Patients with sickle cell disease and suspected COVID-19 in a paediatric intensive care unit

Introduction

Concern has been raised for patients with sickle cell disease (SCD) and the new viral infection severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), as patients with SCD are particularly prone to infectious diseases and acute chest syndrome (ACS). Although case reports have been published to describe coronavirus disease 2019 (COVID-19)-related ACS in adult patients,[1–4] paediatric data are lacking.

Patients and methods

We conducted a single centre retrospective observational study, between 1 March and 15 April 2020, in the paediatric intensive care unit (PICU) of Necker Hospital for Sick Children in Paris (tertiary care, SCD reference centre, regional reference centre for emerging infectious diseases). All patients with SCD with suspected COVID-19 admitted to the PICU were eligible for the study.

Confirmed COVID-19 was defined as a positive SARS-CoV-2 reverse transcriptase-polymerase chain reaction (RT-PCR) from a nasal swab.

ACS was defined according to the Vichinsky's criteria[5]

Our local protocol for ACS was as follows:

- Intravenous fluid
- Prophylactic enoxaparin for all
- Antibiotics: cefotaxim and azithromycin. Antiviral therapy left to physicians' assessment
- Analgesics (except non-steroidal anti-inflammatory drugs)
- Hydroxyurea or deferasirox continued except in case of drug toxicity.
- Early non-invasive ventilation (NIV) for respiratory distress, oxygen for hypoxaemic patients to obtain a peripheral capillary oxygen saturation (SpO_2) >95%.
- Red blood cell (RBC) transfusion or automated exchange transfusion according to the physician's evaluation.[6] Automated erythrocytapheresis was performed with a Spectra Optia® machine on a central venous catheter.

Computed tomography (CT) scans were not mandatory.

A nasal swab was collected in the first 12 h of the patients' arrival and SARS-CoV-2 RT-PCR was performed.

The local Ethics Board (Necker Enfants-Malades) waived the need for approval. All patients were informed about the study.

Results

From 1 March to 15 April 2020, 12 children with SCD were included, aged 5–17.5 years. RT-PCR for SARS-CoV-2 was performed in 11of the 12 children and was positive in four. All four patients were SS patients, with no glucose-6-phosphate dehydrogenase (G6PD) deficiency. Patients 2 and 4 were on hydroxyurea (HU), and patient 2 had also been on a transfusion programme for 3 years before he was switched to HU and received desferasirox. Patient 2 had also undergone splenectomy and had experienced previous ACS episodes. The baseline haemoglobin (Hb) and fetal haemoglobin (HbF) levels, when available, are listed in Table I.

The patients presented COVID-19 symptoms from 2 to 12 days before hospital admission (Fig 1). All four patients experienced chest pain, with patient 4 also experiencing shoulder and back pain, all requiring intravenous morphine. The maximum daily dose of morphine received ranged from 0.6 to 1.5 mg/kg/day.

All four patients presented with ACS. Oxygen requirement before NIV was between 1 and 6 l/min, with a respiratory rate from 32 to 50 breaths/min. Maximum venous partial pressure of CO_2 (PCO_2) was 50 mmHg for all four patients (only one patient had an arterial blood gas). All patients received early NIV on arrival in the PICU, with worst fraction of inspired oxygen (FiO_2) from 30 to 46%, positive expiratory pressure (PEP) between 5 and 7 cmH_2O, and inspiratory pressure between 10 and 15 cmH_2O. NIV was administered continuously at first and then sequentially. Patients received from 58 to 128 h of NIV during their PICU stay.

All patients had favourable respiratory outcome with no apparent respiratory distress remaining after discharge from the PICU.

All patients presented some unilateral or bilateral inferior lobe consolidations. Patients 3 and 4 also had CT scans with mixed ground glass (with or without halo sign) and consolidation opacity (Data S1). Mild pleural and pericardial effusions were also present on the CT scans. Patient 4 had an extensive left lower and sub-segmental right pulmonary embolism.

All patients had a high fever (>39.5 °C) and various degrees of inflammation. None of the patients received steroids.

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Table I. Clinical and biological features of the proven COVID-19 patients.

Variable	Patient 1	Patient 2	Patient 3	Patient 4
Baseline				
Age, years	17.5	11.6	12.5	16.6
Sex F/M	F	M	F	F
Weight (kg)	62	43	50	52.7
Baseline haemoglobin, g/l	75	70	90	90
Baseline HbF, %	16	NA	8.3	12.5
Markers of inflammation and thrombosis (worst values)				
Maximal CRP, mg/l	100	246	145	355
Procalcitonin, ng/ml	0.1	0.28	0.77	7.8
IL-6, pg/ml	NA	215	37.5	724
D-dimers, ng/ml	2007	7115	7564	23600
Fibrinogen activity, g/l	4.2	6.9	8.4	6.8
Factor V, %	126	NA	>150	96
Erythrocytapheresis description				
HbS prior to automated RBC exchange, %	81.1	96.3	48.8	80.9
HbS after RBC exchange, %	28.0	36.7	24.5	22.7
Haematocrit before RBC exchange, %	20	25	23	21
Depletion during RBC exchange, %	0	0	0	0
Targeted haematocrit after RBC exchange, %	28	28	28	24
Obtained haematocrit after RBC exchange, %	28	30	28	26
RBC exchange duration, min	52	39	39	66
Blood volume exchanged, ml (ml/kg)	1500 (24)	800 (19)	1000 (22)	1500 (28)
HbS after RBC exchange, %	28.0	36.7	24.5	22.7

