Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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COVID-19 associated pediatric vasculitis: A systematic review and detailed analysis of the pathogenesis

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ABSTRACT

Objectives: Coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2, has opened a new era in the practice of pediatric rheumatology since it has been associated with inflammatory complications such as vasculitis and arthritis. In this review, we aimed to present a detailed analysis of COVID-19 associated pediatric vasculitis.
Methods: A systematic review of the English literature was performed through Pubmed/MEDLINE and Scopus up to January 1st, 2022. Articles including data about the patients with 1) onset of vasculitis <18 years of age, 2) evidence of SARS-CoV-2 exposure, 3) evidence of vasculitis diagnosis (imaging, histopathologic evidences or fulfilling the specific diagnostic/classification criteria) were included in the final analysis. Patients with Kawasaki disease-like vasculitis associated with multisystem inflammatory syndrome in children (MIS-C) were excluded.
Results: A total of 25 articles describing 36 patients with COVID-19 associated pediatric vasculitis (median age 13 years; M/F: 2.3) were included. The most frequent phenotype was IgA vasculitis (n=9) followed by chilblains (n=7) and ANCA associated vasculitis (AAV) (n=5). Skin (58.3%) and renal (30.5%) involvements were the most common manifestations of vasculitis. The majority of patients received corticosteroids (40%), while rituximab (14.2%) and cyclophosphamide (11.4%) were the most frequently used immunosuppressive drugs. Remission was achieved in 23 of 28 patients. Five patients (4 with central nervous system vasculitis; 1 with AAV) died.
Conclusion: Although COVID-19 associated pediatric vasculitis is very rare, awareness of this rare entity is important to secure earlier diagnosis and treatment. The clinical features of COVID-19 associated pediatric vasculitis subtypes look similar to those in pediatric vasculitis not associated with COVID-19. Whether COVID-19 is the reason of the vasculitis or only the trigger remains unknown.

Introduction

Coronavirus disease-19 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has been a major global health problem causing millions of deaths worldwide[1]. Apart from the acute severe infection, several complications including autoimmune diseases have been noted in COVID-19 patients[2].

Vasculitis is defined as the inflammation of the vessel wall[3]. The most common primary systemic vasculitides in childhood are immunoglobulin A vasculitis/Henoch Schönlein purpura (IgAV/HSP) and Kawasaki disease (KD)[3]. Viral infections have long been associated with autoimmune diseases as triggers. However, the exact nature of this association remains unknown. On the other hand, the most common rheumatic manifestations associated with COVID-19 have been vasculitis and arthritis[2]. Most of these vasculitis patients were children with multisystem inflammatory syndrome in children (MIS-C) who had KD-like features 4-6 weeks later than the acute COVID-19[4]. MIS-C is a life-threatening situation characterized by fever, multiorgan

Abbreviations: ACE2, Angiotensin converting enzyme 2; ACR, American college of rheumatology; AHEI, Acute hemorrhagic edema of infancy; ATII, Angiotensin II; AVV, ANCA associated vasculitis; AZA, Azathioprine; CDC, Center for disease control; CNS, Central nervous system; COVID-19, Coronavirus disease-19; CYC, Cyclophosphamide; GIS, Gastrointestinal system; GPA, Granulomatosis with polyangiitis; HSP, Henoch Schönlein purpura; IgAV, Immunoglobulin A vasculitis; IL-6, Interleukin-6; KD, Kawasaki disease; MIS-C, Multisystem inflammatory syndrome in children; MMF, Mycophenolate mofetil; NETs, Neutrophil extracellular traps; MTX, Methotrexate; NO, Nitric oxide; NSAID, Nonsteroidal anti-inflammatory drugs; RTX, Rituximab; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2; TF, Tissue factor; WHO, World health organization.

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involvement, and prominent elevation of acute phase reactants[5]. MIS-C develops as a result of the cytokine storm triggered by SARS-CoV-2[6].

Other than KD-like vasculitis in MIS-C, there have been rare reports of pediatric vasculitis associated with COVID-19. Whether these are primary vasculitides *triggered* by SARS-CoV-2 or secondary vasculitides *caused* by SARS-CoV-2 (such as hepatitis B virus associated vasculitis) remains unknown. The data regarding the disease course, treatment, and outcome are scarce in COVID-19 associated childhood vasculitis. In this review, we aimed to present a detailed analysis of COVID-19 associated pediatric vasculitis (excluding KD-like vasculitis in MIS-C) and summarize the data from published cases. The presented analysis will hopefully contribute to the development of personalized and effective management in these patients.

Search strategy for systematic review

We performed a search through Pubmed/MEDLINE and Scopus using the following keywords: "COVID-19", "coronavirus disease 2019", "SARS-CoV-2", "vasculitis", and "children" from the inceptions of the regarding databases to January 1st, 2022, according to the PRISMA guidelines. The complete list of the search terms has been provided in the Supplementary Table 1. The search was restricted to English articles. Case reports/series, original research articles, editorials and review articles about pediatric patients with COVID-19 associated vasculitis were analyzed. The reference lists of the relevant articles were also meticulously examined. The articles including data about these patients have been included in the final analysis. Two authors (EDB and SS) performed the literature searches independently based on inclusion and exclusion criteria, deleting irrelevant literature, abandoning duplications and screening titles and abstracts. The following parameters were assessed from the included studies: gender, age, comorbidity, diagnostic tests for COVID-19, diagnosis of vasculitis, time between COVID-19 and vasculitis, symptoms, laboratory results, imaging and/or histopathological findings, treatment, and outcome. The authors independently extracted data from the included studies. Disagreements between two authors (EDB, SS) were resolved by consensus with the inclusion of the third author (SO).

