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LETTER TO THE EDITOR

Addressing the impact of SARS-CoV-2 infection in persons with congenital bleeding disorders: The Italian MECCOVID-19 study

Since January 2020, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic is challenging healthcare systems worldwide with the impact of the associated disease (COVID-19), often characterized by severe interstitial pneumonia and respiratory insufficiency, up to need for intensive care (IC) and fatal outcome, particularly in elderly individuals and those with multi-morbidities. On the other hand, the scientific community is deeply involved to fill the numerous pathophysiological and clinical knowledge gaps.

The large allocation of human and economic resources to face the pandemic and the lockdown mobility restrictions led to develop strategies to minimize risks of inadequate access to the standard medical care for patients with chronic diseases and/or requiring regular clinical monitoring, like those with congenital bleeding disorders (CBD).[1] A Spanish experience recently showed that the use of remote telematic communication by physicians and nurses of the Haemophilia Centre (HC) and the logistics for the home transport of the life-saving treatment products ensured the continuity of diagnostic and therapeutic services and follow-up of patients, including those enrolled in the clinical studies.[2] Further challenges are related to the specific risks and the management of symptomatic disease in patients with CBD.[1,3] Indeed, COVID-19 is associated with an acquired coagulopathy (COVID-19-Associated Coagulopathy, CAC), triggered by a powerful storm of inflammatory cytokines, resulting in a hypercoagulable state and risk of venous and arterial thromboembolic events.[4] Different protocols of thromboprophylaxis with low-molecular-weight heparin (LMWH) are therefore currently used and studied in clinical trials to reduce thrombotic complications and mortality.[5] Specific guidance about the management of hospitalized persons with CBD and COVID-19 has been proposed, highlighting the need for rapid identification of the CBD status, undelayed and close contacts with the specialists of the HCs, continuing/intensifying prophylaxis regimens (both replacement and non-replacement therapy) according to the actual bleeding risk and the association of LMWH thromboprophylaxis.[3]

At present, limited literature data are available about the prevalence and clinical implications of COVID-19 in patients with haemophilia and CBDs. A registry of patients with CBDs and COVID-19 was set up in Madrid, Spain by a telephone survey.[6] Suggestive symptoms were reported in 42 patients, but SARS-CoV-2 infection was confirmed by RT-PCR only in 6, accounting for a cumulative incidence of 1.73%. All patients showed a mild course of the disease, not requiring hospitalization.[6] Restrictions due to the lockdown and limited access to diagnostic tests in the first phase of pandemic clearly affect these data. Furthermore, larger collections of data are needed to address the intriguing issue of the impact of CAC and the related hypercoagulability in infected persons suffering from a congenital condition of hypocoagulability. Indeed, a letter by Iranian authors questioned whether CBD patients could somehow be spared from thrombotic complications. In a series of 9 CBD patients, a single thrombotic event was reported, occurring in a young type 1 von Willebrand disease patient needing IC admission due to severe COVID-19.[7] The authors concluded that patients with moderate to severe CBD with COVID-19 appear to be less likely to have a hypercoagulable state.[7] Few data are available also concerning the bleeding risk in patients with CBDs and COVID-19. In the Iranian series, two patients experienced bleeding.[7] A severe abdominal hematoma in a woman with inherited FXIII deficiency and severe cough due to COVID-19 has been reported. She was able to receive LMWH thromboprophylaxis after treatment of acute bleeding and prolonged prophylaxis with FXIII concentrate.[8] LMWH was used in a patient with severe haemophilia A on emicizumab prophylaxis and COVID-19,[9] as well in a patient with mild haemophilia A hospitalized because of acute respiratory failure, in whom, consistent with the hyperinflammatory state, high FVIII levels were found.[10] Both these patients did not experience thrombotic or haemorrhagic complications. However, the safety of LMWH in CBD patients with COVID-19 and indications about concomitant haemostatic prophylaxis are still uncertain, poorly supported by clinical data.

