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Severe and fatal forms of COVID-19 in children

Short title: Severe and fatal forms of COVID-19 in children

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Conflicts of interest: None

ABSTRACT:

OBJECTIVES:

The aim of this study was to describe severe forms of novel coronavirus disease 2019 in children, including patient characteristics, clinical, laboratory, and imaging findings, as well as the disease management and outcomes.

METHODS:

This was a retrospective, single-center, observational study conducted in a pediatric intensive and high-dependency care unit (PICU, HDU) in an urban hospital in Paris. All patients, aged from 1 month to 18 years, admitted for confirmed or highly suspected SARS-CoV-2 were included.

RESULTS:

We analyzed the data of 27 children. Comorbidities ($n = 19$, 70 %) were mainly neurological ($n = 7$), respiratory, ($n = 4$), or sickle cell disease ($n = 4$). SARS-CoV-2 PCR results were positive in 24 children (nasopharyngeal swabs). The three remaining children had a chest CT scan consistent with COVID-19. Respiratory involvement was observed in 24 patients (89%). Supportive treatments were invasive mechanical ventilation ($n = 9$), catecholamine ($n = 4$), erythropheresis ($n = 4$), renal replacement therapy ($n = 1$), and extracorporeal membrane oxygenation ($n = 1$). Five children died, of whom three were without past medical history.

CONCLUSION:

This study highlighted the large spectrum of clinical presentation and time course of disease progression as well as the non-negligible occurrence of pediatric life-threatening and fatal cases of COVID-19 mostly in patients with comorbidities. Additional laboratory investigations are needed to further analyze the mechanism underlying the variability of SARS-Cov-2 pathogenicity in children

Keywords: COVID-19; coronavirus; SARS-Cov-2

1/ Introduction

The novel coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 is more likely to infect older men; those with chronic comorbidities are at a higher risk of severe acute respiratory syndrome and even death [1,2]. Since the beginning of the COVID-19 pandemic, the symptomatic infection rate of children is known to be lower than that of adults. Pediatric clinical manifestations are not typical, and mainly milder, compared with those of adult patients [3–5], and descriptions of pediatric severe and life-threatening forms are very scarce [6,7]. The impact of underlying diseases on the severity of illness has been disputed [8,9]. Information on the characteristics of severely affected pediatric patients is scarce. We report herein the first descriptive French study of children with severe and life-threatening COVID-19.

2/ Patients and methods

Necker Hospital, a tertiary teaching institution, has been identified as the regional (Ile-de-France) reference center for COVID-19-infected children. Children with severe forms of the disease were admitted in the pediatric intensive and high-dependency care units (PICU and PHDU) at our institution from the beginning of the epidemic (January 2020). Children were admitted through the local and regional emergency departments or regional hospital wards. All children with confirmed or suspected COVID-19 who exhibited acute organ dysfunction and/or respiratory distress requiring nasal oxygen therapy at a flow rate greater than 1 L/min and/or with a chronic underlying disease were admitted to the PICU and HDU. The remaining children with confirmed or suspected COVID-19 were admitted to the general pediatrics department if hospital care was indicated; these children were not included in this study. Real-time polymerase chain reaction (RT-PCR) was used to diagnose

COVID-19, testing nasopharyngeal and lower respiratory tract secretions or other biological fluids. We systematically screened for viral co-infections. Other laboratory investigations as well as chest X-ray and chest computed tomography (CT) were performed at the discretion of the physician. Organ dysfunction and severity of illness were assessed using the International Pediatric Sepsis Consensus Conference and PELOD 2 scores, respectively [10]. COVID-19 cases were considered plausible if at least the following criteria were present: (a) a SARS-CoV-2-positive PCR result or a chest CT scan suggestive of COVID-19 coupled with suspected or confirmed COVID-19 exposure [11]; and (b) any symptomatic organ involvement. This study was approved by the local ethics committee. Data were extracted from the electronic medical records and de-identified. Descriptive statistics were used for all study variables. Continuous data are expressed as median and range values, while categorical data are expressed as proportions (%).

