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Commentary

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COVID-19 Related Myocarditis and Stroke in Children: Spared but not Safe

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Abstract

Beginning in Wuhan China in 2019, the SARS-CoV-2 infection, or COVID-19, has spread to become a devastating worldwide pandemic. Myocarditis and stroke are known direct and indirect complications of SARS-CoV-2 infection. There is a growing body of literature describing the incidence of myocarditis and stroke in adults with COVID-19 related illness, and therapies to mitigate or prevent these catastrophic complications. In children, only a small number of case reports, case series, and expert consensus statements have been published regarding these aspects of COVID-19 related conditions. The incidence of these serious complications appears to be less frequent and less fatal compared to the adult population, yet fatal outcomes from both myocarditis and stroke have been reported in infants and children. Although rare events, I hope to briefly summarize what is known about COVID-19 related myocarditis and stroke in children for this commentary in the International Journal of Integrative Cardiology.

Keywords: COVID-19; MIS-C; PIMS-TS; Stroke; Myocarditis; Thromboembolism

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Abbreviations

MIS-C: Multisystem inflammatory syndrome associated with SARS-CoV-2; LVEF: Left ventricular ejection fraction; ECMO; Extracorporeal membrane oxygenation; PIMS-TS: Pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2; VTE: Venothromboembolism.

Introduction

Beginning in Wuhan China in 2019, the SARS-CoV-2 infection, or COVID-19, has spread to become a devastating worldwide pandemic with over 104 million cases and 2.2 million deaths at the time of this report [1]. The acute and delayed multisystem effects of this virus are beginning to be more comprehensively described in the literature, however predominantly in adult patients. Fortunately, although millions of children have tested positive for COVID-19 to date, the mortality rate for children (0.01%) appears to be considerably less than that of adults (1.7%) [2]. However, children are not entirely spared from the serious and fatal effects of COVID-19. Many reports have described respiratory failure, myocarditis, and stroke in children with COVID-19. In September 2020 we published a case report entitled "Arterial ischemic stroke as an unusual first manifestation of parvovirus B19 myocarditis in an infant" [3]. At the time of this review, there has not been a report of a child with COVID-19 related myocarditis presenting with a cardioembolic stroke. However, for this commentary in the International Journal of Integrative Cardiology, I hope to briefly summarize what has been published about COVID-19 and myocarditis or stroke in children, highlight key studies (Table 1), and I offer suggestions for areas for future investigation.

COVID-19 Related Myocarditis

Myocarditis has been a well-described feature of both acute SARS-CoV-2 infection as well as the delayed onset multisystem inflammatory syndrome associated with SARS-CoV-2 infection (MIS-C) [4,5]. Some studies estimate that 53-80% of children with COVID-19 with have cardiac involvement such as reduced left ventricular ejection fraction (LVEF) or myocarditis as a clinical feature [6-8]. There are even reports of patients whose initial presentation is due to signs and symptoms of myocarditis related to COVID-19 [9]. There are reports of fulminant myocarditis requiring extracorporeal membrane oxygenation (ECMO), and fatal cases of myocarditis, but most children with COVID-19-related myocarditis recover [10-13]. One study showed that despite a significant reduction in LVEF, >70% of children normalized their LVEF before discharge from the intensive care unit, and another showed a 95% recovery of normal LVEF [7,10]. In one study of 15 children with pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS), 12 (80%) had reduced LVEF, but no cases were reported to have intracardiac thrombi [14]. Although thromboembolism has been described in adults with COVID-19, the prevalence of intracardiac thrombi, a known complication of the reduced LVEF in myocarditis patients, has yet to be determined. As more pediatric cases of SARS-CoV-2 and MIS-C are described, the

Table 1: Selected studies of COVID-19, stroke, myocarditis, and thromboembolism in children.