In light of these considerations, the urgent need to perform *ad hoc* clinical studies in patients with haemophilia and other CBDs infected by SARS-CoV-2 emerged. These patients are carefully monitored by HCs for their bleeding disorder and the related or unrelated co-morbidities, therefore accurate information can be retrieved and prospective follow-up can be planned. Moreover, national/regional registries of CBD patients are available for epidemiological assessments. An observational retrospective-prospective multicentre cohort study evaluating the impact of COVID-19 in the Italian population of patients with haemophilia and other CBDs was recently designed on behalf of the Italian Association of Haemophilia Centers (AICE). The study (named MECCOVID-19, acronym from the Italian *Malattie Emorragiche Congenite* and COVID-19) is aimed to collect epidemiological data about prevalence and incidence of COVID-19 in

AICE, Italian Association of Haemophilia Centres; MECCOVID-19, *Malattie Emorragiche Congenite e COVID-19*. The co-authors participating in the Study Group are listed in the Appendix 1.

patients registered at AICE HCs and information on clinical course, management and outcome of those diagnosed with COVID-19 since the outbreak of SARS-CoV2 pandemic in Italy (February 2020). According to the study design, enrolment of patients up to the end of 2021 and at least 1-yr follow-up (end-of-study December 2022) are planned. The study started in August 2020 and is currently being approved by the Institutional Review Boards and Hospital Directions of each participating HC.

A feasibility survey was carried out in May 2020 among all AICE HCs by means of a web-based questionnaire to assess the interest in the study issues and the number and characteristics of registered patients with COVID-19. Twenty-eight out of 50 HCs answered the questionnaire, and 13 CBD patients with SARS-CoV-2 infection from 5 HCs were reported at that time and at a re-call in September 2020. Patients' clinical characteristics, including COVID-19 symptoms and complications, are summarized in Table 1. Although most patients were asymptomatic or had mild/moderate respiratory symptoms, at variance with the Spanish report,[6] 4 patients had severe disease and needed hospitalization due to pneumonia and acute respiratory failure, including one in IC and one with fatal outcome. No thrombotic complications were reported, while one patient experienced severe bleeding, that is the woman with severe FXIII deficiency mentioned above.[8]

These figures are highly underestimated, being referred to the first phase of the pandemic, in which diagnostic tests were limited and mainly performed in symptomatic subjects. Moreover, information was provided about hospitalized patients or by those contacting the HCs only. Considering epidemiologic data by the Italian Institute of Health about COVID-19 (www.epicentro.iss/coronavirus) at the time of the survey and the prevalence of CBD in our country, at least 50 CBD patients should have been diagnosed with COVID-19, 10 with severe or critical symptoms. On the other hand, many additional patients have been identified over the last months thanks to the huge increase in serologic and molecular tests in the second wave of pandemic.

In the AICE study, all CBD patients registered at the HCs at the COVID-19 outbreak are eligible and will be asked to be enrolled, irrespective of age and CBD severity, at routine visits or by telematic communications. At enrolment, patients' demographic data, CBD history, treatment and co-morbidities will be registered. Moreover, specific case report forms will collect data about exposition to SARS-CoV-2 infection in the retrospective phase (February 2020-enrolment), including possible symptoms of disease, close contacts with infected individuals and quarantine, diagnostic tests performed (antigenic or PCR nasopharyngeal swabs, serologic tests for anti-SARS-CoV-2 antibodies). In patients diagnosed with

