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Study of Cardiac Injury In Post COVID Children

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Abstract

Introduction: Starting in late 2019, a novel coronavirus rapidly spread throughout the world, resulting in a global pandemic. aim of the work: The virus was designated severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the illness it caused coronavirus disease 2019 (COVID-19). Patients and methods: The clinical spectrum of COVID-19 ranges from asymptomatic infection to mild respiratory tract symptoms to severe pneumonia with acute respiratory distress syndrome and multiorgan dysfunction.

Key words: COVID-19; SARS-CoV-2; Pediatrics; Cardiac Injury

Introduction

The 2019 coronavirus pandemic (COVID-19) was caused by the SARS-CoV-2 virus, which led to a worldwide outbreak of sickness. Symptoms such as cough, fever, chills, and subsequent difficulty breathing and low oxygen levels are the acute manifestations of the condition. Ischemia, arrhythmias, venous thromboembolism, acute coronary syndrome, myocardial damage, and other cardiovascular problems may occur in adults due to this infection. [(1-3)].

In adults infected with SARS-CoV-2, the risk of morbidity and death is higher if they have preexisting cardiovascular disorders. However, the majority of SARS-CoV-2 infected children and teenagers either show no symptoms at all or have a mild case of the illness. Acute cardiac dysfunction, arrhythmias or conduction anomalies, and coronary artery dilatation may be caused by the uncommon but severe post inflammatory consequence of SARS-CoV-2 infection in children, known as multisystem inflammatory syndrome in children (MIS-C).

Fig. (1) [(4-7)].

Patients in their youth who have a history of congenital or acquired cardiac disease may need specialised evaluation and care, but there is still a lot we don't know. This scientific statement summarises the current understanding of COVID-19 and MIS-C in children and young adults, including its epidemiology, pathophysiology, clinical manifestations, therapy, and prognosis. We assess the public health burden and distribution of COVID-19 infections, review the current knowledge regarding the health consequences of this virus in children and young adults with congenital and acquired heart disease, and review the COVID-19 vaccine in relation to myocarditis in this age group.

Fig. (1) [(8, 9)].

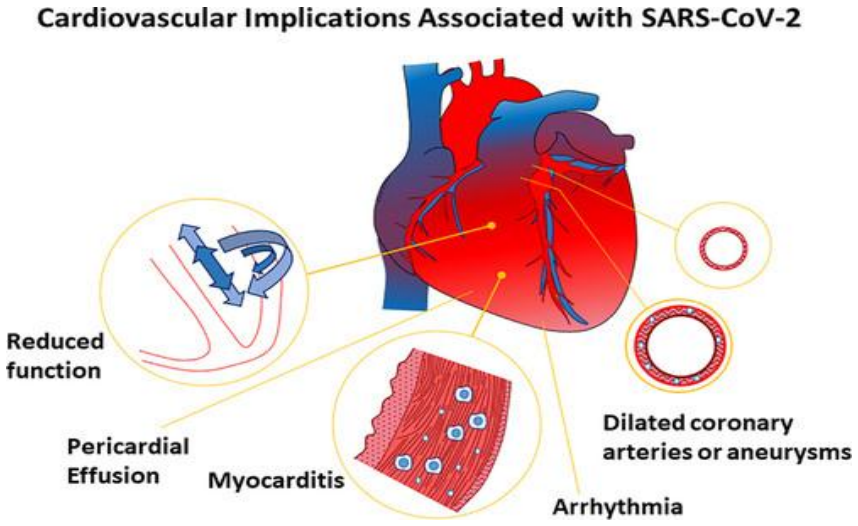

Fig. (1) Reduced function, pericardial effusion, myocarditis, arrhythmia, dilated coronaries or aneurysms are some of the cardiovascular consequences of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). [(8)]

Epidemiology

People of various ages, colours, and nationalities have been impacted by the COVID-19 pandemic. Compared to adults, children and young adults were less likely to contract and have a milder case of COVID-19 in the early stages of the pandemic. In the US, as of February 24, 2022, around 17.6% of all cases were attributed to persons under the age of 18, and about 0.1% of all fatalities were recorded in this age group. Similarly, according to the CDC, young people (18–29 years old) accounted for 21.3% of cases and 0.8% of fatalities. [10-12].

