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Congenital Bleeding Disorders amid the COVID-19 pandemic: open questions and recommendations

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Summary. This article reviews the current knowledges of congenital bleeding disorders (CBD) amid the COVID-19 pandemic. It appears that CBD is not associated with higher risk of getting COVID-19 and so the prevalence of COVID-19 among them seems not higher compared to the general population. In absence of specific therapeutic recommendations, it is essential to make a correct assessment of the risk of haemorrhage/thrombosis. Based on expert opinion, strategies for outpatient management include adherence to prescribed regimens, telemedicine, and communication about COVID-19 in patients with CBD. More data should be also collected to better characterize the impact of COVID-19 on patients with CBD. The current findings encourage further studies to determine the prevalence of SARS-CoV2 infection in CBD patients to understand more fully the burden of this novel pathogen and to develop adequate preventive measures against this infection. (www.actabiomedica.it)

Key words: COVID-19, congenital bleeding disorders, treatment, surveillance

Background

The SARS-CoV-2 causing COVID-19 has reached pandemic levels since March 2020. In the absence of vaccines or curative medical treatment, COVID-19 exerts an unprecedented global impact on public health and health care delivery. Current available data show that the mortality is very low in those <20 year of age but much higher, up to 20%, in older patients presenting with comorbidities (1).

The hemostatic balance is the result of normal functioning of the blood vessel wall, platelets and plasma agents which include the coagulation and fibrinolytic systems and their inhibitors.

Congenital bleeding disorders (CBD) include a spectrum of disorders that affect clotting factors, platelets or the vessel wall, and the clinical manifestation varies depending on the underlying cause.

von Willebrand disease (vWD) is the most common inherited bleeding disorder, affecting 0.1% to 1% of the total population, followed by haemophilia A and B. Inherited platelet disorders are rare, found in about 1 out of 10.000 patients. The remaining defects, generally transmitted as autosomal recessive traits, are rare with prevalence of the presumably homozygous forms in the general population of 1:500,000 for FVII deficiency and 1 in 2 million for prothrombin (FII) and factor XIII (FXIII) deficiency (2).

The clinical history of patients should focus on the site and severity of previous episodes of bleeding, including requirements for blood transfusion, nature of the provoking injury, consequences of exposure to

previous haemostatic challenges (such as surgery, tooth extraction, childbirth) and presence of a family history (2,3).

Patients suffering from vWD usually present with mucocutaneous bleeding, including epistaxis, easy bruising, menorrhagia and excessive bleeding from minor wounds, tooth extractions and surgery. The clinical presentation is, however, very heterogeneous and the rate of spontaneous bleeding may be low, even in patients with severe vWF deficiency. There is frequently a family history of abnormal bleeding and excessive bruising, as vWD is an inherited disorder that most frequently displays an autosomal dominant pattern. The standard diagnostic tests include measurement of total vWF protein (vWF antigen), a vWF activity (such as ristocetin-cofactor activity) and ristocetin-induced platelet aggregation (RIPA), which determine the ability of vWF to bind platelets. Coagulation factor VIII levels are also measured. Levels of vWF vary among different ethnic groups and blood types (4-6)

Many therapeutic options are available. DDAVP is the first line of treatment for bleeding. vWF concentrates are used to treat bleeding that is unresponsive to DDAVP and as prophylaxis before procedures (2,7).

Bleeding in haemophilia can be spontaneous or after trauma. The hallmark of haemophilia is spontaneous intra-articular bleeding. The most affected joint is the knee, followed by the ankle, elbow and hip joints (8). The diagnosis of haemophilia should be confirmed with coagulation and/or genetic testing. Haemophilia typically shows a prolonged activated PTT (aPTT) with a normal INR. The current standard of care in haemophilia is to prevent bleeding by prophylactic infusion of the deficient clotting factor.

In patients with rare CBD, consultation with a hematologist is advised to facilitate accurate diagnosis and to ensure proper management and follow-up. The approach to bleeding episodes and invasive procedures is individualized and depends on the severity, frequency, and, in the case of procedures, likelihood of bleeding. The first line of treatment is replacement of the deficient factor, using specific plasma-derived or recombinant products and using fresh frozen plasma or cryoprecipitate when specific products are not available or in resource-limited countries. Prophylaxis may be considered in individuals with recurrent serious bleeding and especially after life-threatening bleeding episodes (9-11).

Epidemiologic and clinical data about COVID-19 in CBD are substantially lacking. Therefore, we aimed to search the current literature on COVID-19 disease and CBD, through PubMed, Publon, Scopus and ISI, Webinars, and congresses from December 2019 to June 2020, in patients with hereditary bleeding disorders in order to have a better view on open questions and current recommendations based on evolving data.