Inclusion and exclusion criteria

Patients with COVID-19 associated pediatric vasculitis were selected based on a set of inclusion and exclusion criteria during the literature review. Inclusion criteria were as follows: 1) onset of vasculitis <18 years of age, 2) evidence of SARS-CoV-2 exposure, 3) evidence of vasculitis diagnosis (imaging or histopathologic features suggesting vasculitis OR fulfilling the specific diagnostic/classification criteria for vasculitis). The evidence of SARS-CoV-2 exposure was verified in the presence of one of the following four features: 1) history of COVID-19, 2) history of contact with a COVID-19 patient, 3) positive SARS-CoV-2 PCR, 4) positive SARS-CoV-2 serology. Indicating a history of SARS-CoV-2 infection (COVID-19) in the report was sufficient for meeting the "evidence of SARS-CoV-2 exposure" criterion even if the authors did not specifically mention a positive PCR test back at the time of COVID-19. The patients with chilblain or pernio lesions were included only if vasculitis was verified in the biopsy, since every chilblain lesion does not represent vasculitis[7, 8].

Exclusion criteria were as follows: 1) vasculitis onset ≥18 years of age, 2) coronary arterial vasculitis in patients with MIS-C who met CDC (Center for Disease Control)[9] or WHO (World Health Organization)[1] definitions, 3) no evidence of SARS-CoV-2 exposure or vasculitis; 4) patients with chilblain or pernio lesions if vasculitis was not demonstrated in the biopsy.

Results of the systematic review

The schematic overview of the studies included in this review was shown in Fig. 1. We identified 25 articles describing 36 pediatric patients with COVID-19 associated vasculitis during our literature search [10–34]. The characteristics of this cohort were summarized in Table 1. The detailed data about the patients with COVID-19 associated pediatric vasculitis was presented in Table 2.

The data regarding the characteristics of patients were deficient in a few articles. In a study by Mohta et al., urticarial vasculitis was reported in two pediatric patients with MIS-C, but the authors did not specify the characteristics of these two patients[34]. Therefore, although this study and its patients were included in the total numbers obtained as a result of systematic review (Fig. 1), the patients were not included in Table 2.

In three papers, the data regarding the patients' ages and SARS-CoV-2 exposure status were presented for the study group as a whole and not available for the vasculitis patients individually[35–37]. Thus, we did not include the patients with vasculitis in these three papers in our study group.

The median (min-max) age of the patients with COVID-19 associated pediatric vasculitis in the literature was 13 (1.1-17) years and 11 (32.3%) patients were female (M/F: 2.3) (Table 1). The median (min-max) time between SARS-CoV-2 exposure to vasculitis was 17.5 (2-150) days and this time interval was reported for only 10 patients (but not certain in some cases).

The diagnoses of the included patients were as follows (in order of frequency); IgAV/HSP (25%)[10–17], [38], chilblains (19.4%)[19], post-viral renal graft vasculitis (13.8%)[20], ANCA associated vasculitis (AAV) (13.8%) (3 associated with PR-3 ANCA; 2 associated with MPO ANCA)[21–25], central nervous system (CNS) vasculitis (11.1%)[26], [27], [30], [39], retinal vasculitis (5.5%)[29], [31], urticarial vasculitis (5.5%)[34], cutaneous leukocytoclastic vasculitis (2.7%)[33], and acute hemorrhagic edema of infancy (AHEI, 2.7%)[32]. The biopsy findings of 18 patients were consistent with the diagnosis of vasculitis (chilblains in 7, AAV in 5, CNS vasculitis in 3, IgAV/HSP in 2, and cutaneous leukocytoclastic vasculitis in 1 patient)[11], [13], [19], [21–27], [30], [33]. It is noteworthy that SARS-CoV-2 was demonstrated in the biopsy of seven patients (38.8%)[19]. Imaging findings were consistent with vasculitis in nine patients (postviral graft vasculitis in 5, retinal vasculitis in 2, AAV in 1, and CNS vasculitis in 1 patient)[20], [24], [28], [29], [31]. All IgAV/HSP patients fulfilled the Ankara 2008 (EULAR/PRES/PRINTO) criteria[40]. All diagnostic features developed by Fiore et al.[41] were present in the patient with AHEI[32].

The organ that was most frequently affected by vasculitis was the skin (58.3%), followed by the kidney (30.5%), gastrointestinal system (GIS, 13.8%), CNS (13.8%), and lung (11.1%).

Regarding management, all patients with chilblains, retinal vasculitis, and AHEI improved without any therapeutic intervention[19], [31], [32]. Corticosteroids were used in the treatment of five (55.5%) IgAV/HSP patients while NSAID was the only drug used by the rest of the IgAV/HSP patients (n=4)[10–17], [38]. Complete remission was achieved in all nine IgAV/HSP patients.

Extensive immunosuppressive treatment was introduced to AAV patients in addition to corticosteroids[17], [21–25]. The most frequently used immunosuppressive drug was rituximab (RTX) followed by cyclophosphamide (CYC). Of note, only one patient received antiplatelet and anticoagulant treatment since she had myocardial infarction. Out of five patients with COVID-19 associated AAV, one died despite treatment with several immunosuppressant drugs such as RTX, CYC, mycophenolate mofetil (MMF), and azathioprine (AZA)[23].