Author/year	Study type	Patient population	Findings	Conclusions
Tiwari L 1/2021	Case report	9-year-old female	Multifocal arterial stroke due to multi-vessel stenosis with MIS-C.	Pathogenesis of acute ischemic stroke in COVID-19 is not fully known
				Cerebral endothelitis in this patient was like reports in kidney, heart, bowel, and lung
Kaushick S 9/2020	Retrospective case series	33 children with MIS-C	Depressed LVEF in 63%, all survived to discharge except 1 patient (3%) who died after withdrawal of care after a stroke on ECMO	Critically ill children with MIS-C requiring intensive care have a broad-spectrum illness severity
Mirzaee S 6/2020	Case report	12-year-old male	Presented with a seizure and right-sided hemiparesis, found to have ischemic stroke due to focal cerebral arteriopathy and SARS-CoV-2 by PCR	Infectious agents are known causes of focal cerebral arteriopathy, a common cause of childhood stroke
				Patient did not have respiratory symptoms of active SARS-CoV-2 infection or systemic vasculitis seen in MIS-C
Essajee F 9/2020	Case report	2-year-old female	Presented with acute left-sided weakness and lethargy, preceding lymphadenopathy and decreased appetite found to have TB, SARS-CoV-2 by PCR, and thrombosis of cerebral sinus venosus	Cerebral sinus venosus thrombosis is a rare complication of either COVID-19 or tuberculosis meningitis
				Prothrombotic state due increased release of proinflammatory cytokines can be seen in infection with either pathogen
Gulko E 12/2020	Case report	13-year-old female	Presented with headache, speech difficulty and right sided weakness who was SARS-CoV-2 PCR and antibody positive	Focal cerebral arteriopathy is a focal vasculitis that can be detected by MR vessel wall imaging
				Steroid therapy may improve the outcomes in focal cerebral arteriopathy
Goldenberg NA 8/2020	Expert consensus guidelines	N/A	A phase 2 clinical trial of anticoagulant therapy to decrease the risk of venothromboembolism in children hospitalized with COVID-19 is underway	There is currently a paucity of evidence to base recommendations
				Consensus of expert opinion suggest low dose low molecular weight heparin twice daily and mechanical thromboprophylaxis for those who have markedly increased D-dimer or risk factors for VTE
Al-Ghafry M 12/2020	Case series	8 children with SARS-CoV-2 infection	Elevated D-dimer (75%), fibrinogen (88%) and hypercoaguable state with increased clot strength with ROTEM analysis	Evidence of hypercoagulability in children with SARS-CoV-2 infection
				Despite coagulation abnormalities symptomatic thromboembolic events did not occur
Kotula JJ 1/2021	Case report	15 y/o female bilateral pulmonary embolism	Obese female presented after sudden cardiac arrest found to have multiple pulmonary embolisms, and had SARS-CoV-2 antibodies	Thromboembolism is a known complication of MIS-C and can potentially be fatal
				PE is much more common in COVID-related ARDS than other etiologies
Sanna G 5/2020	Systematic review	N/A	Data relating to COVID-19 in the pediatric age were sparse at the time	Myocarditis related cardiac dysfunction and arrhythmias are consequences of COVID-19
				Children with underlying conditions and congenital heart disease are at increased risk
Pouletty M 8/2020	Retrospective multi-center cohort	16 children with PIMS-TS	Myocarditis was seen in 44% of children with PMIS-TS and predicts more severe disease. 92% of patients received IVIG and 62% received a second dose	Myocarditis predicts more severe disease in those with PIMS-TS
				Poor prognostic factors include age >5 years and ferritin >1400 ug/L
Dufort E 7/2020	Retrospective cohort	99 cases of confirmed or potential MIS-C in New York state	Tachycardia in 97%, elevated troponin in 71%, 62% received vasopressor support, 53% with myocarditis, 80% admitted to intensive care unit and 2 deaths	MIS-C coincided with widespread SARS-CoV-2 transmission
				The hyperinflammatory syndrome with dermatologic, mucocutaneous, gastrointestinal manifestation was associated with cardiac dysfunction
Belhadjer Z 8/2020	Observational study	35 children with acute heart failure with SARS-CoV-2 infection	LVEF was <30% in 1/3 of patients, 80% required inotropic support, 28% treated with ECMO, all received IVIG, LVEF normalized in 71% by ICU discharge with no deaths	Children may experience acute cardiac decompensation after SARS-CoV-2 infection
				Treatment with IVIG appears to be associated with recovery of LVEF
Matsubara D 10/2020	Case control study	28 MIS-C children and 20 controls and 20 with Kawasaki disease	Only 4% of MIS-C had coronary artery dilation. Left ventricular systolic and diastolic function were worse in MIS-C compared to Kawasaki's disease. Diastolic dysfunction persisted when LVEF returned to normal	Unlike Kawasaki disease, coronary arteries may be spared in MIS-C
				Evidence of subclinical myocardial injury was suggested