NA, data not available; CRP, C-reactive protein; RBC, red blood cells.

Biological markers of inflammation and thrombosis are listed in Table I.

All patients received cefotaxim and azithromycin according to the local protocol. No patient received antiviral therapy or hydroxychloroquine.

One patient (patient 4) with substantial inflammation (Table I) received tocilizumab (8 mg/kg/dose, one intravenous dose) at day 16 of COVID-19 (day 4 in the PICU), with good tolerance and a favourable outcome. That same patient had a high heart rate, anxiety and high D-dimers, and presented with a segmentary pulmonary thrombosis on CT scan performed at day 13 of COVID-19 (day 1 in the PICU), which was treated with enoxaparin.

Patients 2 and 3 received RBC transfusion in their local hospitals before their transfer to the PICU, patient 4 received RBC transfusion on day 16 of COVID-19 (day 4 in the

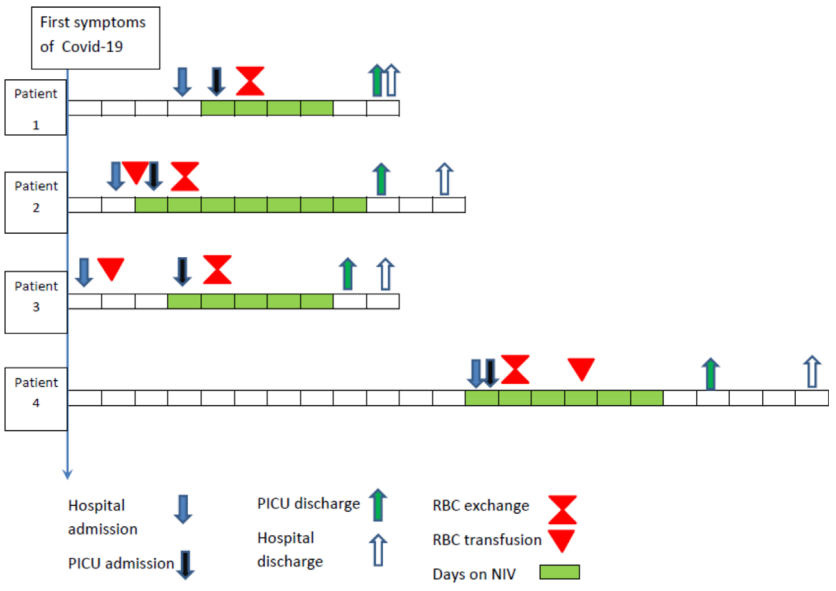

Fig 1. Clinical timeline of the four patients with COVID-19.

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PICU) for an Hb level at 63 g/l (27g/l from baseline) with no sign of haemolysis (Fig 1).

All four confirmed COVID-19 patients had automated RBC exchanges as early as possible after PICU admission, which were well tolerated.

No patient developed any other organ dysfunctions.

Discussion

Due to expanding knowledge on different forms of COVID-19, it is now common practice to perform CT scans for adults to diagnose patients with no viral excretion. It is not certain if CT scans are as reliable for paediatric patients and for patients with SCD, because of a probable overlap of some radiological findings with sickle cell images.[7–9]

As to thrombotic risk, ACS in adult patients had already been associated with high risk of thrombosis in the pulmonary arteries but pulmonary thrombosis is also a major concern in COVID-19, both conditions combined might generate an even higher risk for patients.

In our usual protocol for ACS, we normally limit RBC transfusion or exchange to the most severe patients with NIV failure or with other sickle cell conditions requiring exchange transfusion, e.g. stroke.[6] In patients with COVID-19, we chose aggressive treatments because of the high lethality of COVID-19-related acute respiratory distress syndrome; however, it is possible that our patients would have also had a favourable outcome without this aggressive treatment.

Importantly, specific attention must be taken in caregivers' protection while performing long procedures like RBC exchange for patients with COVID-19.

Conclusion

This is the first case series of ACS related to COVID-19 in children. All patients with COVID-19 with ACS received erythrocytapheresis for their ACS with NIV and usual supportive treatment. One patient received tociluzimab. All patients had favourable outcomes. Screening for pulmonary thrombosis might be useful. Future studies are mandatory to determine the best therapeutic options for these patients.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Data S1. Patient 3 radiographs and CT scans.