COVID-19 in patients with CBD

It seems that all types of congenital coagulation disorders, including patients with hemophilia and rare bleeding disorders, can be involved by COVID-19 disease (12). However, due to a paucity of data available in the literature, it is not clear whether these patients are prone to the severe form of the disease.

Nine patients were reported by Dorgalaleh et al. (12), 5 with hemophilia A, 2 with vWD, 1 with hemophilia B and 1 with FXIII deficiency. All except one of these patients were males, with a mean age of 48.2 years (range: 26–59 years), and most were symptomatic at the time of SARS- CoV- 2 infection. Among the nine patients, two (~22%) experienced bleeding and one (~11%) experienced thrombosis. Both patients with bleeding events had contributing risk factors: one with lymphoma and another with factor VIII inhibitor. Thrombosis was observed in a young hospitalized patient with type 1 vWD, who was treated in the intensive care unit for two days.

A telephone survey was used to collect data on 345 patients with CBD (246 of haemophilia, 69 of von Willebrand Disease, 2 rare bleeding disorders and 28 carriers of haemophilia). Forty two patients presented symptoms suggestive of infection by COVID-19 and in 6 cases the disease was confirmed by RT-PCR. The cumulative incidence of SARS-CoV-2 infection was 1.73% and the course of disease was mild and none of them required admission or specific treatment for COVID-19 (13).

Therefore, it appears that CBD is not associated with higher risk of getting COVID-19 and so

the prevalence of COVID-19 among them seems not higher compared to the general population. The reason is not fully known yet, but it might be due to the constant vigilance of patients implemented by hemophilia centers. Moreover, a severe hypocoagulability state may be protective against COVID-19 hypercoagulability- related adverse effects in the absence of comorbidities, including diabetes mellitus, heart disease, or hypertension (14).

Effects of SARS-CoV-2 infection on blood coagulation

Significant inflammation is present in patients with SARS-CoV-2 infection, based on elevated levels of IL-6, increased C-reactive protein and erythrocyte sedimentation rate, and elevated fibrinogen at presentation (15). In general, viral infections elicit the systemic inflammatory response and cause an imbalance between procoagulant and anticoagulant homeostatic mechanisms.

The mechanisms that activate coagulation in SARS-CoV-2 infection are not known at present but appear to be linked to inflammatory responses rather than specific properties of the virus.

Blood coagulation, in COVID-19 patients, seems to be clearly altered compared with a healthy control population. Consistent evidence shows that COVID-19 is associated with significant changes in coagulation laboratory testing, mainly prolonged prothrombin time (PT) and elevated D-dimer (16). PT, D-Dimer, and fibrin/fibrinogen degradation products (FDP), were found to be especially predictive of disease progression (16,17).

Pooled results revealed that PT and D-Dimer levels were significantly higher in patients with severe COVID-19. Increasing values of D-Dimer and PT support the notion that disseminated intravascular coagulation (DIC) may be common in COVID-19 patients (17). In addition, the rise of D-Dimer level also indicates secondary fibrinolysis conditions in these patients. Several studies showed severe COVID-19 disease accompanied by coagulopathy with both features of DIC and thrombotic microangiopathies as poor prognosis symptoms and adverse outcome in which anticoagulation therapy may decrease mortality rate (14,18,19). However, up to date, no breakthrough bleeding, DIC, or thrombotic events have been reported among patients with CBD (18).

A vicious cycle of inflammation and coagulation activation is likely to be responsible for lung microvascular thrombosis and systemic venous thromboembolism (VTE), reported in patients with COVID-19 (18, 20–22). Therefore, thromboprophylaxis with low-molecular weight or unfractionated heparin has been advised hospitalized COVID-19 patients (23).

While the scientific community is waiting for more robust evidence from properly designed clinical trials with strong end points, the International Society of Thrombosis and Hemostasis (ISTH), guidance documents approve the prophylactic anticoagulation (low molecular weight heparin) in all COVID-19 patients in the absence of contraindications including active bleeding and thrombocytopenia (less than 25 × 109/L) but abnormal PT or activated partial thromboplastin time (APTT) is not a contraindication. In non-bleeding patients, maintain platelet count above 25 × 109/L, and in case of bleeding patients, keep platelet count above 50 × 109/L, fibrinogen above 1.5 g/L, and PT ratio <1.5 are recommended (18).

Patients with CBD and COVID-19 encounter the risk of thrombosis in one hand and, on the other hand, are predisposed to bleeds, especially the most symptomatic forms, such as severe hemophilia.

The data among patients with CBD affected by COVID-19 are minimal. To date, one study including 9 patients with CBD from Iran was reported. Moreover, a single case report from China has been published describing a 35-year-old man with severe hemophilia A in Wuhan, China, with mild symptoms due to confirmed SARSCoV- 2 pneumonia (12, 24). No bleeding events occurred under active treatment at home with antiviral agents, empirical antibiotics, and supportive therapies. In conclusion, clinical manifestations, and outcomes of this mild COVID-19 patient with haemophilia were similar to that in non-haemophilic individuals. Therefore, there is no reason to think that susceptibility to SARS-CoV-2 infection or clinical course should differ in CBD patients from the general population (25).