All four patients with COVID-19 associated CNS vasculitis died [26–28], [30]. CNS vasculitis was diagnosed in the autopsy in one of these patients[27], so he had not received any treatment for the vasculitis. Another one had received only corticosteroids and hydroxychloroquine[26]. The other two patients, on the other hand, died despite corticosteroid and immunosuppressive therapy[28], [30]. Only one out

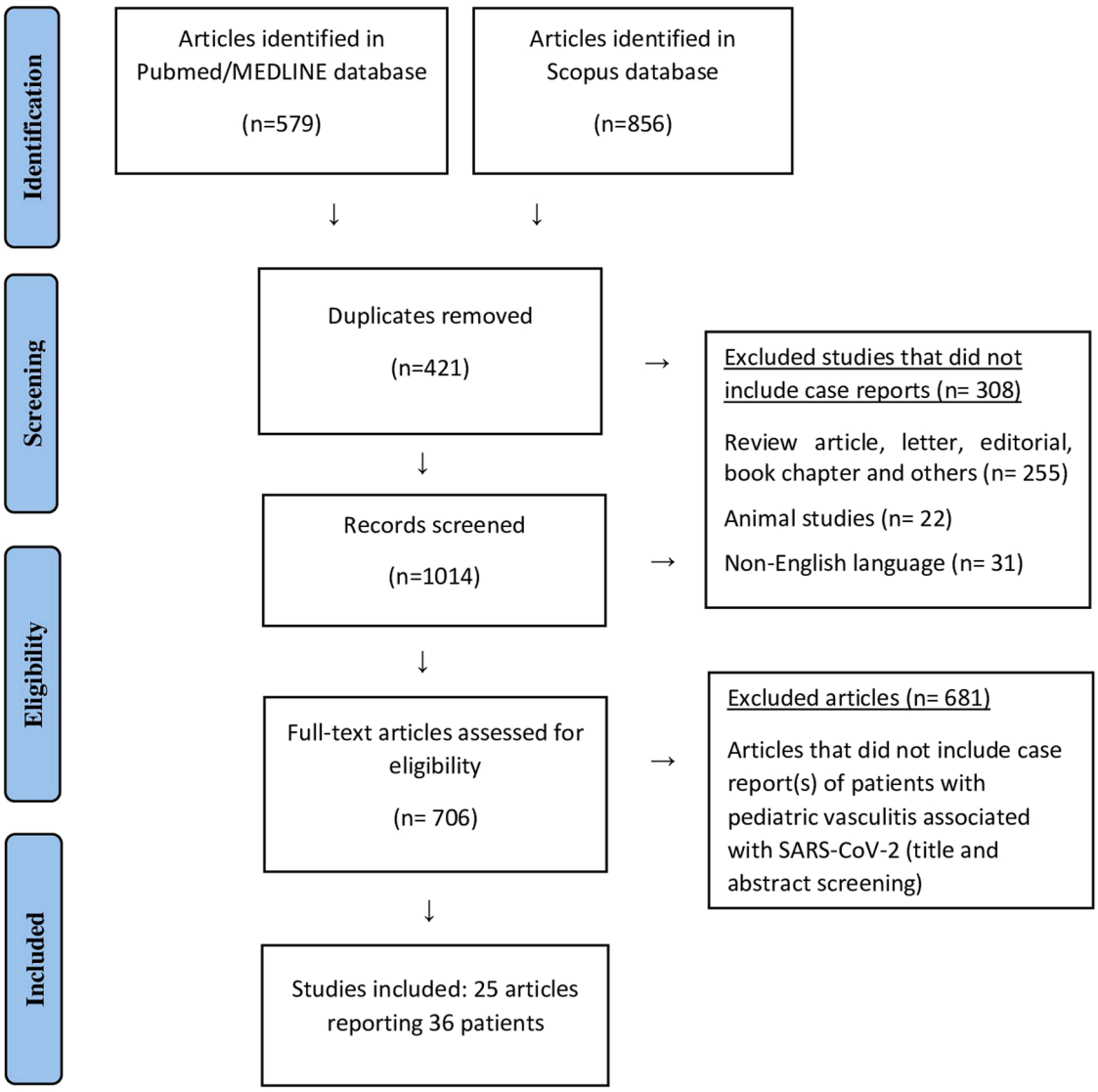

Fig. 1. The PRISMA flow diagram of literature screening for patients with COVID-19 associated pediatric vasculitis.

of four COVID-19 associated CNS vasculitis patients received anti-platelet treatment.

Overall, remission was achieved in 23 of 28 patients and five patients died. The outcome was not mentioned in 8 patients.

Discussion

COVID-19 associated pediatric vasculitis (excluding KD-like vasculitis in MIS-C) is very rare. There are only 36 cases reported in the literature to date. In order to implement personalized medicine strategies in the management of these patients, it is critical to analyze the possible mechanisms underlying this complication and treatment/outcome in the light of the available scientific data.

Suggesting possible mechanisms for COVID-19 associated pediatric vasculitis

The direct effects of the virus itself (via viral replication) and the damage caused by the immune response against the virus are possibly intertwined in the pathogenesis of COVID-19 associated vasculitis (Fig. 2).

Transmembrane angiotensin converting enzyme 2 (ACE2), which is highly expressed in the endothelium, acts as a receptor for SARS-CoV-2 [42]. Normally, ACE2 converts angiotensin II (ATII) to AT1-7, which stimulates endothelial cells to produce nitric oxide (NO)[43]. Besides maintaining vascular homeostasis and modulating vasodilation, NO prevents inflammation by resetting macrophages to M2 (anti-inflammatory) status[44]' [45]. When SARS-CoV-2 binds and down-regulates ACE2, the balance changes in favor of ATII which causes a decrease in NO, vasoconstriction, and reduced blood flow and ischemia in target tissues/organs[46]. These changes render the microenvironment prone to coagulation and inflammation.

