Scientific Foundation SPIROSKI, Skopje, Republic of Macedonia
Open Access Macedonian Journal of Medical Sciences. 2022 Jul 30; 10(F):648-654.
https://doi.org/10.3889/oamjms.2022.9837
eISSN: 1857-9655
Category: *F - Review Articles*
Section: *Narrative Review Article*

COVID-19 and Thrombosis Complication in Children

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Edited by: Eli Djulejic
Citation: Dimiati H, Widasari N. COVID-19 and Thrombosis Complication in Children. Open Access Maced J Med Sci. 2022 Jul 30; 10(F):648-654. https://doi.org/10.3889/oamjms.2022.9837
Keywords: COVID-19; Thrombosis; Children
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Received: 17-Apr-2022
Revised: 20-Jun-2022
Accepted: 20-Jul-2022

Funding: This research did not receive any financial support
Competing Interest: The authors have declared that no competing interest exists

Abstract

Since it was discovered in Wuhan in December 2019, most studies on COVID-19 have been centered on symptomatic adults. An expanded pro-inflammatory cytokine reaction, abnormal clot formation, overactive platelets, and hypercoagulable state are among the well-known clinical characteristics of endothelial dysfunction that may arise in patients with COVID-19. These conditions can lead to venous thromboembolism, arterial thrombosis, and pulmonary embolism. To date, the predominance of thromboembolic complications in children infected with severe acute respiratory syndrome coronavirus 2 has not been fully documented, and there is no explicit recommendation for the prevention of thrombosis in children.

Introduction

In December 2019, a flare-up of COVID-19, brought by an original CoV, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1], was found in Wuhan, China [2]. The contamination promptly extended globally and on March 11, 2020, declared a pandemic by the World Health Organization.

Innate immune response, thrombotic response, and acute-phase reactants (like fibrinogen and fibrinogen) are recognized to be firmly related [3], [4]. The surge in the levels of IL-6, C-reactive protein (CRP), and erythrocyte sedimentation rate in SARS-CoV-2 patients is considered as a significant inflammation [5]. CRP might cause the hypercoagulable state related to COVID-19 and increment the seriousness of the sickness [3], [4]. Furthermore, inflammation caused by COVID-19 plays a critical part in cardiovascular complications, where IL-6, alongside different cytokines, sets up a pre-thrombotic condition by paralyzing regular hemostatic inhibitors. Endothelial cell dysfunction caused by COVID-19 contamination creates too much thrombin clog and fibrinolysis shutdown. The hypoxia seen in serious COVID-19 can accelerate thrombus production by expanding blood consistency. Furthermore, initiation of the hypoxia-inducible factor 1 signaling pathway expands blood coagulability [6], [7].

COVID-19 in Children

Majority of COVID-19 are asymptomatic or mild in children aged <18 years [8]. Most cases were less severe on younger patients than grown-ups. The main rational explanation behind why most youths had a harmless symptom with gentle respiratory manifestations remains undisclosed. The host might clarify this condition as children have less angiotensin-converting enzyme 2 (ACE2), the key principle for pathogenesis, than adults. Furthermore, children's immunity is less mature to react with SARS-CoV-2 infection, so there is a tendency to underestimate the COVID-19 infection in children, in consequence of under standard screening to identify COVID-19 infection based on clinical symptoms [9].

The most general symptoms of children infected by COVID-19 were pyrexia and cough. Other symptoms are fatigue, myalgia, nausea, vomiting, and diarrhea stool, which are milder than adult [10], [11], [12], [13]. Children infected with SARS-CoV-2 may also have serious symptoms. On January 27, 2020, Wuhan reported its first critical case of childhood infection. The patient was a 13-month-old boy. At first, he often vomited and had diarrhea. After 6 days, he quickly developed other severe symptoms, such as difficulty breathing and oliguria, and eventually developed to acute

respiratory distress syndrome (ARDS), septic shock, and acute kidney failure [14].

As of April 2020, there have been reports of fever, cardiovascular shock, and/or Kawasaki disease characteristics that arose in previously healthy children. Excessive inflammation and multiple system involvement time related to exposure to SARS-CoV-2 [15], [16]. Data regarding several children with severe COVID-19 illness requiring hospitalization are lacking. According to the statistics, the cumulative hospitalization rate related to COVID-19 among children <18 years for the period of March 1, 2020–July 25, 2020, was 8.0/100,000 inhabitants, with the biggest proportion of kids aged <2 years (24.8) [17]. The beginning phases of the COVID-19 pandemic primarily involved adults beyond 15 years old, suggesting that confirmed children cases can be spread from relatives or the local neighborhood [18]. Furthermore, the chance of children passing on the virus is small, and there is no obvious report indicating that they can transmit the infectious disease to adults [19].

