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LETTER TO THE EDITOR

Severe cases of COVID-19 in children with sickle cell disease during the Omicron wave in France: a plea for vaccination

During the first successive waves of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) variants, adult patients with sickle cell disease (SCD), particularly older patients and those with the SC genotype, were reported to be at risk of severe coronavirus disease 2019 (COVID-19), whereas children seemed relatively spared.[1] Although the B.1.1.529 (Omicron) variant was considered to induce less severe forms than the Delta variant in adults, the last Omicron wave resulted in a surprising increase in hospitalised paediatric cases.[2] Nevertheless, little is known about the severity of the Omicron variant in patients with SCD, especially in children. In France, the COVID-19 vaccine has been recommended for adolescents with SCD aged >12 years since 28 May 2021, and for children with SCD aged 5–11 years since 30 November 2021. The objective of this study was to focus on severe outcomes in children with SCD infected by SARS-CoV-2 during the Omicron wave within the landscape of widespread COVID-19 vaccination.

All paediatricians and adult-patient practitioners involved in SCD management in France were contacted by our national SCD consortia (see Ref. [1] for details) to report patients with SCD hospitalised with severe COVID-19 infection from 27 December 2021 to 30 April 2022, corresponding to the Omicron wave in France. SARS-CoV-2 infection was confirmed by reverse transcription polymerase chain reaction or rapid antigen-detection tests.

Severe COVID-19 was defined as hospitalised patients with SCD with at least one of the following criteria: oxygen therapy >3 L/min, intensive care unit (ICU) admission, pulmonary embolism (PE), deep vein thrombosis (DVT), stroke, multisystem inflammatory syndrome in children (MIS-C), or a haemoglobin (Hb) level of <50 g/L.

Anonymised data were collected by the investigators using standardised forms with a minimal dataset (Table 1). The only recorded biological value was the Hb level at admission. In line with the French legislation on retrospective studies of routine clinical practice, participants were not required to give their written informed consent. Patients or their parent/guardian were informed that their medical data could be used for research purposes, in accordance with General Data Protection Regulation 2016/679.

During the 4-month Omicron wave, 29 patients with SCD with severe COVID-19 were reported by 13 French centres. In all, 17 (59%) were children (aged < 18 years), which is the opposite ratio compared to what has been reported thus far among hospitalised patients with SCD during previous COVID-19 waves in France.[1] Because data on hospitalised children with COVID-19 are scarce, we report the main characteristics of these patients.

The first child was hospitalised on 27 December 2021; 12 of the 17 reported children (70.6%) were hospitalised between 8 January 2022 and 8 February 2022. All patients were discharged after hospitalisation. The median (range) age was 9.4 (3.3–17.1) years; 14 of the patients (82.3%) carried the SS or $S\beta^0$ genotype (Table 1). Seven patients (41.2%) had a past medical history of acute chest syndrome (ACS), with a median of one episode for those patients. Hydroxycarbamide (hydroxyurea) was taken at admission by seven patients (41.2%); transfusion in the 3 months before admission occurred in only one patient. In all, 13 children (76.5%) were aged >5 years, which is the cut-off for the recommended COVID-19 vaccine for children with SCD in France, although only two of them (15.4%) received the vaccine: one dose for a 14-year-old child and two doses for a 16-year-old child.

In all, 14 children (82.7%) presented with severe ACS, with ICU admission required for 13 and associated bone pain for all. Two patients (11.8%) presented thrombotic events (one with PE and DVT; one with DVT). Two patients (11.8%) were diagnosed with MIS-C; one of them developed anti-Jka immunisation at 3 weeks after a single red blood cell transfusion, which was achieved during the inflammatory period of MIS-C. One patient had severe anaemia (Hb level of 30 g/L) associated with mild ACS (maximal oxygen flow 2 L/min).

In all, 15 (88.2%) of the 17 children were admitted to the ICU. None died or required invasive mechanical ventilation, but 13 (86.7%) required non-invasive respiratory support (i.e., nasal high-flow therapy or non-invasive ventilation). Overall, 16 patients (94.1%) underwent transfusion after admission to the hospital. The median (range) length of hospital stay was 13 (8–33) days.

The Omicron variant has been demonstrated to lead to less severe forms of COVID-19 in adults, a reduction that has been at least partly attributed to the widespread distribution of COVID-19 vaccines.[3] In the general paediatric population, this variant is associated with significantly less severe outcomes than the Delta variant.[4] In France, in week 13 of 2022, the weekly rate of new hospital and ICU admissions

TABLE 1 Characteristics of 17 children with sickle cell disease with severe coronavirus disease 2019