While most cases of clinical COVID-19 do not affect children and young adults, there are those who are more susceptible to contracting the virus and may have serious complications as a result. When looking at the percentage of infected and severely ill persons, Black and Latino people have been hit the worst by the COVID-19 epidemic.

Children with preexisting medical issues, such as obesity or chronic lung illness, as well as those with impaired immune systems, are at increased risk of hospitalisation, ICU admission, and mortality due to COVID-19, just as they are in adults. When it comes to congenital heart disease, there have been mixed findings on the likelihood of severe COVID-19 in children and young people. While some research has shown a slightly higher risk of severe COVID-19 in patients with congenital heart disease, especially those with cyanotic congenital heart disease and pulmonary hypertension, other studies have shown a variable risk of severe disease in this population. More research is required to fully comprehend the dangers of congenital cardiac disease. [13-16].

An extremely uncommon and severe inflammatory disease known as MIS-C may develop in children and young adults 2 to 6 weeks after contracting SARS-CoV-2. This illness has the potential to impact several organ systems, including the heart. Over 2,600 cases of MIS-C were reported to the CDC in the first year of the pandemic, with an estimated incidence of 1 case every 3,164 cases of SARS-CoV-2 infection in children. Among children infected with SARS-CoV-2, the majority of cases of MIS-C were found in Black children (1 case every 16,23 cases) or Hispanic/Latino children (1 case per 21,141 cases). Certain racial and ethnic groups continue to be disproportionately affected by MIS-C, even after accounting for overall COVID-19 rates. [17-19]:

1. The presence of MIS-C is higher among non-Hispanic Black children and lower among non-Hispanic White children that meet expectations.
2. MIS-C is more common among Hispanic children and less common among non-Hispanic Asian children, contrary to expectations based on COVID-19 rates. [20].

Pathophysiology

The SARS-CoV-2 virus attaches itself to the host cell's surface via the angiotensin-converting enzyme (ACE) 2 (ACE2) receptor using the viral spike protein. The virus is big, enveloped, and has single-stranded RNA. After binding to the ACE2 receptor, the viral S protein triggers the activation of the SARS-CoV-2 protein, which in turn activates the host cell's type 2 transmembrane serine protease, facilitating viral uptake and coronavirus entrance into the host's alveolar epithelial type II cells. Some possible ways that SARS-CoV-2 infection affects the cardiovascular system include [21]:

cellular damage that occurs directly in cardiomyocytes due to the increased expression of ACE2 receptors.

cytokine storm and overactive immune response causing cardiac myocyte damage.

damage due to a lack of oxygen, which causes myocardial ischemia. Children may have milder acute SARS-CoV-2 infections due, in part, to lower ACE2 levels, as ACE2 receptors grow with age.

According to other research, SARS-CoV-2 has a lower binding affinity in children because there are less ACE2 receptors in their noses. This, in turn, leads to milder sickness. It is possible that the increased susceptibility of adults to SARS-CoV-2 infection is due to the fact that one research found that expression profile for type 2 transmembrane serine protease was much higher in adult mice compared to juveniles. [22].

Children who do not experience severe illness may also benefit from a distinct cytokine response compared to adults, as well as trained immunity from exposure to live vaccinations and numerous virus infections. [23].

Researchers have shown that vaping increases the expression of the ACE2 protein, which in turn increases the risk of SARS-CoV-2 infections and worsens the condition in young people and children who use e-cigarettes regularly. Contrary to popular belief, there is no correlation between the use of angiotensin receptor blockers and an increased risk of infection or severe illness while treating SARS-CoV-2. ACE inhibitors and angiotensin receptor blockers are safe to use during infection. [24].

Acute and hyperinflammatory phases, often known as cytokine storms, are the two distinct clinical manifestations of COVID-19. During the acute phase, SARS-CoV-2 infects type II lung alveolar epithelial cells via the host ACE2 receptor, setting off a chain reaction that involves the activation of macrophages in the lungs.7 Acute respiratory distress syndrome and other respiratory symptoms might manifest in otherwise asymptomatic patients. The severity of the sickness is correlated with the cytokine storm that is produced when the virus replicates and initiates the hyperinflammatory phase, which is characterised by tissue destruction caused by the host's innate immune response. [(25)].