The Incidence of Thromboembolism in Children

COVID-19 attacks the respiratory tract by pneumonia and ARDS. However, the latest data emphasized that COVID-19 is linked to a higher risk of thrombotic complications: Microvascular thrombosis, venous thromboembolic disease, and stroke. Thrombotic complications become a remarkable sign of severe COVID-19 and are linked with multiple organ failure with a higher mortality burden [20]. The previous research by Panigada *et al*. stated that COVID-19 patients are more vulnerable to venous thrombosis because of hypercoagulability caused by inflammation [21].

Bigdelian *et al*. have reported intracardiac thrombosis in children with COVID-19. Three cases of significant intracardiac mobile masses were found from transthoracic echocardiography then treated with surgical procedure, whereas hypercoagulopathy related with COVID-19 in young patients was rarely announced. Their blood test result shows leukocytosis with a high CRP [22]. Another case reported by Chima *et al*. Showed pulmonary embolism in children [23]. Pulmonary embolism is an uncommon condition involving around two to six out of 10,000 discharged younger patients. Although, its appearance seems to be more common in hospitalized children with COVID-19 [24], [25]. Figure 1 shows the appearance of intracardiac thrombus on transthoracic echocardiogram.

Obesity is known to be the predisposing factor in developing pulmonary embolism. Two subjects from Chima *et al*.'s investigation had a BMI >40 [23]. In grown-up COVID-19 patients, a raised BMI is related to severity as well as death. Obesity is believed to increase the sickness severity due to the pro-inflammatory condition and other related vascular comorbidities (i.e., coronary artery disease) [26]. Due to the correlation between obesity and hypercoagulability, the danger of aspiratory embolus may likewise be expanded in fat grown-up patients [27]. The information in COVID-19-positive teens population, nonetheless, is restricted. However, it is widely recognized that obesity is the basic factor for youths to be hospitalized because of COVID-19 [17].

Thrombosis and Inflammation

Viral, bacterial, or contagious microbes can provoke infection and start complex systemic inflammatory responses as a feature of intrinsic invulnerability. Initiation of host protection system leads to ensuing initiation of coagulation and thrombin as basic correspondence parts among humoral and cellular defense mechanism pathways, labeled as thromboinflammation or immunothrombosis [28], [29], [30]. The significance of the development from adaptive hemostasis to pathologically induced DIC with multiorgan malfunction is continuously assessed in patients with sepsis-induced coagulopathy (SIC).

Coagulation is initiated by the inflammatory reaction through a few procoagulant pathways. Polyphosphates, a microorganisms derivative, stimulate the platelets, mast cells, and factor XII as a part of coagulation and display other downstream tasks in intensifying the procoagulant reaction of the intrinsic coagulation pathway [31]. Complement pathways also take part in the initiation of coagulation factors [32].

The individual neutrophil extracellular locks in the element of cell-free DNA, and histones stimulate the contact pathway and improve other prothrombotic pathways, leading to thrombin production [33], [34]. Pathogen molecular inducing immune response plays a significant role in forming coagulation and increases sepsis risk [33], [35]. Cytokines stimulate inflammation also trigger vascular endothelial cells to become active, causing a prothrombotic state as a result of endothelial injury [33], [36].

Endotheliopathy, coherent with vascular endothelial dysfunction with SIC, seems to influence the pathophysiology of microcirculatory changes in SARS-CoV-2 infections [36], [37]. ACE2 is the receptor for viral attachment on endothelial cells [38], with viral replication inducing inflammatory cell penetration, endothelial cell apoptosis, and microvascular prothrombotic consequence. Postmortem examination exhibits that viral infection causes sequestered mononuclear and polymorphonuclear cell invasion,

Table 1: Several case reports using anticoagulants as treatment in children with COVID-19