3/ Results

From February 10 to April 20, 2020, 27 children were included in the study. Demographic data and clinical features are summarized in Table 1. The main comorbidities were neurological ($n = 7$), respiratory ($n = 4$), and sickle cell disease ($n = 4$). The neurological diseases comprised epileptic encephalopathy ($n = 4$); there were two cases of genetic ($n = 1$) and metabolic ($n = 1$) disease; respiratory diseases were chronic obstructive pulmonary disease ($n = 1$), asthma ($n = 1$), and chronic lung disease ($n = 2$). Ten children were reported to have had close contact with COVID-19-diagnosed relatives. SARS-CoV-2 PCR results were positive in 24 children (nasopharyngeal swabs). The three remaining children had a chest CT scan consistent with COVID-19. We observed an elevated neutrophil count ($n = 9/25$), an elevated C-reactive protein level ($n = 23/26$), an elevated procalcitonin level ($n = 10/17$), and lymphopenia ($n = 14/24$). Viral ($n = 2$) and bacterial ($n = 2$) co-infections were identified during the hospital stay. Detailed laboratory and radiological findings are provided in Table 2 and Figure 1. The median length of hospital stay was 6 days (2–35). The median duration of invasive mechanical ventilation was 5 days (1–18), and the median duration of hemodynamic support was 3 days (1–5). One patient needed continuous renal replacement therapy and another required

extracorporeal membrane oxygenation (ECMO) for 3 and 9 days, respectively. Eight children received specific SARS-CoV-2 treatments: remdesivir ($n = 2$), hydroxychloroquine ($n = 1$), tocilizumab ($n = 3$), anakinra ($n = 2$), and eculizumab ($n = 1$). Erythropheresis was performed for the four patients with sickle cell disease because of deterioration in their respiratory parameters. Five children died. Their respective cases are detailed here.

3.1 Case 1:

A 16-year-old girl without a past medical history presented with respiratory distress and hypoxia following 1 week of cough and fever. A CT scan was performed, and findings were typical of COVID-19 infection, which was confirmed by PCR (nasopharyngeal swabs). She was admitted to the PICU 24 h after the onset of respiratory distress. Within 6 h of admission, we observed rapid respiratory deterioration leading to refractory hypoxia despite the initiation of invasive mechanical ventilation and cardiopulmonary resuscitation.

3.2 Case 2:

A 16-year-old boy without a past medical history presented with aseptic meningitis associated with stupor and a score of 11 on the Glasgow coma scale. The result of SARS-CoV-2 PCR (nasopharyngeal swabs) was positive; the patient did not have respiratory symptoms. Sphenoidal sinusitis with cavernous sinus thrombosis was identified on magnetic resonance imaging (MRI). Blood cultures were positive for *Fusobacterium necrophorum* and *Streptococcus constellatus*. Despite surgical drainage, antibiotics, and anticoagulation therapy, right hemiparesis related to a left middle cerebral artery stroke occurred on day 4 followed by severe deterioration in the level of consciousness on day 7, leading to coma. The coma was a result of refractory and fatal intracranial hypertension in association with progressive stenosis of all cerebral vessels and brain ischemia. This time course of disease progression was unexpected, and the possibility of SARS-CoV-2-related inflammatory damage of the cerebral vessel associated with COVID-19 was maintained. The patient died on day 17 of the PICU stay of brain death.