Type I interferon response against SARS-CoV-2 could also be a factor contributing to vasoconstriction. Chilblains associated with COVID-19 resemble the skin lesions observed in type I interferonopathies[47]. Although the exact pathogenesis of these lesions remains unknown in type I interferonopathies, the possible inhibition of NO synthase pathway could be the explanation for vasospasm causing chilblains[48]. The patients with chilblains are usually children and adolescents who experienced mild or symptomatic COVID-19[19]' [49]. It may be speculated that the strong type I interferon response in response to acute SARS-CoV-2 infection leading to mild or asymptomatic COVID-19, leads to complications such as chilblains. On the other hand, when the patient cannot exert a robust type I interferon response, COVID-19 is severe but complications associated with elevated type I interferons are absent [50]. Having said that, a few patients with severe COVID-19 also had

Table 1
The features of all patients with COVID-19 associated pediatric vasculitis in the literature.

Number of patients, n	36
Age, years, median (min-max)	13 (1.1-17)
Gender, female, n (%)	11/34 (32.3)
Evidence of SARS-CoV-2 exposure, n (%)	
COVID-19 history	3 (8.3)
Positive COVID-19 PCR	16 (44.4)
Positive COVID-19 serology	18 (50)
Contact with a COVID-19 patient	8 (22.2)
Diagnosis, n (%)	
IgAV/HSP	9 (25)
Chilblains	7 (19.4)
Postviral graft vasculitis	5 (13.8)
AAV	5 (13.8)
CNS vasculitis	4 (11.1)
Retinal vasculitis	2 (5.5)
Urticarial vasculitis	2 (5.5)
Cutaneous leukocytoclastic vasculitis	1 (2.7)
AHEI	1 (2.7)
Time between SARS-CoV-2 exposure and vasculitis, days, median (min-max)	17.5 (2-150)
Elevated inflammatory markers, n (%)	15/22 (68.1)
Positive imaging findings suggesting vasculitis, n (%)	9/12 (75)
Histopathological proof of vasculitis, n (%)	18/19 (94.7)
Presence of SARS-CoV-2 in biopsy verifying vasculitis, n (%)	7/18 (38.8)
Organ effected by vasculitis, n (%)	
Skin	21 (58.3)
Kidney	11 (30.5)
GIS	5 (13.8)
CNS	5 (13.8)
Lung	4 (11.1)
Eye	2 (5.5)
Liver	1 (2.7)
Treatment, n (%)	
CS	14/33 (42.4)
NSAID	6/33 (18.1)
RTX	5/33 (15.1)
CYC	4/33 (12.1)
IVIG	2/33 (6.1)
Plasmapheresis	2/33 (6.1)
MMF	1/33 (3.05)
AZA	1/33 (3.05)
TOC	1/33 (3.05)
IFNX	1/33 (3.05)
HQ	1/33 (3.05)
Outcome, n (%)	
Improved	23/28 (82.1)
Deceased	5/28 (17.8)

AAV, antineutrophil cytoplasmic antibody (ANCA) associated vasculitis; AHEI, acute hemorrhagic edema of infancy; AZA, azathioprine; CNS, central nervous system; CS, corticosteroid; COVID-19, coronavirus disease 2019; CYC, cyclophosphamide; GIS, gastrointestinal system; HSP, Henoch-Schonlein purpura; HQ, hydroxychloroquine; IFNX, infliximab; IgAV, immunoglobulin A vasculitis; IVIG, intravenous immunoglobulin; MMF, Mycophenolate mofetil; NSAID, nonsteroidal anti-inflammatory drugs; PCR, polymerase chain reaction; RTX, rituximab; TOC, tocilizumab

high type I interferon signature[51], [52], contradicting to this hypothesis.

SARS-CoV-2 itself directly damages endothelium and causes "endothelitis". Viral inclusions in the endothelial cells and increased endothelial apoptosis have been demonstrated in histopathological studies including COVID-19 patients[53]. Further proofs of endothelial damage are the increase in detectable circulating endothelial cells[54], [55] and endothelial cell progenitors[56]. Normally, endothelium serves as a barrier between platelets and collagen/tissue factor (TF). Endothelial cell damage causes the exposure of basal membrane and triggers the thrombotic cascade via platelet-TF and platelet-collagen interactions [57]. Moreover, the direct interaction of platelets with viral RNA augments platelet activation[58]. These lead to thrombotic micro and macroangiopathy. Immunothrombosis and microemboli could affect especially the organs which get a relatively high portion of cardiac output such as the brain[50]. Actually, thrombus and thrombotic microangiopathy were demonstrated in the biopsy of an adolescent with COVID-19 associated CNS vasculitis[27]. The actived platelets and dysregulated endothelial cells release proinflammatory cytokines which probably contribute to the vessel wall inflammation[59]. Besides causing endothelitis, the proinflammatory cytokines such as interleukin 6 have been hypothesized to be a factor causing alterations in IgA1 glycosylation[60]. This altered IgA1 forms immune complexes which leads to IgAV/HSP[61]. Having said that, we have observed a decrease in the frequency of IgAV/HSP during pandemic compared to the pre-COVID era, in our recent study[62]. This decrease could be due to the decreased spread of other cold viruses as a result of the precautions (such as wearing masks and quarantine) introduced by the pandemic. We may therefore suggest that SARS-CoV-2 may not be as strong a trigger as the other cold viruses/bacteria for IgAV/HSP.