Case reports (year)	Sign and symptom	Location of thrombosis	Medication	Outcome
A 10-year-old female in India reported by Kenchappa *et al*. (2020) [45]	Dyspepsia, abdominal discomfort	Obstruction of venules due to platelets and thrombi	LMWH	Healed
A 2-year-old female in South Africa reported by Essajee *et al*. (2020) [46]	Limb weakness, loss of consciousness	Thrombosis in sinus venosus of cerebri	ASA 3 mg kg BW/d, prednisone 2 mg kg BW, rifampicin 20 mg kg BW, isoniazid 20 mg kg BW, pyrazinamide 40 mg kg BW, and ethionamide 20 mg kg BW	Discharged
A 14-year-old male in India reported by Hussain *et al*. (2020) [47]	Chest discomfort, fever, and cough	Femoral vein thrombus	Dexamethasone, hydroxychloroquine, acetylsalicylic acid, LWMH 40 mg then continue with warfarin, low-dose heparin	Hospitalized only for 40 days and then discharged
A 10-year-old female in Germany reported by Lang *et al*. (2020) [48]	Abdominal discomfort associated with fever	Clot firmness (3 mm)	Low-dose defibrotide dose 25 mg kg BW qd	Discharged 17 days after admission
A 12-year-old female in the USA reported by Visveswaran *et al*. (2020) [49]	Erythema and pain in left thigh	Iliac vein thrombosis, pulmonary embolism	Solu-Medrol, prednisone, and enoxaparin	Discharged after 20 days hospitalized

LMWH: Low-molecular-weight heparin.

with proof of endothelial apoptosis at patients with COVID-19 [39].

The microcirculatory dysfunction contributes to the systemic hypercoagulability and possibility of thromboembolic complication as a clinical sequela in COVID-19. From clinical perception, the portrayed microvascular endothelial injury with microcirculatory clot found in the deceased body is predictable with thrombotic microangiopathy that might take place [39]. The endotheliopathy may likewise support reports of other complications from cerebrovascular in more youthful patients, myocardial ischemia, and expanding reports of micro- and macro-circulatory thromboembolic complications [39], [40], [41], [42].

Anticoagulant

Newborns and children are treated similarly to adults, yet the results differ. So far, there are no particular medications for treating COVID-19, and the vaccine provided is on observation. The treatment intends to enhance the symptoms and offer better assistance. The best one is oxygen therapy, pivotal for treating infants with symptoms and severely ill children [43].

Major hematology organizations: The American Society of Hematology, International Society for Hemostasis and Thrombosis, Anticoagulation Network, and the Hemostasis and Thrombosis Working Group of the British Society of Hematology have issued a report on the treatment of symptomatic adults hospitalized with COVID-19 [44], [45]. Recommendations for anticoagulation treatment remain limited so that suggestion is formed based on the current knowledge of adults and the assessment of the risk of thrombosis in children [46]. Hereby, several case reports around the world using anticoagulant as therapy in children with COVID-19 presented in Table 1 [47], [48], [49], [50], [51].

Unfractionated heparin (UFH) and LMWH work as anticoagulants through a remarkable pentasaccharide succession that ties either antithrombin III or factor Xa separately (Figure 2a and b). However, other than their impacts on anticoagulation, the heparins show multiple phenotypic expressions that are likely to provide specific advantages concerning viral infection, including anti-inflammatory effects due to their ability to combine to danger-associated molecular patterns, such as HMGB-1 and pro-inflammatory cytokines [52], [53]. UFH and heparan sulfate have a similar structure, and sulfated polysaccharides exist on the cell surface and extracellular matrix, with multiple disaccharide units, while on the contrary, low-molecular-weight heparin has shorter polysaccharide chains [20].

Heparin is biologically an inflammation regulator. Its anti-inflammatory effects are varied. Heparin obstructs the activation and performance