Acute respiratory distress syndrome (ARDS) is a clinical manifestation of SARS-CoV-2 infection, which may damage the alveoli throughout the body via perivascular T-cell infiltration and severe endothelial destruction caused by intracellular virus. Interferon γ-induced protein 10, granulocyte-macrophage colony-stimulating factor, macrophage inflammatory protein-1α, tumour necrosis factor-α, and monocyte chemoattractant protein-1 levels in the blood are greater in patients admitted to the intensive care unit compared to those who were not admitted to the ICU. [(26)].

In severely sick individuals, inflammation of the pulmonary endothelial cells may cause microthrombi to develop, which in turn increases the risk of deep vein thrombosis, pulmonary embolism, limb ischemia, ischemic stroke, and myocardial infarction. There was a notable increase in biomarkers linked to myocardial damage in the adult group that did not survive, including creatine kinase MB, myoglobin, and high-sensitivity cardiac troponin I. I can reliably foretell unfavourable results on my own. [(27)].

While our understanding of the pathophysiology of MIS-C is limited, what little is known suggests that the immune response to MIS-C differs from that of acute SARS-CoV-2 infection. A genetically vulnerable child's hyperimmune reaction to the virus is thought to be the pathophysiology of MIS-C. One research found that compared to children with moderate SARS-CoV-2 infection, those with MIS-C had much less CD8+ T cells. [(28)].

Despite the usual occurrence of substantial lymphopenia at first presentation with MIS-C, children with MIS-C exhibited more robust T-cell activation and proliferation, particularly of CD8+ T cells, when contrasted with seriously sick adults with COVID-19. Further, autoantibody binding to proteins involved in immune cell signalling and structural proteins in heart and blood arteries was discovered using global autoantibody screening. [(28)].

Researchers have discovered that children with MIS-C have a distinct repertoire of T-cell receptors, which is in line with the presence of a superantigen. Currently, there is no evidence that children with MIS-C have a T-cell deficiency. The pathophysiology of MIS-C may include a decrease in exhausted cytotoxic T lymphocytes and natural killer cells, according to recent RNA sequencing of blood from individuals with the disease compared to control people. [(29)].

Clinical symptoms of COVID-19 in children

These days, it's obvious that SAR-CoV-2 strains, coexisting diseases, age, race/gender, genetics, immune response features, and so on all have a role in how COVID-19 manifests clinically. [(30)].

The serious sickness caused by COVID-19 and the genetic variables that influence susceptibility have just been reported. Multiple genome-wide association studies have shed light on the role of shared genetic variants. COVID-19 revealed a link between 12–15 locus and a number of genetic loci, most notably 3p21.31 locus 12–16, and between SARS–CoV-2 severity and infection risk. [(31)].

At the outset of the COVID-19 pandemic, there was a general belief that children often had a mild or asymptomatic illness and a limited fraction of confirmed cases in this cohort. The literature reports that between 1% to 16% of children and adolescents have a new coronavirus infection, which is far lower than the adult population. The majority of children infected with COVID-19 have mild cases, and between fifteen and forty-two percent of those infected youngsters show no symptoms at all. [(32)].

Some writers have provided an explanation for the lack of T and B lymphocytes in the population by pointing to mild COVID-19 in children. The prevention of TB has been proposed by several writers as a protective function. According to some research, variations in the expression of the ACE2 receptor, which is essential for the attachment of SARS-CoV-2, may explain why children often have mild cases of COVID-19. [(33, 34)].

Further differences in the disease's presentation in children can be attributed to differences in the innate and adaptive immune responses, a lack of co-morbid illnesses, and, to a lesser extent, the presence of cross-reactive T cells resulting from prior coronavirus infections (HCoV-229E, -OC43, -NL63, and -HKU1). Nevertheless, there have

been instances of serious infection accompanied by other disorders, much as in adults. [(35)].