Other crucial mechanisms in COVID-19 immunopathy are neutrophil activation and NETosis[63]. NETosis is a programmed cell death in which neutrophils die by excreting extracellular traps (neutrophil extracellular traps; NETs) that contain neutrophil granule proteins and host nuclear material[64]. NETosis has been demonstrated to be elevated in COVID-19 patients[65], [66]. NETs are strong triggers of immunothrombosis[63]. Furthermore, NETs can pull the trigger for autoimmunity since self-antigens are exposed within them. Torres-Ruiz et al. have recently demonstrated that anti-NET antibody positivity was correlated with antinuclear antibody and ANCA positivity in COVID-19 [67]. Besides NETosis, other factors could contribute to development of autoimmune conditions such as AAV associated with COVID-19. These are molecular mimicry (some human proteins are homologous to SARS-CoV-2 proteins), cytokine storm (hyperinflammation triggered by the virus), and viral persistence causing continuous polyclonal activation[2]. ANCA positivity was found in COVID-19 patients even in the absence of clinically overt AAV[68], [69].

The time between COVID-19 and vasculitis was indicated for ten patients[10], [12–14], [22], [23], [25], [30], [31], [38]. The duration was $\leq$1 week in four patients (3 IgAV/HSP and 1 AAV patient) while it was around 2-5 weeks in five patients (2 IgAV/HSP, 2 AAV, 1 CNS vasculitis patients). The latency was five months in one patient with retinal vasculitis[31]. It is not possible to draw a conclusion regarding the latency and vasculitis subtypes based on these data. However, it is clear that vasculitis occurred during the acute infection in some patients while it was observed weeks later than the acute infection in others. The prominent mechanism of vasculitis during acute infection could be the damage caused by the virus itself rather than the immune response of the individual. On the other hand, the late immune reactivation triggered by the virus may be the main factor in the pathogenesis of late-onset vasculitis.

The variation regarding the time of SARS-CoV-2 exposure and onset of vasculitis may also suggest an incidental occurrence of vasculitis. Since the pandemic has affected a lot of children, it may well be that a child with newly diagnosed vasculitis had a history of COVID-19 incidentally. This could be the case especially in the relatively more frequent pediatric vasculitis such as IgAV/HSP. On the other hand, the possibility of a real COVID-19 association is high with specific subtypes such as chilblains or catastrophic CNS vasculitis.

Treatment and outcome in COVID-19 associated pediatric vasculitis

It is important to analyze treatment response and outcome in COVID-19 associated pediatric vasculitis in order to highlight differences from pediatric vasculitis not associated with COVID-19 and implement personalized medicine practice in management of these patients.

The treatment in COVID-19 associated IgAV/HSP was consistent

Table 2
The characteristics of pediatric patients with coronavirus disease 2019 (COVID-19) associated vasculitis in the literature.

First author, year (ref. no.)	Number of patients	Age (years)	Sex	Comorbidity	Evidence of SARS-CoV-2 Exposure	Diagnosis (vasculitis)	Time between COVID-19 and vasculitis	Clinical features suggesting vasculitis	Laboratory findings suggesting vasculitis	Imaging findings suggesting vasculitis	Histopathological evidence of vasculitis	Treatment for vasculitis	Outcome
El Hasbani, 2021[10]	1	16	M	None	PCR (+)	IgAV/HSP	2 days	Palpable purpura, abd. pain, hemoptysis, hematochezia	Elevated APR and IgA Proteinuria and hematuria	NA	NA	CS	Improved
Hoskins, 2021 [11]	1	2	M	None	PCR (+)	IgAV/HSP	NA	Purpura, abd. pain, hematemesis, hematochezia	Elevated APR	EGD: edema, erythema and superficial erosions in the stomach and duodenum	Skin biopsy: superficial perivascular inflammation with neutrophils, (+) immunostain for IgA	CS	Improved
Jacobi, 2021 [12]	1	3	M	Hirschsprung disease	Contact history	IgAV/HSP	2 days (?)	Purpura, abd. pain, emesis	NA	NA	NA	NSAID,CS	Improved
Kumar, 2021 [13]	1	13	M	None	COVID-19 history	IgAV/HSP	4 weeks	Petechia, purpura	Normal APR Elevated IgA Hematuria	NA	Small vessel neutrophilic vasculitis, superficial epidermal necrosis, intraepidermal pustules, no IgA staining	CS	Improved
Al Ghoozi, 2020[14]	1	4	M	None	PCR (+)	IgAV/HSP	37 days	Palpable purpura, arthralgia, edema of the ankles	NA	NA	NA	NSAID	Improved
Borocco, 2020 [15]	1	13	F	Panhypopituitarism, suprasellar germinoma, concomitant EBV infection	PCR (+)	IgAV/HSP	NA	Fever, purpura, ankle edema, abd. pain	Elevated APR and IgA	NA	NA	NSAID	Improved
Riscassi, 2021 [16]	1	3	M	None	PCR (+)	IgAV/HSP	NA	Fever, palpable purpura, swelling of the dorsal feet, arthralgia, claudication	Elevated APR Hematuria Proteinuria	NA	NA	NSAID	Improved
Bekhit, 2021 [17]	1	5.8	F	Atopic dermatitis	PCR (+)	IgAV/HSP	NA	Fever, palpable purpura, myalgia, bilateral ankle edema	Elevated APR and IgA	NA	NA	NSAID, CS	Improved
Falou, 2021 [18]	1	8	M	None	PCR (+)	IgAV/HSP	1 week	Ecchymosis and purpura, bilateral ankle edema	Elevated APR	NA	NA	NSAID	Improved
Colmenero, 2020[19]	7	Median: 15 [11–17]	3F/ 4M	ADHD (n=2)	Contact history (n=4) SARS-CoV-2 spike protein in biopsy (n=7)	Chilblains	NA	Minimally painful or pruritic skin lesions	NA	NA	Lymphocytic vasculitis/ infiltration, endotheliitis, mild interface dermatitis, red cell extravasation and dermal edema (n=7) Exocytosis of lymphocytes (n=3) Scattered necrotic keratinocytes (n=4) Fibrinoid necrosis (n=2) Microthrombosis (n=4) Transmural lymphocytic infiltration of a vessel	None	Improved (n=7)