Characteristic	Value
Total number of children	17
Genotype: SS, $S\beta^0$, SC, $S\beta^+$, *n* (%)	13 (76.4), 1 (5.9), 1 (5.9), 2 (11.8)
Age, years, median (IQR)	9 (3–18)
0–4 years, *n* (%)	4 (23.5)
5–11 years, *n* (%)	6 (35.3)
12–18 years, *n* (%)	7 (41.2)
Male sex, *n* (%)	12 (70.6)
Body mass index, kg/m^2, median (IQR)	15 (12.5–21.3)
COVID-19 vaccination, *n* (%)	2 (11.8)
Previous COVID-19, *n* (%)	1 (5.9)
Acute chest syndrome history, *n* (%)	7 (41.2)
Comorbidities, *n* (%)	
Hypertension	1 (5.9)
Diabetes	0
Transplantation	1[a] (5.9)
Diagnostic: PCR/RAD test, *n*	16/1
Omicron variant, *n*	7/7
Hydroxycarbamide treatment at admission, *n* (%)	7 (41.2)
Transfusion exchange programme at admission, *n* (%)	1 (5.9)
Severe events during COVID-19 hospitalisation, *n* (%)	
VOC	15 (88.2)
Acute chest syndrome	14 (82.4)
Vascular event	2 (11.8)
Pulmonary embolism	1
Deep vein thrombosis	2
Stroke	0
MIS-C	2 (11.8)
ICU admission, *n* (%)	15 (88.2)
Length of ICU stay, days, median (IQR)	5 (2–38)
Invasive mechanical ventilation or death, *n* (%)	0
Non-invasive respiratory support, *n* (%)	13 (86.7)
Red blood cells transfusion, *n* (%)	16 (94.1)
Delay between admission and transfusion, days, median (IQR)	2 (0–10)
Automated exchange, *n*	4
Exchange transfusion, *n*	2
Transfusion, *n*	10
Specific treatment, *n* (%)	6 (35.3)
Corticoids	4
Specific monoclonal antibodies	1
Polyclonal immunoglobulins	2
Anakinra	1
Length of hospital stay, days, median (IQR)	13 (8–33)

Abbreviations: COVID-19, coronavirus disease 2019; ICU, intensive care unit; IQR, interquartile range; MIS-C, multisystem inflammatory syndrome in children; PCR, polymerase chain reaction; RAD, rapid antigen detection; SCD, sickle cell disease; VOC, vaso-occlusive crisis.

[a]Liver transplantation.

per 100 000 habitants were respectively 13.0 and 1.2 for all ages, 5.3 and 0.6 for the 0–9 years age group, and 2.2 and 0.2 for the 10–19 years age group (https://www.santepubliquefrance.fr/en/covid-19-epidemiological-update.-weekly-report.-week-13.-7-april-2022).

Nevertheless, the US National COVID cohort collaborative reported that the COVID-19 paediatric ICU rate increased during the Omicron surge and that more than one-fifth of children in the ICU infected with SARS-CoV-2 developed severe symptoms.[5]

As also reported for previous COVID-19 waves in France,[1] mechanical ventilation or mortality did not occur in hospitalised children with SCD. However, we report in this study that severe cases still occurred in children with SCD during the Omicron wave, with the use of non-invasive respiratory support or transfusion and a long hospital stay for most of them.

Walter et al.[6] found that the BNT162b2 COVID-19 vaccine was safe and effective in children aged between 5 and 11 years. Price et al.[7] showed that this vaccine reduces the risk of Omicron-associated hospitalisation by two-thirds among children aged 5–11 years and prevents critical illness caused by other variants among adolescents aged 12–18 years. None of the 107 children with MIS-C in a French series had been fully vaccinated, suggesting that COVID-19 messenger RNA vaccination was associated with a lower incidence of MIS-C in adolescents.[8] Whether all healthy children aged >5 years should be vaccinated against COVID-19 remains an ongoing debate,[9] but the prevention effort should certainly concern high-risk populations such as children with SCD. In France, all children with SCD aged 12–17 years were eligible for COVID-19 vaccines in May 2021, and as of 2 January 2022, 77.7% of those in this age group received the first two doses of vaccine (https://datavaccin-covid.ameli.fr/pages/type-vaccins/).

In our study, only two of the 17 children had received the COVID-19 vaccine, and only one of the seven patients aged 12–17 years (14.3%) had received two doses. The very low prevalence of vaccination in our cohort might reflect a detection bias (we only recruited severe hospitalised patients, who were less prone to be immunised) or a lower COVID-19 vaccine acceptance in the SCD paediatric population compared to the general population.

One of the limitations of our study is that few patients benefited from variant characterisation (Omicron for all seven characterised patients), even if most circulating

variants were Omicron (89% and 99% during the first and fifth weeks of January 2022 respectively; https://www.santepubliquefrance.fr). Another limitation is that the study was declarative.

In conclusion, this study emphasises the urgent need to expand vaccination for COVID-19 in children with SCD aged >5 years, as there was a low rate of vaccination among the children reported in this study who were hospitalised with severe outcomes.

AUTHOR CONTRIBUTIONS

Stephanie Eyssette-Guerreau wrote the manuscript and contributed to the analysis and interpretation of data. Jean-Benoit Arlet conceived the study; contributed to patient recruitment; acquired, analysed and interpreted the data. Djamal Khimoud contributed to the acquisition, analysis and interpretation of data. Katell Michaux, Marie-Hélène Odièvre, Slimane Allali, Sophie Pertuisel, Cécile Guillaumat, Marie Monfort, Corinne Guitton, Alice Miquel, Camille Runel, Alexandra Gauthier contributed to patient recruitment and the acquisition and interpretation of data. All authors confirm that they had full access to all the data in the study.

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CONFLICT OF INTEREST

All authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author upon reasonable request.

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