Legend: MIS-C = Multisystem inflammatory syndrome associated with SARS-CoV-2; LVEF = Left ventricular ejection fraction; ECMO = Extracorporeal membrane oxygenation; PCR = Polymerase chain reaction; TB = Tuberculosis mycobacterium; MR = Magnetic resonance, VTE = Venothromboembolism; ROTEM = Rotational thromboelastometry; PE = Pulmonary embolus; ARDS = Acute respiratory distress syndrome; PMIS-TS = Pediatric multisystem inflammatory syndrome-temporally related to SARS-CoV-2; IVIG = Intravenous immunoglobulin; ICU = Intensive care unit.

frequency of intracardiac thrombi formation or thromboembolism will hopefully be determined.

Stroke as a Complication of COVID-19

Much of the morbidity of COVID-19 in adults is linked to the

vasculitis and thromboembolic complications related to SARS CoV-2 infection. However, direct thromboembolic complications resulting in stroke from SARS-CoV-2 and MIS-C have yet to be described in children. In a large series of adult COVID-19 patients, cerebrovascular accident was described in approximately ~3% of all cases, but ~6% in more serious cases, and surprisingly disproportionately increased in patients <50 years old [15]. Another study described the prevalence of stroke in hospitalized patients with COVID-19 to be ~1.1%, with the average time between COVID-19 diagnosis and stoke diagnosis being ~9 days [16]. Matthew et al. cited a stroke rate ~2.5%, and of patients with stroke, 92% were found to ischemic, 3% hemorrhagic and 5% cardioembolic in origin [17]. Furthermore, acute stroke in COVID-19 patients is a marker of worse outcome [18]. Studies have shown that acute ischemic stroke in COVID-19 patients have worse survival than non-COVID related stroke patients, and one study reported an over 4-fold increased odds of in-hospital death [19]. Compared to adults, the stroke rates and types in children has yet to be described comprehensively, but stroke has been described in children with COVID-19, and it is a complication providers need to be aware of.

Stroke in Children with COVID-19

Of the few case reports of children described with COVID-19 and stroke, 1 patient was a child with myocarditis who suffered a stroke as a complication of ECMO [7]. The study does not describe a preceding or identified intracardiac thrombus. In another report, a 31-month-old child presented with medical attention after presenting with left-sided weakness and lethargy and was subsequently found to have a cerebral sinus venosus thrombosis from both tuberculosis meningitis and COVID-19 co-infection, however myocarditis was not described [20]. Her cerebral sinus venosus thrombosis was thought to be due to the hypercoaguable state caused by both tuberculosis meningitis and COVID-19, and was successfully treated with isoniazid, rifampicin, pyrazinamide, ethionamide, prednisone, dexamethasone, aspirin and an emergent ventriculoperitoneal shunt. Finally of pediatric reports, focal cerebral arteriopathy was thought to be the etiology of stroke in two adolescent children with COVID-19 [21,22]. However, unlike our report, no cases had identified a pre-existing intracardiac thrombi from reduced LVEF at the time of the arterial stroke.