There have been instances of children developing multisystem inflammatory syndrome (MIS-C) as a result of COVID-19 since April 2020. MIS-C is a hyperinflammatory viral illness that manifests in children after an infection. More than 2,600 cases of MIS-C were reported in 2020 by the Centres for Disease Control and Prevention. There were 86,390 reported instances of this illness and 70 fatalities in the United States alone by the end of June 2022. [(36)].

An intriguing finding emerged from the MIS-C analysis: it manifested in both asymptomatic and severely COVID-19 infected infants. So yet, research on what causes MIS-C following SARS-CoV-2 infection is lacking. While some writers have suggested that individuals who are overweight may be more likely to acquire MIS-C, the exact function of co-occurring disorders in this condition is still unclear. Numerous studies have shown that individuals tend to have a history of good health and very seldom suffer from chronic conditions like autoimmune disease or bronchial asthma. [(37)].

It is worth mentioning that some case series include a disproportionate number of African American and Latino patients. A hyperinflammatory response to COVID-19 causes MIS-C to develop in genetically susceptible people, and it impacts several organs, including the cardiovascular system, according to some evidence. [(38)].

As a consequence of systemic hyperinflammation or vasodilation, significant myocardial dysfunction, hypotension, and shock (20-100%) were seen in some individuals. Arrhythmia occurred in 7-60% of patients, while coronary artery enlargement or aneurysms were reported in 6-24%. Nearly all children diagnosed with MIS-C had systolic left ventricular dysfunction (LVSD). Take the first case series of MIS-C recorded in the UK as an example. Six out of eight patients (or 75% of the total) had cardiac dysfunction. Ventricular dysfunction was documented in 35-100% of cases in children with MIS-C in subsequent studies.

Conclusions:

Only troponin stood up as a strong predictor of left myocardial disease among the cardiac biomarkers studied. It is also possible that Procalcitonin and Pro-BNP are very sensitive and specific predictors of left myocardial affection. In patients with COVID-19, these results point to the possibility that Troponin, Procalcitonin, and Pro-BNP are valuable biomarkers for tracking cardiac involvement.

References

[1] Ranard, LS, Fried, JA, Abdalla, M, Anstey, DE, Givens, RC, Kumaraiah, D, et al. Approach to acute cardiovascular complications in COVID-19 infection. Circulation: Heart Failure. 2020;13(7):e007220.

[2] Nishiga, M, Wang, DW, Han, Y, Lewis, DB and Wu, JC. COVID-19 and cardiovascular disease: from basic mechanisms to clinical perspectives. Nature Reviews Cardiology. 2020;17(9):543-58.

[3] Long, B, Brady, WJ, Koyfman, A and Gottlieb, M. Cardiovascular complications in COVID-19. The American journal of emergency medicine. 2020;38(7):1504-7.

[4] Riphagen, S, Gomez, X, Gonzalez-Martinez, C, Wilkinson, N and Theocharis, P. Hyperinflammatory shock in children during COVID-19 pandemic. The Lancet. 2020;395(10237):1607-8.

[5] Godfred-Cato, S, Bryant, B, Leung, J, Oster, ME, Conklin, L, Abrams, J, et al. COVID-19–associated multisystem inflammatory syndrome in children—United States, March–July 2020. Morbidity and mortality weekly report. 2020;69(32):1074.

[6] Yasuhara, J, Watanabe, K, Takagi, H, Sumitomo, N and Kuno, T. COVID- 19 and multisystem inflammatory syndrome in children: A systematic review and meta- analysis. Pediatric pulmonology. 2021;56(5):837-48.

[7] Shi, S, Qin, M, Shen, B, Cai, Y, Liu, T, Yang, F, et al. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. JAMA cardiology. 2020;5(7):802-10.

[8] Jone, P-N, John, A, Oster, ME, Allen, K, Tremoulet, AH, Saarel, EV, et al. SARS-CoV-2 infection and associated cardiovascular manifestations and complications in children and young adults: a scientific statement from the American Heart Association. Circulation. 2022;145(19):e1037-e52.