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Table 2 (*continued*)

First author, year (ref. no.)	Number of patients	Age (years)	Sex	Comorbidity	Evidence of SARS-CoV-2 Exposure	Diagnosis (vasculitis)	Time between COVID-19 and vasculitis	Clinical features suggesting vasculitis	Laboratory findings suggesting vasculitis	Imaging findings suggesting vasculitis	Histopathological evidence of vasculitis	Treatment for vasculitis	Outcome
											(n=1) Presence of SARS-CoV-2 in biopsy (n=7)		
Berteloot, 2020[20]	5	Median: 15 [5–17]	1F/4M	CKD and kidney transplant (n=5), liver transplant (n=1)	PCR (+) (n=1), positive (n=3) or borderline (n=1) SARS-CoV-2 serology	Postviral graft vasculitis	NA	Hypertension (n=3)	Elevated APR	Abdominal angio-CT: a thin and irregular artery (n=2), an anastomotic stenosis and an irregular shape of the segmental arteries (n=1), an irregular shape of the middle third of the artery (n=2), two liver's graft arteries, which appeared filiform and irregular (n=1)	Renal transplant biopsy: microcalcifications (n=1), normal (n=4)	Conservative therapy	Improved (n=1), NA (n=4)
Powell, 2021 [21]	1	12	F	NA	SARS-CoV-2 serology (+)	AAV	NA	Fever, hemoptysis, arthralgia, arthritis, macular rash	Elevated APR Hematuria Proteinuria MPO-ANCA (+)	Chest CT: dense consolidation in the left lower lobe and patchy infiltrate in the right middle and upper lobes	BAL: diffuse alveolar hemorrhage consistent with possible vasculitis Renal biopsy: a pauci-immune necrotizing and crescentic glomerulonephritis	CS, RTX, CYC	Improved
Reiff, 2021 [22]	1	17	M	None	PCR (+)	AAV	1 week	Fever, night sweats, cough, hemoptysis, chest tightness, lightheadedness, weight loss	Elevated APR PR3-ANCA (+)	Chest CT: multiple bilateral cavitary lung lesions (the largest, 6.5 cm)	Lung biopsy: mixed perivascular inflammation and necrotic debris	CS, RTX	Improved
Raeeskarami, 2021[23]	1	14	F	NA	SARS-CoV-2 serology (+)	AAV (GPA)	3 weeks	Fever, migratory pain and swelling in the joints, recurrent headaches and epistaxis, fatigue, weakness, abd. pain, palpable petechia and purpura, chest pain, seizure	Elevated APR PR3-ANCA (+)	Chest CT: bilateral multifocal nodular infiltrates with halo sign view (vasculitis) Paranasal sinuses CT: acute sinusitis Abdominopelvic CT angiography: enhancement areas adjacent to the portal vein, linear hypodense areas in both kidneys, a hypodense area in the liver, some lymph nodes and mild pelvic fluid Cranial MRI/MRA: signal increases in cortical and subcortical areas of the posterior brain (PRES? or vasculitis?)	Sinus biopsy: necrotizing sinusitis and vague granulomatosis reaction compatible with GPA Bronchoscopic biopsy: inflammation and necrosis consistent with GPA	CS, IVIG, CYC, AZA, MMF, RTX, ASA. Heparin Clopidogrel	Deceased
Wintler, 2021 [24]	1	13	F	None	SARS CoV-2 serology (+)	AAV	NA	Peri-rectal necrotic wounds, purpura, fever, hypertension, exudative tonsillitis	Elevated APR PR3-ANCA (+)	Pelvic MRI: diffuse bowel wall thickening of the sigmoid colon and rectum with surrounding edema and moderate	Rectal and colonic tissue biopsies: leukocytoclastic vasculitis involving small vessels (negative IgA	CS, RTX	Improved

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Table 2 (*continued*)