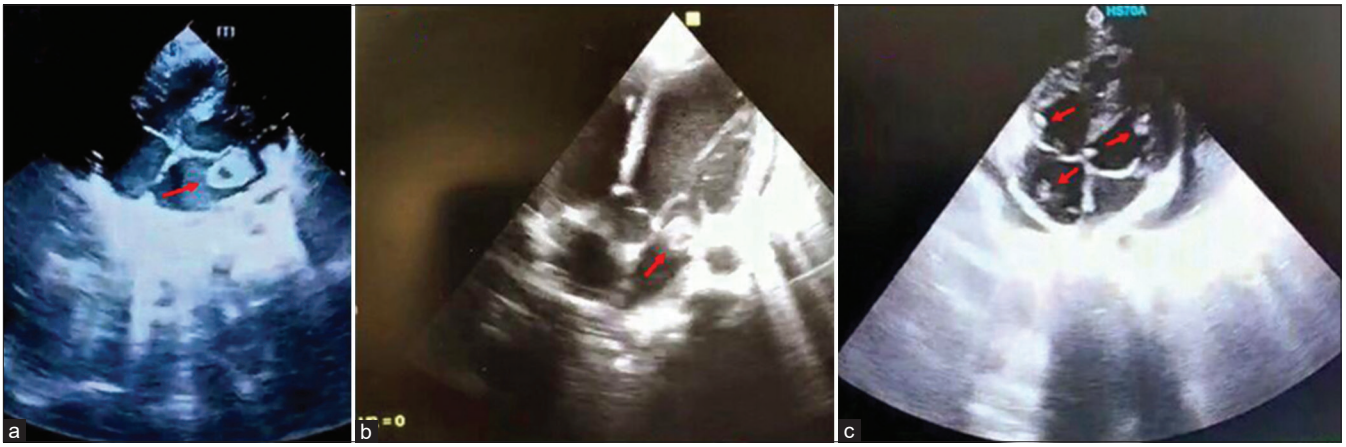

Figure 1: Transthoracic echocardiogram examination confirming a mobile mass in the left atrium that bonds to the posterior leaflet of the mitral valve (a), a large mobile mass in the left atrial chamber (b), and several uniform mobile masses in the right area of the heart and left ventricle (c) [22]

of neutrophils. Neutrophils' act begins by inhibiting selectin expression, limiting neutrophil enrollment into tissues [55]. Next, heparin impedes neutrophil function by restraining the role of the neutrophil proteases human leukocyte elastase and cathepsin G, stimulating inflammation in adult cystic fibrosis and respiratory distress syndrome [56].

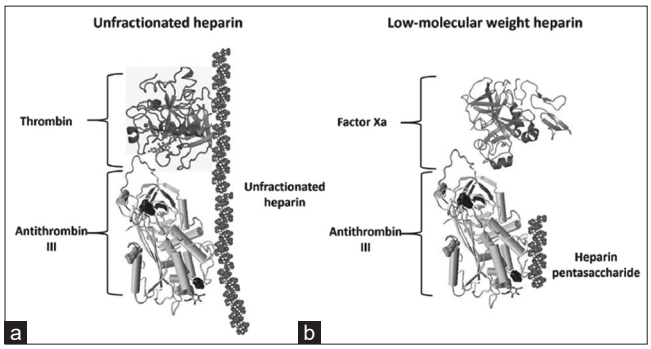

Figure 2: Component and mechanism of action of UFH and LMWH [53]

Heparin and the vascular endothelium interact to suppress the inflammatory mediators that start and trigger the natural immune system. The collaborations include reducing the movement of nuclear factor kappa-B from the cytoplasm to the nucleus [57] and lessening the levels of TNF-alpha, IL6, IL8, and IL1 beta [58]. Studies in humans and animals have shown that heparin can reduce the ability of TNF-α [59] and withhold the activation of receptors for advanced glycation end-products [60].

Heparin also restrains the multiplication of the vascular smooth muscle cell. Since the proliferation of vascular smooth muscle cells can lead to restrictive stenosis over time; heparin can avoid the progression of arterial disease [49]. At last, heparin reduces inflammation through its anticoagulant activity. Thrombosis and inflammation are closely related, so preventing thrombosis can diminish inflammation. The reduction of thrombin arrangement decreases the VCAM1, ICAM1, PDGF, MCP1, and MIF of endothelial cells and limits the permeability of endothelial cells induced by thrombin in a PAR1-dependent manner [61], and activates those platelets that are dependent on thrombin.

LMWH offers anti-inflammatory benefits equally potent as UFH [53], [54]. A study by Chima *et al*. showed that seven out of eight subjects received either heparin or enoxaparin, while one subject received apixaban. None of the subjects are reported deaths, and only one patient required mechanical ventilation [23].

Conclusion

Hypercoagulopathy state in COVID-19 patients, particularly in younger patients, is distressing. Accordingly, treatment with anticoagulation alongside thorough examination and observation is encouraged in all COVID-19 patients to anticipate the hypercoagulable conditions.

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