In brief, we do not know yet whether these patients are at higher risk of disease severity with COV-

ID-19, including coagulopathy and no specific data exists regarding management of patients with CBD who are infected with COVID-19, however, standard prophylactic doses of heparin are considered safe in patients with hemophilia, as in the case of thromboembolic complications (18). Concomitant use of standard prophylactic doses of heparin are considered safe in hospitalized hemophilic patients affected by COVID-19, as in the case of thromboembolic complications.

In those patients who are on prophylaxis, the treatment must be continued during COVID-19 disease (26).

General recommendations for patients with inherited coagulation disorders

- Physicians should inform patients and caregivers about the importance of strict social distancing, hand hygiene, and symptoms of COVID-19.
- Teleconsultations have an essential role in this regard, specially for children with comorbidities (27).
- Hemophilic patients receiving immunosuppressive treatments for eradication of inhibitors must take precautions more seriously. According to scarcely available literature, mild infection of SARS-CoV-2 may not raise the rate of bleeding events in hemophilic patients and such cases may benefit from the administration of replacement factors at the onset of COVID-19 (20,28).
- Patients on the prophylactic clotting factor should have one month of dose on hand. Medications with the earliest expiration date must use first as well as patients that treat bleeding episodes with clotting factor may have at least 2-3 emergency doses nearby. Physical activities to prevent the worsening of joint stiffness and prevent muscle loss is recommended (20,28)
- Acetaminophen is a reasonable choice for reducing fever in patients with bleeding disorders (29).
- Viral inactivation methods are appropriate to eradicate lipid-enveloped viruses like SARS-CoV-2, and blood and plasma donation remains to be a safe practice. Moreover, for those patients who are receiving platelets or cryoprecipitate, the administration may base on the clinical risk/benefit balancing (28,30).

Action plans for inherited bleeding disorders in hospitalized patients due to COVID-19

- If COVID-19 is diagnosed, prophylaxis with factor replacement therapy should be continual, and in case of severe infection, higher trough levels may need to consider (23,25).
- At the time of hospital admission, the staff must be well-informed about the type of bleeding disease. Essential biological assessment consisted of CRP, full blood count, renal function, aPTT (activated partial thromboplastin time), PT, fibrinogen, D-Dimers, FVIII or FIX assay, ferritin, inhibitor screening, and troponin levels and imaging workup should be performed (28).
- Electrocardiogram (ECG) is necessary to rule out any cardiac disease and to measure the QTc interval if treatment with hydroxychloroquine is considered (31).
- Patients with inherited coagulation disorders must not have arterial blood gases or central venous access route if needed without replacement of the coagulation factor (> 50 %) (28).
- Coagulation pathways activate in the process of COVID-19, so D-Dimer is raised in most cases of hospitalized COVID-19 patients and it is the indicator of thrombus formation and degradation. Anticoagulants suggest as a measure of treatment protocols for patients with elevated D-Dimer and infection and should convey by factor replacement therapy simultaneously (29).
- Extra Corporeal Membrane Oxygenation (ECMO) is indicated if close monitoring of coagulation parameters is achieved. Checking of vWF concentrations is recommended for a possible acquired VWF deficiency that could be triggered by ECMO (28).
- Tight co-operation between all the specialists involved in the treatment of COVID-19 patients is also recommended.

Conclusion

At the present time, it is impossible to estimate how many patients with CBD will become infected and whether their factor deficiency and their treatment could influence the manifestations of the infection, its natural course, treatment, and consequences. The few reported cases of SARS-CoV-2 infection in people with CBD might reflect the efforts of clinicians to minimize social contacts. This effort might be considered a success, but there is no room for complacency and the directive for social shielding of both the patient and family members remains clear and important. The disease course does not seem to differ from the general population, but the current numbers are too small to draw firm conclusions. Caution must be exercised when interpreting coagulation parameters. Antithrombotic prophylaxis/treatment is challenging in the management of CBD patients with COVID-19, as well all conditions inducing increased bleeding risk, due to the disease or to its management and treatment (33,34). In absence of specific therapeutic recommendations, it is essential to make a correct assessment of the risk of haemorrhage/thrombosis. Based on expert opinion, strategies for outpatient management include adherence to prescribed regimens, telemedicine, and communication about COVID-19 with patients with CBD.

The current findings encourage further studies to determine the prevalence of SARS-CoV2 infection in CBD patients to understand more fully the burden of this novel pathogen and to develop adequate preventive measures against this infection.

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