[9] Alsaied, T, Aboulhosn, JA, Cotts, TB, Daniels, CJ, Etheridge, SP, Feltes, TF, et al. Coronavirus disease 2019 (COVID-19) pandemic implications in pediatric and adult congenital heart disease.

Journal of the American Heart Association. 2020;9(12):e017224.
[10] Wojcicki, JM, Escobar, M, Mendez, AD and Martinez, SM. Household and social characteristics associated with COVID-19 vaccine intent among Latino families in the San Francisco Bay Area. BMC Infectious Diseases. 2022;22(1):527.
[11] Yonker, LM, Neilan, AM, Bartsch, Y, Patel, AB, Regan, J, Arya, P, et al. Pediatric severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2): clinical presentation, infectivity, and immune responses. The Journal of pediatrics. 2020;227:45-52. e5.
[12] Patel, NA. Pediatric COVID-19: Systematic review of the literature. American journal of otolaryngology. 2020;41(5):102573.
[13] Martin, B, DeWitt, PE, Russell, S, Anand, A, Bradwell, KR, Bremer, C, et al. Characteristics, outcomes, and severity risk factors associated with SARS-CoV-2 infection among children in the US national COVID cohort collaborative. JAMA network open. 2022;5(2):e2143151-e.
[14] Lewis, MJ, Anderson, BR, Fremed, M, Argenio, M, Krishnan, U, Weller, R, et al. Impact of coronavirus disease 2019 (COVID- 19) on patients with congenital heart disease across the lifespan: the experience of an academic congenital heart disease center in New York city. Journal of the American Heart Association. 2020;9(23):e017580.
[15] Broberg, CS, Kovacs, AH, Sadeghi, S, Rosenbaum, MS, Lewis, MJ, Carazo, MR, et al. COVID-19 in adults with congenital heart disease. Journal of the American College of Cardiology. 2021;77(13):1644-55.
[16] Shekerdemian, LS, Mahmood, NR, Wolfe, KK, Riggs, BJ, Ross, CE, McKiernan, CA, et al. Characteristics and outcomes of children with coronavirus disease 2019 (COVID-19) infection admitted to US and Canadian pediatric intensive care units. JAMA pediatrics. 2020;174(9):868-73.
[17] Yousaf, AR, Cortese, MM, Taylor, AW, Broder, KR, Oster, ME, Wong, JM, et al. Reported cases of multisystem inflammatory syndrome in children aged 12–20 years in the USA who received a COVID-19 vaccine, December, 2020, through August, 2021: a surveillance investigation. The Lancet Child & Adolescent Health. 2022;6(5):303-12.
[18] Heald-Sargent, T, Muller, WJ, Zheng, X, Rippe, J, Patel, AB and Kociolek, LK. Age-related differences in nasopharyngeal severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) levels in patients with mild to moderate coronavirus disease 2019 (COVID-19). JAMA pediatrics. 2020;174(9):902-3.
[19] Belay, ED, Abrams, J, Oster, ME, Giovanni, J, Pierce, T, Meng, L, et al. Trends in geographic and temporal distribution of US children with multisystem inflammatory syndrome during the COVID-19 pandemic. JAMA pediatrics. 2021;175(8):837-45.
[20] Stierman, B, Abrams, JY, Godfred-Cato, SE, Oster, ME, Meng, L, Yip, L, et al. Racial and ethnic disparities in multisystem inflammatory syndrome in children in the United States, March 2020 to February 2021. The Pediatric infectious disease journal. 2021;40(11):e400.
[21] Hoffmann, M, Kleine-Weber, H, Schroeder, S, Krüger, N, Herrler, T, Erichsen, S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. cell. 2020;181(2):271-80. e8.
[22] Bunyavanich, S, Do, A and Vicencio, A. Nasal gene expression of angiotensin-converting enzyme 2 in children and adults. Jama. 2020;323(23):2427-9.
[23] Lu, X, Xiang, Y, Du, H and Wing-Kin Wong, G. SARS-CoV-2 infection in children - Understanding the immune responses and controlling the pandemic. Pediatr Allergy Immunol. 2020;31(5):449-53.
[24] Hippisley-Cox, J, Young, D, Coupland, C, Channon, KM, Tan, PS, Harrison, DA, et al. Risk of severe COVID-19 disease with ACE inhibitors and angiotensin receptor blockers: cohort study including 8.3 million people. Heart. 2020;106(19):1503-11.
[25] Chung, MK, Zidar, DA, Bristow, MR, Cameron, SJ, Chan, T, Harding, CV, 3rd, et al. COVID-19 and Cardiovascular Disease: From Bench to Bedside. Circ Res. 2021;128(8):1214-36.
[26] Klok, FA, Kruip, M, van der Meer, NJM, Arbous, MS, Gommers, D, Kant, KM, et al. Confirmation of the high cumulative incidence of thrombotic complications in critically ill ICU patients with COVID-19: An updated analysis. Thromb Res. 2020;191:148-50.