First author, year (ref. no.)	Number of patients	Age (years)	Sex	Comorbidity	Evidence of SARS-CoV-2 Exposure	Diagnosis (vasculitis)	Time between COVID-19 and vasculitis	Clinical features suggesting vasculitis	Laboratory findings suggesting vasculitis	Imaging findings suggesting vasculitis	Histopathological evidence of vasculitis	Treatment for vasculitis	Outcome
										volume ascites, an inferior anal sphincter fistula communicating with probable intersphincteric superior abscess and substantial subcutaneous edema	staining) Renal biopsy: Normal		
Fireizen, 2021,[25]	1	17	M	Obesity, asthma	COVID-19 history	AAV	2 months	Cough, fatigue, exertional dyspnea, amber-colored urine, generalized body aches	MPO-ANCA (+)	Chest CT angiography: extensive heterogeneous infiltrates in both lungs concerning for diffuse alveolar hemorrhage	BAL: RBC presence, along with (+) hemosiderin-laden macrophages Renal biopsy: necrotizing glomerulonephritis with limited immune complex deposition	CS, plasmapheresis, CYC	Improved
Freij, 2020 [26]	1	5	F	None	PCR (+) SARS-CoV-2 serology (+)	CNS vasculitis	NA	Fever, headache, confusion, then lethargy, hypertension	Elevated APR	Cranial MRI: progressive inflammation with supratentorial and infratentorial edema, hypoxic/ischemic changes, cerebellar tonsillar herniation, lack of normal flow at the circle of Willis	Necrotizing granulomatous inflammation, medium-sized blood vessel with numerous inflammatory cells, severe damage to the vessel wall with complete loss of internal elastic lamina	HQ, CS	Deceased
Daisley, 2021 [27]	1	16	M	None	PCR (+)	CNS vasculitis	NA	None	NA	NA	Autopsy: Vasculitis with a moderate infiltrate of lymphocytes, thrombotic microangiopathy, thrombus in medium sized vessels	None	Deceased
De Marcellus, 2021[28]	1	16	M	None	PCR (+)	CNS vasculitis	NA	Fever, neck stiffness, stupor, brisk reflexes; then, right hemiplegia and aphasia	Elevated APR	Brain angio-MR: recent arterial ischemic stroke in the left middle cerebral territory with hypoperfusion, severe and bilateral vasculitis and left ophthalmic vein thrombosis	NA	CS, TOC, ASA	Deceased
Poisson, 2022 [30]	1	8	F	None	PCR (+) serum SARS-CoV-2 IgG and CSF SARS-CoV-2 IgM (+)	CNS vasculitis	2 weeks (?)	Left hemiparesis	Elevated APR	Cranial MRI: a right frontal lobe enhancing lesion with vasogenic edema, incidental encephalomalacia in the left basal ganglia	Infarct-like necrosis with perivascular lymphohistiocytic inflammatory infiltrates, diffuse acute hypoxic/ischemic changes, massive parenchymal infarct, multifocal hemorrhages, perivascular inflammatory infiltrates and scattered small parenchymal infarcts	CS, plasmapheresis, CYC, RTX, IVIG, INFX	Deceased

(*continued on next page*)

Table 2 (*continued*)

First author, year (ref. no.)	Number of patients	Age (years)	Sex	Comorbidity	Evidence of SARS-CoV-2 Exposure	Diagnosis (vasculitis)	Time between COVID-19 and vasculitis	Clinical features suggesting vasculitis	Laboratory findings suggesting vasculitis	Imaging findings suggesting vasculitis	Histopathological evidence of vasculitis	Treatment for vasculitis	Outcome
Fernández Alcalde, 2021[29]	1	11	M	NA	SARS-CoV-2 serology (+)	Retinal vasculitis	NA	Chilblains (visually asymptomatic)	NA	Ocular fundus exam (ophthalmoscopy): retinal vasculitis with perivascular infiltrate and retinal exudates on retinal equator of the left eye OCT: normal	NA	None	Improved
Abbinante, 2021[31]	1	6	M	Mixed astigmatism	COVID-19 history	Retinal vasculitis	5 months	Asymptomatic	NA	OCT/angio-OCT: Cotton wool exudates, tortuous aspect of the superficial retinal plexus and of the deep retinal plexus	NA	NA	NA
Saraiva, 2021 [32]	1	1.1	M	Vesicoureteral reflux and recurrent pyelonephritis	PCR (+)	AHEI	NA	Fever, vomiting, palpable maculopapular and purpuric rash, edema of the extremities	Elevated APR	NA	NA	None	Improved
Schnapp, 2020[33]	1	16	M	None	SARS-CoV-2 serology (+)	Cutaneous leukocytoclastic vasculitis	NA	Fever, abd. pain, migratory rash, multiorgan dysfunction, erythematous plaques over the posterior scalp	Elevated APR and creatinine levels	NA	Leukocytoclastic vasculitis including necrosis of the epidermis and most of the dermis with extravasation of erythrocytes and fibrin thrombi in the capillaries, infiltration of neutrophils with nuclear debris in vessels' walls, deposition of C3 and IgA in a vascular pattern	CS	NA

AAV, ANCA associated vasculitis; abd., abdominal; ADHD, attention deficit hyperactivity disorder; AHEI, acute hemorrhagic edema of infancy; ANA, anti-nuclear antibody; ANCA, antineutrophil cytoplasmic antibody; anti-dsDNA, anti-double stranded DNA antibody; APR, acute phase reactants; ASA, acetylsalicylic acid; AZA, azathioprine; BAL, bronchoalveolar lavage; CKD, chronic kidney disease; CNS, central nervous system; CS, corticosteroid; COVID-19, coronavirus disease 2019; CRP, C reactive protein; CSF, cerebrospinal fluid; CT, computed tomography; CYC, cyclophosphamide; EBV, Epstein–Barr virus; EGD, esophagogastroduodenoscopy; ESR, erythrocyte sedimentation rate; F, female; GPA, granulomatosis with polyangiitis; HSP, Henoch-Schonlein purpura; HQ, hydroxychloroquine; IFNX, infliximab; Ig, immunoglobulin; IgAV, immunoglobulin A vasculitis; IVIG, intravenous immunoglobulin; M, male; MMF, Mycophenolate mofetil; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; NA, not assessed; NSAID, nonsteroidal anti-inflammatory drugs; OCT, optical coherence tomography; PCR, polymerase chain reaction; PCT, procalcitonin; PRES, posterior reversible encephalopathy syndrome; RTX, rituximab; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TOC, tocilizumab