TABLE 1 Clinical features of patients with CBD and COVID-19

Centre/Patient	Gender/Age	Type of CBD	CBD treatment regimen	Co-morbidities	COVID−19 Symptoms	Hospitalization/Complications
1/1	M/77	Mild HA	On demand	Hypertension, previous prostatic cancer	Fever, cough, dyspnoea	Yes/Acute respiratory failure[a]
1/2	M/39	Moderate HA	On demand	No	Fever, cough	No
2/1	M/5	Severe HA	Prophylaxis	Autism spectrum disorder	No	No
2/2	M/20	Severe HA	Prophylaxis	No	No	No
2/3	M/3	Severe HA	Prophylaxis	No	No	No
3/1	M/30	Severe HA	Prophylaxis	No	No	No
4/1	M/55	Severe HA	Prophylaxis	HIV infection	Fever, dyspnoea	Yes, ICU/Acute respiratory failure
5/1	F/61	FXIII deficiency	On demand	No	Fever, severe cough	Yes/Severe abdominal bleeding[b]
5/2	M/41	Mild HA	On demand	No	Fever, dyspnoea	No
5/3	M/24	Severe HA	Prophylaxis	No	Ageusia, anosmia	No
5/4	M/50	Mild HB	On demand	No	Ageusia, anosmia	No
5/5	M/39	FXI deficiency	On demand	Hypertension, previous subarachnoid haemorrhage	Fever	No
5/6	M/69	Mild HA	On demand	Diabetes mellitus, schizophrenia	Fever, dyspnoea	Yes/Acute respiratory failure; death

Abbreviations: CBD; congenital bleeding disorders; HA: haemophilia A; HB: haemophilia B; ICU: intensive care unit.

[a]Case report published.[10]

[b]Case report published.[8]

SARS-CoV-2 infection and COVID-19, additional forms will register information about the clinical course and outcome (type, intensity and duration of symptoms; need for hospitalization and IC; pharmacological treatment, with emphasis on use of antithrombotic and haemostatic drugs; bleeding manifestations and thrombotic complications; other clinical complications and outcome). In the 1-yr prospective follow-up, re-assessment of enrolled patients will be carried out every 3 months, at planned visits or by telemedicine approaches.

Reduced participation of the HCs and patients' enrolment, even due to the persistent healthcare emergency and variable lockdown measures according to the epidemiologic risk, are possible threats to the study conduct. However, feasibility data from the survey and the number of HCs active in the study or with authorizations in progress make these limitations unlikely. Telematic procedures have been included in the study protocol to facilitate patients' enrolment and follow-up, in the presence of mobility restrictions or reluctance to hospital access. This approach will also minimize possible selection bias in the study population. The study was designed before the availability of vaccines, currently administered according to priority groups, even in Italy. General information (type of vaccine, immunologic and clinical outcomes, adverse events) and specific vaccination issues (need for haemostatic prophylaxis and bleeding complications of i.m. injections) in CBD patients should be collected in *ad hoc* studies; however, main data could be included in the patients' report forms of this study.

In conclusion, the Italian MECCOVID-19 study was designed and started to gather information as accurate and complete as possible about the epidemiological and clinical impact of COVID-19 in CBD patients. The systematic investigation in this population and the study design, with retrospective and prospective homogeneous data collection, will confidently help to better elucidate these issues, also providing insights about the implications and the challenging management of the coexisting bleeding and thrombotic risk in this setting.

KEYWORDS

congenital bleeding disorders, COVID-19, epidemiology, haemophilia, observational study, SARS-CoV-2

DISCLOSURES

IR acted as a paid consultant to Sobi, Bayer and Takeda/Shire. ACop acted as a paid consultant to Bayer and Novo Nordisk and received fees as an invited speaker by Novo Nordisk, Roche and Werfen. AR acted as paid consultant/member of advisory board/speaker for Bayer, CSL Behring, Kedrion, Novo Nordisk, Roche, Shire/Takeda and Sobi. ACol, EM, ACG, GFR, EZ, ML and RDC had no interests which might be perceived as posing conflict or bias.

AUTHOR CONTRIBUTIONS

ACol, EM and ACG designed the study and the preliminary feasibility survey and collected data. GFR, IR, EZ, LM and RDC provided patients' information. ACol and ACop wrote the manuscript. AR, EM and ACG revised it critically. The co-authors listed in the Appendix 1 participated in the survey and are study investigators. All the authors approved the final version submitted to the journal.

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APPENDIX 1

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