[27] Chi, Y, Ge, Y, Wu, B, Zhang, W, Wu, T, Wen, T, et al. Serum Cytokine and Chemokine Profile in Relation to the Severity of Coronavirus Disease 2019 in China. J Infect Dis. 2020;222(5):746-54.

[28] Consiglio, CR, Cotugno, N, Sardh, F, Pou, C, Amodio, D, Rodriguez, L, et al. The Immunology of Multisystem Inflammatory Syndrome in Children with COVID-19. Cell. 2020;183(4):968-81.e7.

[29] Beckmann, ND, Comella, PH, Cheng, E, Lepow, L, Beckmann, AG, Tyler, SR, et al. Downregulation of exhausted cytotoxic T cells in gene expression networks of multisystem inflammatory syndrome in children. Nat Commun. 2021;12(1):4854.

[30] Viner, RM, Ward, JL, Hudson, LD, Ashe, M, Patel, SV, Hargreaves, D, et al. Systematic review of reviews of symptoms and signs of COVID-19 in children and adolescents. Archives of disease in childhood. 2021;106(8):802-7.

[31] Noval Rivas, M, Porritt, RA, Cheng, MH, Bahar, I and Arditi, M. Multisystem Inflammatory Syndrome in Children and Long COVID: The SARS-CoV-2 Viral Superantigen Hypothesis. Front Immunol. 2022;13:941009.

[32] Howard- Jones, AR, Burgner, DP, Crawford, NW, Goeman, E, Gray, PE, Hsu, P, et al. COVID- 19 in children. II: pathogenesis, disease spectrum and management. Journal of paediatrics and child health. 2022;58(1):46-53.

[33] Dolinger, MT, Person, H, Smith, R, Jarchin, L, Pittman, N, Dubinsky, MC, et al. Pediatric Crohn Disease and Multisystem Inflammatory Syndrome in Children (MIS-C) and COVID-19 Treated With Infliximab. J Pediatr Gastroenterol Nutr. 2020;71(2):153-5.

[34] Belhadjer, Z, Méot, M, Bajolle, F, Khraiche, D, Legendre, A, Abakka, S, et al. Acute Heart Failure in Multisystem Inflammatory Syndrome in Children in the Context of Global SARS-CoV-2 Pandemic. Circulation. 2020;142(5):429-36.

[35] Sperotto, F, Friedman, KG, Son, MBF, VanderPluym, CJ, Newburger, JW and Dionne, A. Cardiac manifestations in SARS-CoV-2-associated multisystem inflammatory syndrome in children: a comprehensive review and proposed clinical approach. Eur J Pediatr. 2021;180(2):307-22.

[36] Dufort, EM, Koumans, EH, Chow, EJ, Rosenthal, EM, Muse, A, Rowlands, J, et al. Multisystem Inflammatory Syndrome in Children in New York State. N Engl J Med. 2020;383(4):347-58.

[37] Cheung, EW, Zachariah, P, Gorelik, M, Boneparth, A, Kernie, SG, Orange, JS, et al. Multisystem Inflammatory Syndrome Related to COVID-19 in Previously Healthy Children and Adolescents in New York City. Jama. 2020;324(3):294-6.

[38] Ermolaeva, Y, Samoilova, Y, Oleinik, O, Yun, V and Kudlay, D. COVID-19 in children: Generalization of world experience. Pediatrics. 2022;101:80-7.