospital, Plovdiv, Bulgaria*

[7] *Department of Pediatrics and Medical Genetics, Faculty of Medicine, Medical University of Plovdiv, Plovdiv, Bulgaria*

[8] *Department of Medical Informatics, Biostatistics and E-learning, Faculty of Public Health, Medical University of Plovdiv, Plovdiv, Bulgaria*

[9] *National Center of Infectious and Parasitic Diseases, Sofia, Bulgaria*

Corresponding author: Andreana Angelova, Department of Microbiology and Immunology, Faculty of Pharmacy, Medical University of Plovdiv, 15A Vassil Aprilov Blvd., 4002 Plovdiv, Bulgaria; Email: andreana.angelova@mu-plovdiv.bg; Tel.: +359 897 764 494

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Abstract

The Coronavirus Disease 2019 (COVID-19) caused by a novel coronavirus (SARS-CoV-2) affects mainly older adults. Those with comorbidities are at a higher risk of severe disease and even death. The symptomatic infection rate of children is lower, manifestations are milder, and severe forms are scarce. We present here two children with severe COVID-19 and a respiratory syncytial virus, with the goal of emphasizing the possibility of coinfection with a severe course and a different result. The microbiological diagnosis was made using multiplex PCR. This assay not only provided an early and accurate diagnosis but also aided in the implementation of contact precautions. Further research should be done to determine the influence of coinfection on the clinical course and outcome of pediatric patients.

Keywords

COVID-19, multiplex PCR, RSV, severity

INTRODUCTION

Since 1918, no pandemic has ever been as devastating as the coronavirus disease 2019 (COVID-19) that is currently sweeping the globe.[1] COVID-19 is caused by a novel coronavirus (SARS-CoV-2), which has quickly spread over the globe wreaking havoc worldwide.[2] From the onset, the COVID-19 pandemic resulted in more severe infections requiring hospitalization and intensive care admission in adults and older individuals, with higher mortality rates.[3]

For reasons still unclear, about 30% of the infected children are more likely than adults to have an asymptomatic infection. In addition, in the few with clinical manifestations, the disease is often mild.[4] The proportion of children with severe disease is in the range of 1-6%, even with the recently recognized pediatric multisystem inflammatory syndrome (MIS-C).[5] This is in stark contrast to other

respiratory viruses such as the respiratory syncytial virus (RSV). This pathogen causes severe disease in infancy but is with a milder presentation in adults. The number of hospitalized children with COVID -19 during the current surge with the Delta variant of SARS-CoV-2 has increased. However, this can easily be explained by an overall rise in the number of COVID-19 infected children. Nevertheless, it is reassuring that the number of deaths among infected children has remained low even during the current surge.[6] Detection of SARS-CoV-2 with other respiratory pathogens in adults is infrequent and is not associated with more severe disease.[7] A few studies have addressed SARS-CoV-2 viral coinfections in children, and it is not yet clear how they might influence the clinical course or outcome.[8]

We aimed to describe severe COVID-19 in two children co-infected with RSV and underline the significance of multiplex polymerase chain reaction (mPCR) as an accurate diagnostic tool.

CASE REPORT

The two patients we present are part of a larger, still ongoing study on the potential of multiplex PCR (mPCR) used in making a rapid microbiological diagnosis of acute respiratory infections in children hospitalized in the Clinic of Pediatrics at one of the university hospitals in Plovdiv. Our study has involved 120 pediatric patients' respiratory specimens from 2020 to the present. They were subjected to a conventional microbiological examination and mPCR (FilmArray, BioMerieux, France), which provides simultaneous detection of nucleic acids from multiple viral and bacterial respiratory pathogens in a single sample. Written informed consent was obtained from the patient's legal guardians before enrollment. The mPCR FilmArray Respiratory Panel was used to test the nasopharyngeal swabs for respiratory pathogens while FilmArray Pneumonia Panel Plus was used to test the lower respiratory tract specimens. In addition, since 2021, mPCR Respiratory 2.1.plus panel has been in use and 40 patients have been tested. This assay can detect the membrane protein (M) and spike protein (S) genes of SARS-CoV-2.[9]

In two of these 40 patients treated in late 2021, SARS-CoV-2 and RSV were co-detected.

Case 1

A two-month-old previously healthy male patient was admitted to the hospital for bronchiolitis. His rapid antigen test for SARS-CoV-2 was negative. Because his oxygen saturation was 70% on ambient air, supplemental oxygen was given via nasal cannula. On hospital day 5, the physical findings suspected atelectasis, which was confirmed by a chest X-ray, and the child was transferred to the Intensive Care Unit. SARS-CoV-2 and RSV were detected from his nasopharyngeal swab by mPCR ***(Table 1)****. The local health authorities were notified, and an epidemiological investigation commenced. The patient was treated with humidified supplemental oxygen, antibiotics, corticosteroids, and bronchodilators; intravenous immunoglobulin was given once. He recovered uneventfully and was discharged on day 14.*

Table 1. FilmArray Multiplex PCR Respiratory 2.1. plus panel (Biofire®) results in the two patients with a total run time of about 45 minutes