Stroke in Myocarditis

Stroke is a known complication of myocarditis with a prevalence of approximately 4-11% in children [23,24]. Furthermore, myocarditis and/or reduced LVEF is seen frequently in children with COVID-19 and MIS-C. A fatal stroke was described in a 5 y/o with reduced LVEF from MIS-C, but as a complication from ECMO without known intracardiac thrombi [25]. COVID-19 has been described to cause host coagulopathy and a pro-thrombotic state, but it is interesting to note that there are not yet reports of intracardiac thrombi formation and subsequent stoke in children with either direct SARS-CoV-2 infection or MIS-C.

Transient Hypercoaguable State in COVID-19

Several studies describe a hypercoagulable state during COVID-19 infection. The risk for thrombosis appears to be multifactorial, from direct viral cytopathological effects, a pro-inflammatory state, cytokine storm, hypoxia-inducible thrombosis, and endothelial inflammation leading to fibrin clots [26]. This is critical because thromboembolism, hypercoagulability, and overproduction of proinflammatory cytokines can lead to multi-organ failure [27]. In a study by Al-Ghafry M, et al. laboratory tests such as elevated D-dimer and maximal clot firmness by rotational thromboelastometry were able to identify a hypercoagulable state in 8 children with SARS-CoV-2 infection [28]. Furthermore, in a study of 109 adults, 31 (28%) receiving routine venothromboembolism (VTE) prophylaxis still suffered a VTE after admission for COVID-19 at an average of 8 +/- 7 days from hospital admission [29]. In that study, both elevated admission d-dimer and peak d-dimer levels were significantly predictive of VTE development. Finally, of 3334 adults with COVID 19, thrombotic events were present in 16%, of which 11% were arterial, 6% venous and 1.6% suffered a stroke [30]. These studies support the hypothesis of a hypercoagulable state related to COVID-19 that may contribute to risk for morbidity and mortality, but pediatric data are lacking.

Prophylactic Antithrombotic Therapy for COVID-19 Patients

Although thrombotic events are well described in patients with COVID-19, myocarditis, or both, the evidence describing effective prophylaxis against these events is limited. For adults with COVID-19, thromboprophylaxis is associated with lower mortality [31]. However, there are risks associated with prophylactic therapy, as there is a report of fatal gastrointestinal bleeding in an adult receiving thromboprophylaxis with enoxaparin during his hospitalization for COVID-19 [32]. There are yet to be studies of the safety and efficacy of thromboprophylaxis in COVID-19 related myocarditis or MIS-C children currently. However according to a study published by Goldenberg et al, despite lack of evidence in children at the time, there was a consensus among pediatric subspecialists that low-dose low molecular weight heparin is administrated twice daily for thromboprophylaxis for those children hospitalized with COVID-19 related illness and markedly elevated D-dimers or other risk factors for VTE [33]. More study is required to determine the safety and efficacy of thromboprophylaxis in children with COVID-19, and a phase 2 trial is clinically underway.

Summary and Future Research

In summary, we continue to learn rapidly about COVID-19 and SARS-CoV-2 related conditions in children. Although overall mortality of COVID-19 is much lower for children than adults, it still can cause significant morbidity and mortality. Although rare cases of stroke in children with COVID-19 have been described, it seems to be much less prevalent than in adults. At the time of this report, fortunately no children have been described to have presented to medical attention after cerebral embolism of intracardiac thrombi from COVID-19 myocarditis. Future research will need to determine the overall prevalence of myocarditis in children with COVID-19-related disease, the prevalence of stroke in those patients, and finally the prevalence of intracardiac thrombi in these patients to help guide recommendations for thromboprophylaxis or treatment in this unique population.

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Conflicts of Interest

None.

Ethical Standards

This research does not involve human and/or animal experimentation.

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