3.3 Case 3:

A 6-year-old girl without a past medical history presented with fever, respiratory distress, stupor, and hypotensive shock. She had uncomplicated varicella 14 days before her PICU admission. The hemodynamic failure was associated with echocardiographic and biological features of myocarditis and vasoplegia. The result of SARS-CoV-2 RT-PCR (tracheal aspirate) was positive. The patient developed septic shock with multiorgan *Staphylococcus aureus* involvement: lung, blood, and cerebrospinal fluid. She received the appropriate antibiotic and intravenous immunoglobulin therapies. After a transient improvement, the patient developed necrotizing pneumonia, refractory hypoxemia, and pericarditis. SARS-CoV-2 was identified in the pericardial fluid. She underwent ECMO. On day 14 there was acute neurological deterioration and brain death related to a massive brain hemorrhage. We assume a plausible role of COVID-19 in this case, in addition to varicella zoster virus and *Staphylococcus aureus* disseminated infection with lung damage and pericardial involvement. The patient died on day 15 of the PICU stay.

3.4 Case 4:

The fourth case was a 4-year-old boy who received chemotherapy for refractory relapse of acute lymphoblastic leukemia. During his hospital stay he developed a cough and rapid respiratory distress related to bilateral pneumonia. SARS-CoV-2 was identified on nasopharyngeal swabs and blood samples via PCR. He received hydroxychloroquine and interleukin 6 receptor antagonist followed by interleukin 1 receptor antagonist for presumed interleukin 6 receptor antagonist liver toxicity. The patient initially needed standard oxygen therapy (nasal cannula) and showed transient improvement. On day 10, there was rapid respiratory deterioration progressing to acute respiratory distress syndrome. The patient was intubated but developed refractory hypoxemia and multiorgan failure. No alternative infective agents were identified, and SARS-CoV-2 was found in tracheal aspirates. He died on day 14 of the PICU stay.

3.5 Case 5:

A 17-year-old girl with a past history of epilepsy and major neonatal encephalopathy was admitted for respiratory distress with fever related to bilateral pneumonia. SARS-CoV-2 was identified on nasopharyngeal swabs by RT-PCR. She underwent noninvasive mechanical ventilation but was not intubated because of a previous mutual decision of treatment withdrawal as her underlying disease was extremely severe. She died on day 9 of the PICU stay.

4. Discussion

We report herein the first French experience of pediatric severe and life-threatening forms of novel coronavirus disease 2019. This series is representative of the most severely infected children in the Ile de France region, one of the regions most affected by COVID-19.

We highlighted the occurrence of life-threatening forms of the disease with an unexpected and non-negligible rate of death (18%) in PICU patients compared with the initial pediatric reports from China and Italy [3,4]. The characteristics of patients revealed several clinical profiles: previously healthy patients (30%) or with comorbidities (70%; sickle cell disease, $n = 4$; hematological diseases, $n = 2$). Some expected clinical profiles are missing in this single-center cohort, notably children with chronic respiratory diseases such as cystic fibrosis as well as those with heart diseases and severe congenital disorders [12].

Worldwide, death associated with SARS-CoV-2 infection in children has been very rarely reported [3,4,13,14]. To the best of our knowledge, we gathered the largest series of fatal and life-threatening cases of COVID-19 in children. A fatal outcome was observed in two patients with underlying disease, but also in three patients without a past medical history; their clinical history was not similar and their poor outcomes were unexpected. The role of SARS-CoV-2 in the clinical symptoms and outcome of two children without underlying disease is uncertain since other infective agents were found (Case 2 and 3). Nonetheless, one cannot reject the hypothesis of SARS-CoV-2 involvement in the fatal outcome in these cases, given the nontypical clinical presentation, the related time course, and the organ involvement. Analyzing the inflammatory response in these two patients might clarify this issue. Case 1 illustrates the possible excessive cytokine response of the host, the “cytokine storm” that has been described in adults [15,16]. The fatal outcome and the extreme celerity of respiratory deterioration in this patient reinforces this hypothesis. Unfortunately, no specific laboratory investigations were performed.

The surviving children exhibited a large spectrum of respiratory involvement, from an isolated cough and minor hypoxia to severe pneumonia with need for invasive and prolonged mechanical ventilation.