Viruses		Bacteria
Adenovirus	Influenza A	*Bordetella pertussis*
Coronavirus 229E	Influenza A/H1	*Bordetella parapertussis*
Coronavirus HKU1	Influenza A/H1-2009	*Chlamydophila pneumoniae*
Coronavirus OC43	Influenza A/H3	*Mycoplasma pneumoniae*
Coronavirus NL63	Influenza B	
MERS-CoV	Parainfluenza 1	
✓ **SARS-CoV-2 detected**	Parainfluenza 2	
	Parainfluenza 3	
Human metapneumovirus	Parainfluenza 4	
Human rhinovirus/enterovirus	✓ **RSV detected**	

Case 2

A 16-month-old previously healthy female patient was admitted to the ICU for COVID-19 pneumonia after being treated in another hospital. SARS-CoV-2 was detected from her nasopharyngeal swab by mPCR together with RSV ***(Table 1)****. The following day, the patient rapidly deteriorated, was intubated, and was placed on mechanical ventilation. Despite treatment with remdesivir, vasopressor support, antibiotics, intravenous immunoglobulin, fresh frozen plasma, corticosteroids, anticoagulation medications, she continued to deteriorate and developed heart injury with severe hypotension, refractory hypoxemia, seizures, and acute kidney failure in the last few days, necessitating peritoneal dialysis. She died of multiorgan failure on day 19. Some characteristics of the patients are shown in* ***Table 2****.*

DISCUSSION

We presented two children with severe COVID-19 co-infected with RSV with different outcomes – favorable in the male patient and fatal in the female patient. Both children had no comorbidities or risk factors for the severe course. Our results not only confirmed the diagnostic significance of mPCR, but they also pointed out its epidemiological importance. We are not aware of a study of this kind in Bulgaria.

Compared to those in older adults, the clinical manifestations of SARS-CoV-2 infections in children are relatively

Table 2. Some characteristics of the two patients

Characteristic	Patient 1	Patient 2
Age (months)	2	16
Gender	Male	Female
Exposure	Yes *	Yes
Respiratory involvement	Bronchiolitis	Pneumonia
CXR	Hyperinflated lung fields, atelectasis, the left apical region	Bilateral ground-glass opacities
Other organs involvement		
Heart	No	Yes
CNS	No	Yes
Kidneys	No	Yes
Some blood investigations		
CRP, mg/l (<10)**	0.0	16.5
Ferritin, µg/l (113-150)	Not tested	567
LDH, U/l (134-214)	Not tested	1935
Treatment		
Remdesivir	No	Yes
Corticosteroids	Yes	Yes
Antibiotic treatment	Yes	Yes
Supplemental oxygen	Yes	Yes ***
Intravenous globulin	Yes	Yes
Peritoneal dialysis	No	Yes
Clinical course		
ICU	Yes, 5 days	Yes
Duration of hospitalization, days	15	19
Outcome	Recovery	Death

COVID-19: coronavirus disease 19; RSV: respiratory syncytial virus; ICU: intensive care unit; CRP: C- reactive protein; LDH: lactate dehydrogenase; CXR: chest X-ray; *Household exposure was revealed after receiving SARS-CoV-2 positive result in patient 1; **reference range is given in parenthesis; ***via mechanical ventilation.

benign. Asymptomatic infections or mild diseases predominate and the number of hospitalizations is low.[10,11] Possible contributing factors include more robust early innate immune response, cross-protection from previous coronavirus infections, difference in ACE2 expression, protective off-target vaccination effects, and greater memory T-cell diversity.[12-14] Fatalities have been infrequent and mostly in children with severe comorbidities, such as medical complexity, obesity, and diabetes.[10,11] None of these factors were present in the children we discuss. Similar to the cases in this study, Oualha et al.[15] reported a fatal outcome in three children without underlying diseases.

Two forms of severe COVID-19 in children have been reported: a primary pulmonary disease with diffuse alveolar damage, or MIS-C with the involvement of several organs.[16] Serious but rare manifestation, MIS-C is characterized by fever, rash, conjunctivitis, abdominal pain, and cardiac dysfunction. MIS-C is more common in older children, presents later in the disease, and has a favorable outcome.[17,18] Conversely, the patients we presented were young children, treated during the first 10 days of the disease with none of these manifestations, and one died.