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Dynamic relationship between D-dimer and COVID-19 severity

Since December 2019, the severity of the coronavirus disease 2019 (COVID-19) pandemic has been escalating.[1] Coagulopathy is common in critically ill patients with COVID-19.[2] Systemic microvascular thrombosis may occur in most deaths, and was corroborated by a recent autopsy.[3] However, less is known about the coagulation parameter D-dimer in the progression of COVID-19. In this study, we describe 279 COVID-19 patients recruited from three hospitals in Hubei Province, China and investigate the dynamic relationship between D-dimer level and the progression of COVID-19.

According to COVID-19 Diagnosis and Treatment Scheme (Trial Version 7),[4] all laboratory-confirmed COVID-19 patients were mild and moderate cases on admission in our study. We further divided them into three groups according to their clinical courses: an ordinary group (disease was mild or subsided, n = 136), an improved group (disease

Table I. Baseline characteristics and laboratory findings of patients infected with COVID-19 on admission.

	No. (%)				
Characteristics	Total (n = 279)	Ordinary (n = 136)	Improved (n = 23)	Poor (n = 120)	P
Age, median (IQR), years	55 (39–68)	49 (36–56)	58 (41·5–67·5)	65 (51–72)	**<0·001**
Sex					
Male	149 (53·4)	66 (48·5)	12 (52·2)	71 (59·2)	0·31
Female	126 (45·2)	67 (49·3)	10 (43·5)	49 (40·8)	
Cardiovascular disease	77 (27·6)	25 (18·4)	1 (4·3)	51 (42·5)	**<0·001**
Respiratory disease	29 (10·4)	10 (7·4)	1 (4·3)	18 (15·0)	0·08
Immune disease	7 (2·5)	3 (2·2)	0 (0·0)	4 (3·3)	0·61
Endocrine disease	35 (12·5)	12 (8·8)	1 (4·3)	22 (18·3)	**0·03**
Tumour	3 (1·1)	1 (0·7)	0 (0·0)	2 (1·7)	0·67
Infectious disease	9 (3·2)	2 (1·5)	1 (4·3)	6 (5·0)	**0·27**
Signs and symptoms					
Fever	217 (77·8)	106 (77·9)	17 (73·9)	94 (78·3)	0·53
Cough	191 (68·5)	99 (72·8)	17 (73·9)	75 (62·5)	0·54
Chest tightness	31 (11·1)	16 (11·8)	1 (4·3)	14 (11·7)	0·15
Shortness of breath	24 (8·6)	7 (5·1)	3 (13·0)	14 (11·7)	**0·02**
Fatigue	60 (21·5)	27 (19·9)	9 (39·1)	24 (20·0)	0·13
Heart rate, median (IQR), bpm	86 (80–98)	86 (80–98)	87·5 (72–95)	88 (80–98)	0·26
SBP, median (IQR), mm Hg	125 (119–137)	125 (118–136·5)	121 (116–130)	126 (120–139)	0·73
DBP, median (IQR), mm Hg	78 (70–86)	80 (76–87·5)	79 (70–85)	75 (70–80)	**<0·001**
Respiratory rate, median (IQR)	20 (19–22)	20 (18–20)	20 (20–22)	20 (20–25)	**<0·001**
Laboratory indexesm median (IQR)					
White blood cell count, $\times 10^9$/l	5·0 (4·0–7·9)	4·2 (3·6–5·2)	4·8 (4·1–8·0)	6·6 (4·5–8·6)	**<0·001**
Lymphocyte count, $\times 10^9$/l	0·9 (0·6–1·3)	1·2 (0·9–1·6)	0·7 (0·7–1·3)	0·8 (0·5–1·1)	**<0·001**
Lactate dehydrogenase, u/l	263·0 (179·0–360·0)	186·0 (164·0–233·5)	277·0 (190·0–297·5)	335·0 (227·0–408·0)	**<0·001**
Alanine transaminase, u/l	23·0 (16·8–36·5)	23·0 (17·8–30·5)	21·0 (19·0–72·0)	25·0 (16·0–50·0)	**<0·01**
Aspartate transaminase, u/l	27·0 (18·0–45·5)	22·0 (17·5–33·0)	27·0 (23·5–48·0)	33·0 (18·0–49·0)	0·14
Creatinine, μmol/l	73·2 (60·5–92·5)	77·0 (64·4–94·0)	54·9 (48·0–68·0)	73·9 (63·5–95·0)	0·16
Carbamide, mmol/l	5·3 (4·1, 6·9)	4·8 (3·9, 6·5)	4·4 (3·3, 5·0)	5·9 (4·9, 8·2)	0·17
D-dimer, μg/ml	0·3 (0·1-1·3)	0·2 (0·1, 0·4)	0·8 (0·6-7·3)	0·6 (0·2-5·0)	**<0·01**

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