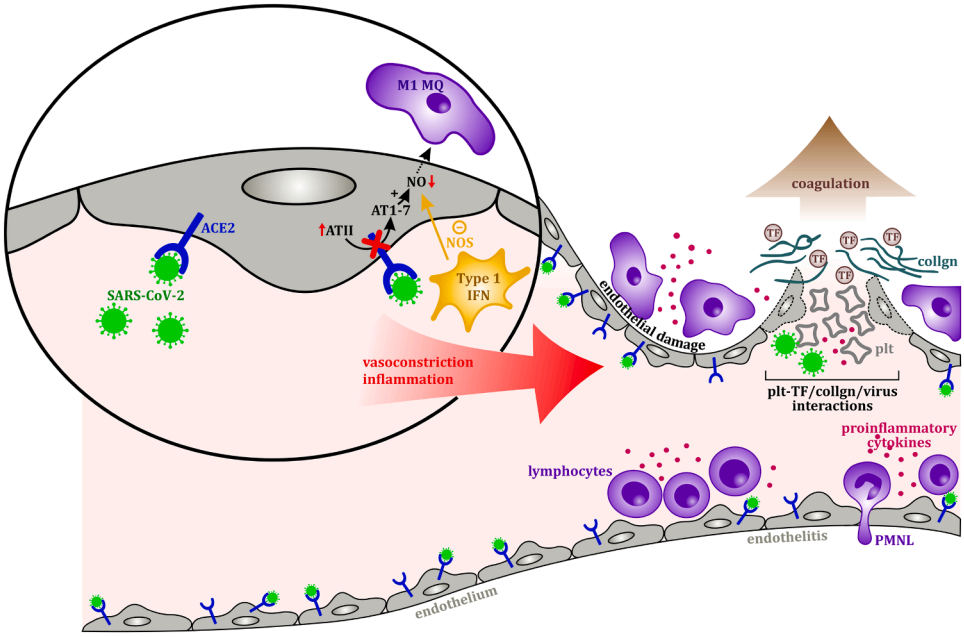

Fig. 2. Possible mechanisms of COVID-19 associated vasculitis: Normally, ACE2 converts ATII to AT1-7 which induces endothelial cells to produce NO. When ACE2 was downregulated by SARS-CoV-2 binding, ATII increases and NO decreases. Type I IFN response against SARS-CoV-2 may further decrease NO by inhibiting NO synthetase. NO is important for vasodilation and control of inflammation since it sets macrophages to M2 (anti-inflammatory) status. Thus, an increase in ATII and decrease in NO lead to vasoconstriction and inflammation. Inflammation and direct damage introduced by viral replication cause endothelitis and loss of endothelial barrier. This exposes collagen and TF in the basement membrane and platelets interact with these. As a result of platelet-TF/collagen/virus interactions, platelet activation occurs which lead to a microenvironment prone to coagulation. Furthermore, activated platelets, M1 macrophages, and activated lymphocytes (as a result of immune response against virus) release proinflammatory cytokines contributing to the vessel wall inflammation. *ACE2, angiotensin converting enzyme; AT, angiotensin; collgn, collagen; IFN, interferon; MQ, macrophage; NO; nitric oxide; NOS, nitric oxide synthetase; plt, platelet; PMNL, polymorphonuclear lymphocyte; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TF, tissue factor.*

with our current practice. Furthermore, the good outcome is similar to what we observed in IgAV/HSP not associated with COVID-19. In our series including 159 children with IgAV/HSP, around 45% of patients received corticosteroids (versus 55% in COVID-19 associated IgAV/HSP) and complete recovery was achieved in almost all patients[70]. Similar results were observed regarding IgAV/HSP treatment and outcome in other studies[71], [72].

The immunosuppressive therapy introduced to COVID-19 associated AAV patients was also consistent with the recommendations in the most recent guidelines for AAV treatment[73], [74]. In these guidelines, RTX or CYC (RTX over CYC in the ACR [American College of Rheumatology] guideline) is recommended in the induction of remission in active and severe AAV while RTX or AZA/methotrexate (MTX) is recommended in the remission maintenance period[73], [74]. Antithrombotic treatment has only been mentioned for AAV patients with venous thrombotic events[73].

There are no standardized treatment protocols for childhood primary CNS vasculitis. In a recent systematic review, high dose corticosteroids (with taper over 3-12 months), anti-thrombotic treatment, and CYC (with trimethoprim-sulfamethoxazole prophylaxis) are recommended in the induction therapy, while MMF/mycophenolic acid and long term antiplatelet therapy are recommended for maintenance[75]. Clinical outcome has been relatively good in pediatric CNS vasculitis not associated with COVID-19 when patients are treated with corticosteroids and immunosuppressive drugs[76]. Thrombotic microangiopathy triggered by SARS-CoV-2 might have contributed to the poor prognosis in the patients with COVID-19 associated CNS vasculitis.

In the most recent ACR guideline[77], low dose aspirin is recommended to all MIS-C patients for at least four weeks. Anticoagulant therapy is also recommended in the presence of coronary arterial aneurysm, thrombosis, or individual risk factors such as age older than 12 years old or elevated D-dimer levels more than five times the upper normal limit[77]. Antiplatelet or anticoagulant therapy could also be considered in COVID-19 associated severe vasculitis such as AAV or CNS vasculitis.

Conclusion

COVID-19 related diseases have introduced a new chapter in the practice of rheumatology. COVID-19 associated pediatric vasculitis (other than KD-like vasculitis in MIS-C) is very rare; however, the clinicians should be aware of this entity to diagnose patients timely and initiate an effective treatment to improve the outcome. In general, the clinical features of pediatric vasculitis subtypes look similar to those in pediatric vasculitis not associated with COVID-19. While conservative measures are sufficient for patients with certain vasculitis types such as IgAV/HSP, isolated skin vasculitis, and AHEI; corticosteroids and immunosuppressive therapies are required for other vasculitis subtypes such as AAV and CNS vasculitis. Antiplatelet or anticoagulant therapies could be considered in COVID-19 associated severe vasculitis since COVID-19 sets an environment prone to coagulation. Prospective cohort studies including COVID-19 associated pediatric vasculitis patients will provide more data and evidence to improve treatment strategies in these patients.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.semarthrit.2022.152047.

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