Diagnostic testing has been front and center in the COVID-19 pandemic and viral detection by nucleic acid amplification tests (NAATs) such as PCR plays a primary role in the diagnosis. Advanced microbiological methods such as mPCR allow for increased recognition of respiratory pathogens. In addition, it can provide simultaneous detection of multiple respiratory pathogens in cases of mixed infections, including ones of SARS-CoV-2 and other respiratory viruses.[9] The mPCR confirmed SARS-CoV-2 in the female patient, already diagnosed in another hospital, and also revealed RSV **(Table 1)**. Moreover, surprisingly, it detected SARS-CoV-2 in the male patient who had a typical course of severe bronchitis. Thus, it was difficult to ascertain its precise role as an acting pathogen. However, this unexpected but important finding resulted in contact tracing and quarantine for potential SARS-CoV-2 cases in

the household – public health measures strategies still crucial for controlling the SARS-CoV-2 expansion. The mPCR positive results for SARS-CoV-2 in both patients were confirmed in a second-day nasopharyngeal sample in the Virology Laboratory of the aforementioned hospital using Real-Time PCR (Bioneer, South Korea). This assay targets two different genes – the E-gene and the RdRp-gene of the viral RNA. Later, SARS-CoV-2 and RSV results in one of the patients were also confirmed in the Reference Laboratory of Influenza and Acute Respiratory Diseases, National Center of Infectious and Parasitic Diseases, Sofia. As the second child died, it was not possible to collect and send more specimens for such confirmation to be carried out.

Some common respiratory viruses are shed very frequently in asymptomatic children.[19] There are a few studies on the simultaneous detection of SARS-CoV-2 and other respiratory pathogens in children. It is not yet clear how they might affect the clinical course or outcome. The most commonly involved pathogen was *M. pneumoniae,* and other respiratory viruses such as RSV and influenza viruses were revealed rarely.[8] Co-infection of SARS-CoV-2 and RSV can pose significant challenges regarding diagnosis and treatment but is not yet associated with more severe disease. Alvares[20] discussed SARS-CoV-2 and RSV co-detection in 6 children and did not find any differences regarding the need for intensive care, mechanical ventilation, or mortality rates. Nevertheless, given the major role of RSV in bronchiolitis and pneumonia in children, we consider RSV a contributory factor in the severe course, especially in the female patient. Similar to Ozaras et al.[21], we detected the two viruses only at admission and did not know their dynamic, shedding, and interactions, which is a limitation of our study. Further studies are required for a better understanding of this coinfection dynamic.

CONCLUSIONS

Our results confirm that, although rarely, a life-threatening disease in SARS-CoV-2-infected children may occur. In addition, mPCR not only provides an early and accurate diagnosis but also unravels SARS-CoV-2 infection in the patient with bronchiolitis. Thus, mPCR may aid in the implementation of contact precautions. The simultaneous detection of RSV merits special attention. Recognition of SARS-CoV-2 associated with other respiratory pathogens can allow understanding of the different clinical features. Moreover, it can aid the appropriate therapeutic management and infection control.

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Тяжелая коинфекция SARS-CoV-2 и респираторно-синцитиального вируса у двух детей

Андреана Ангелова[1,2,3], Мария Атанасова[1,3,4], Костадин Кетев[5,6], Зейра Халил[6], Иванка Паскалева[6,7], Гергана Ленгерова[1,2,3], Теодора Димчева[8], Нели Корсум[9], Мариана Мурджева[1,2,3]

[1] Кафедра микробиологии и иммунологии, Факультет фармации, Медицинский университет – Пловдив, Пловдив, Болгария
[2] Лаборатория микробиологии, УМБАЛ „Св. Георги", Пловдив, Болгария
[3] Научно-исследовательский институт, Медицинский университет – Пловдив, Пловдив, Болгария
[4] Вирусологическая лаборатория, УМБАЛ „Св. Георги", Пловдив, Болгария
[5] Медицинский симуляционный учебный центр при Научно-исследовательском институте Медицинского университета – Пловдив, Пловдив, Болгария
[6] Клиника педиатрии, УМБАЛ „Св. Георги", Пловдив, Болгария
[7] Кафедра педиатрии и медицинской генетики, Медицинский университет – Пловдив, Пловдив, Болгария
[8] Кафедра медицинской информатики, биостатистики и электронного обучения, Факультет общественного здравоохранения, Медицинский университет – Пловдив, Пловдив, Болгария
[9] Националный центр заразных и паразитарных болезней, София, Болгария

Адрес для корреспонденции: Андреана Ангелова, Кафедра микробиологии и иммунологии, Факультет фармации, Медицинский университет – Пловдив, бул. „Васил Априлов" № 15А, 4002 Пловдив, Болгария; E-mail: andreana.angelova@mu-plovdiv.bg; тел.: +359 897 764 494

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Резюме

Коронавирусная болезнь 2019 года (COVID-19), вызванная новым коронавирусом (SARS-CoV-2), поражает в основном пожилых людей. Те, у кого есть сопутствующие заболевания, подвергаются более высокому риску тяжёлой болезни и даже смерти. Симптоматическая заболеваемость детей ниже, проявления более лёгкие, тяжёлые формы встречаются редко. Мы представляем здесь двух детей с тяжёлым течением COVID-19 и респираторно-синцитиальным вирусом с целью подчеркнуть возможность коинфекции с тяжёлым течением и другим результатом. Микробиологический диагноз был поставлен с помощью мультиплексной PCR. Этот анализ не только обеспечил ранний и точный диагноз, но также помог в реализации контактных мер предосторожности. Необходимо провести дальнейшие исследования, чтобы определить влияние коинфекции на клиническое течение и исход у педиатрических пациентов.

Ключевые слова

COVID-19, мультиплексная PCR, RSV, степень тяжести