The presentation of children with asthma was unremarkable and these patients had a good outcome. Among the surviving children, 16 were hospitalized for critical deterioration of their underlying disease during COVID-19 infection with ($n = 14$) or without ($n = 2$) severe respiratory involvement. The primary results of laboratory investigations suggested an underlying inflammatory phenomenon and possible predisposition to prothrombotic events, as described in adult patients; however, further specialized investigations are needed to confirm this assumption [17]. Some patients received specific treatments including presumed antiviral treatments (remdesivir, hydroxychloroquine) and/or anti-inflammatory drugs; one cannot analyze the possible efficacy of these treatments in this small series.

5. Conclusion

This series is mainly descriptive but has the merit of focusing on severe forms of SARS-CoV-2 infection. We highlighted (a) the large spectrum of clinical presentation and time course of disease progression; (b) the non-negligible rate of life-threatening and fatal cases even in patients without preexisting conditions, and (c) the possible role of underlying disease in the development of severe to fatal forms. Additional laboratory investigations are needed to further analyze the mechanisms underlying the variability of SARS-Cov-2 pathogenicity in children.

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Table 1: Patient characteristics and clinical features, *n* = 27

	Value
Age in years, median (range)	6 (0.2–17.8)
Sex, <i>n</i> (%)	
Male	10 (37)
Female	17 (63)
Underlying diseases, <i>n</i> (%)	19 (70)
Neurological	7
Respiratory	5
Sickle cell disease	4
Genetic	3
Hematological and immunological disorders	2
Renal	2
Admission delay from first symptoms in days, median (range)	4 (1–10)
Organ involvement, dysfunction and support, <i>n</i> (%)	
Respiratory, <i>n</i> (%)	24 (89)
Upper and/or lower respiratory tract infection	24
Pneumonia	17
Status asthmaticus	3
Acute chest syndrome	4
Cardiovascular, <i>n</i> (%)	6 (22)
Myocarditis	3
Shock	6
Renal, <i>n</i> (%)	4 (15)
Acute renal failure	4
Neurological, <i>n</i> (%)	2 (7)
Neurological disorders	2
Acute brain dysfunction	2
Other, <i>n</i> (%)	4 (15)
Hepatic dysfunction	3
Hematological disorders	3
Supportive treatments, <i>n</i>	
Standard nasal O ₂ therapy	20
High flow nasal O ₂ therapy	3
Non invasive ventilation	10
Invasive ventilation	9
Catecholamines	4
ECMO	1
CRRT	1

CRRT, continuous renal replacement therapy; ECMO, extracorporeal membrane oxygenation

Table 2: Radiologic findings and laboratory results

	Value
Radiologic finding	
Abnormalities on chest CT, <i>n</i> (%)	14/16
Negative for pneumonia	2
Indeterminate for COVID-19 (consistent)	5
Atypical pattern of COVID-19	3
Typical for COVID-19	6
Laboratory findings^{¶†}, median (range)	
CRP level, mg/L, <i>n</i> = 26	68.5 (0.5–485)
PCT level, ng/mL, <i>n</i> = 17	1.65 (0.03–448)
Lymphocyte counts per mm ³ , <i>n</i> = 24	1850 (100–4700)
Neutrophil count, × per mm ³ , <i>n</i> = 25	6500 (100–21800)
Fibrinogen level, g/L, <i>n</i> = 17	4.6 (2.7–8.6)
D-dimer level, ng/mL, <i>n</i> = 15	2036 (215–23,611)
Creatinine level, μmol/L, <i>n</i> = 23	42 (13–144)
ALT level, U/L, <i>n</i> = 22	26 (6–4300)

ALT, alanine aminotransferase; CRP, C-reactive protein; CT, computed tomography; PCT, Procalcitonin

[¶] Some data on biological findings are missing

[†] Worst values during the stay

Figure 1 legend: Computed tomography (CT) scan performed on a 6-year-old girl with negative PCR test result, shows a typical aspect of pediatric COVID pneumonia: subpleural ground-glass opacity surrounded by a ring of consolidation in the left upper lobe (reverse halo sign) and bilateral posterior consolidations in the lower lobes

