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Review Article

A Review of Multisystem Involvement of SARS-CoV-2 Infection in Children

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ABSTRACT

Coronavirus Disease 2019 (COVID 19) originated in Wuhan, China in late 2019 and within a span of a few months it was deemed as a global pandemic by the World Health Organization (WHO). It was initially only thought to affect the adult population, however soon thereafter, cases of COVID-19 in children started emerging. Many studies have now shown that this virus exhibits a milder infection in children compared to adults. As more and more pediatric cases started unveiling, an entity called Multisystem Inflammatory Syndrome in Children (MIS-C) that replicated Kawasaki was established. More recently, it has been noted that children have persistent symptoms weeks or after months after acute COVID-19 infection and the term coined for these symptoms is Long COVID. This review will summarize all the systemic manifestations of COVID-19 under three broad categories: acute COVID, MIS-C and Long COVID.

Keywords: Toll-like receptors; Exosome; Regulation; Pediatric; Enzyme

INTRODUCTION

The SARS-CoV-2 virus that has ravaged the world the past 2 years has had tremendous impact on the mortality and morbidity of the world's population. Although the morbidity is lesser in children, they continue to experience significant sequelae that affect their quality of life. It was initially thought that COVID-19 only affects the respiratory system, however soon thereafter studies emerged showing the multisystem involvement of the virus [1]. The COVID-19 infection rate is down trending since the introduction of vaccines, but about 25% of children experienced persistent symptoms months after hospitalization with acute COVID-19 infection, with almost one in 10 experiencing multisystem involvement [2]. There is scarce data on the effects of COVID-19 infection in the pediatric age group.

Long term sequalae of COVID-19 can be broadly categorized into multi-system inflammatory MIS-C and Long COVID. Amongst the pediatric population, initially COVID-19 manifested as only an asymptomatic or mildly symptomatic illness with excellent prognosis [3]. Soon thereafter, cases of MIS-C started emerging in April 2020. Formerly thought to be mimicking Kawasaki disease, it has now been established as a separate entity. MIS-C is a post-inflammatory syndrome after an acute COVID infection. It is a relatively rare phenomenon that occurs in children about 2- 6 weeks after COVID infection. The manifestations of MIS-C occur because of marked immune system activation and it involves practically all systems from gastrointestinal to skin, mucous membrane neurological and cardiovascular [4]. It is interesting to note that majority of patients with acute COVID infection presented with mild symptoms whereas about 68% patients diagnosed with MIS-C required critical care [5].

LITERATURE REVIEW

Long COVID also called post-covid syndrome or post-acute sequelae of SARS-CoV-2 infection is defined by The National Institute of Health and Care Excellence (NICE) as symptoms persisting for more than 4 weeks, unexplained by any other diagnosis. This was further divided into ongoing symptomatic COVID-19 consisting of symptoms lasting for 4-12 weeks and post-COVID syndrome comprising of symptoms lasting for more than 12 weeks [6,7]. Post-COVID syndrome is a well-known entity in adults with symptoms ranging from fatigue, dyspnea, chest pain, palpitations, headaches to anxiety, depression, and PTSD [8]. However, very little is known about the manifestations of post-COVID syndrome in children. This can be attributed to the fact that the incidence of COVID-19 in this population is lesser compared to the adult population. In this review article we explore the system-wise effects SARS-CoV-2 virus broadly under the following three lenses: acute COVID, MIS-C and long COVID.

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Neurological

It is well established that COVID-19 virus primarily targets the respiratory system. Although rare, the effect of COVID-19 on the neurological system is serious and can lead to devastating long term neurodevelopmental sequelae. There are limited studies looking at the neurological impact of this virus [9]. The pathophysiology of the COVID-19 inside the human neurons involves the interaction of the spike protein with the Angiotensin-Converting Enzyme-2 (ACE-2) in the neuron, similar to that of respiratory and gastrointestinal system. COVID-19 disseminate through the nervous system in two ways. Hematogenous spread occurs when circulating monocytes take up Human Coronavirus (HCoV) virions and subsequently express chemokines, increasing permeability of the blood-brain barrier. The virions then traverse the blood-brain barrier resulting in Central Nervous System (CNS) disease 10. Alternatively, following intranasal infection, HCoV virions cross the cribriform plate and infect the olfactory bulbs. Thereafter, neuron-to-neuron spread occurs via exocytosis/endocytosis of membrane-enclosed virions across synapses [10,11].

A large review of 3129 cases of children looking at neurological manifestations of COVID-19 concluded that the most common symptom of acute COVID was fatigue/myalgia [12]. This was closely followed by headaches. Few case series have shown specific symptoms suggestive of meningitis or meningoencephalitis in children. However, none of these studies have isolated Cerebrospinal Fluid (CSF) from the cerebrospinal fluid [13]. There have also been a few case reports of children with altered mentation, encephalopathy, headaches, brainstem, and cerebellar ataxia [14]. A handful of studies have reported seizures even in the absence of fever in children [15]. Other well-known effects include anosmia and ageusia in children [16,17]. COVID-19 effects have also extended to peripheral nervous system with several case reports showing Guillain- Barré syndrome. This may also be a component of MIS-C as well as long COVID as it is sometimes seen several weeks following an infection. Electrophysiological studies of patients have demonstrated demyelinating/axonal disease [18]. Muscle injury, rhabdomyolysis albeit very few have also been reported [19,20]. These children should be followed up carefully as there is a risk of involvement of respiratory muscles. It is interesting to note that most of the studies in children focused on respiratory system as opposed to neurological complications. Hence there is a possibly that a lot of the neurological symptoms particularly the non- specific ones have been underreported [12]. Thus, pediatricians should always bear in mind the potential serious acute neurological effects while treating a child with COVID-19 infection.

Although it is well established that long COVID has more psychiatric manifestations, some of effects on neurodevelopment require special mention. While most children with GBS, encephalitis did recover, some of them continued to have long term sequelae such as flaccid or spastic quadriparesis and/or sphincter control issues [21]. There is growing evidence of in-utero vertical transmission of the virus but there is not enough data looking at long term developmental/neurological consequences of these babies [22]. Several theories have been put forth regarding the pathogenesis of neurocognitive manifestations. Alteration of neuronal function in the context of the profound increase of circulating cytokines, and particularly IL-6, which can penetrate the blood-brain barrier, may contribute to neurocognitive impairment [23]. In addition, COVID-19-associated inflammation might lead to Gamma–Aminobutyric Acid (GABA)-ergic impairment which can lead to cognitive fatigue, apathy, and executive deficits [24].

Psychiatry

The mental health of children and young adults are disproportionately affected in the context of emergencies and disasters. Studies in children have shown cognitive and memory impairment and confusion [25]. Zhang, et al. carried out the first cross sectional study which showed psychological impact of COVID-19 virus on young female with major depressive disorder. Several studies have reported that having a pre-existing diagnosis of major depressive disorder, predicted a higher vulnerability to the Post-Traumatic Stress Disorder (PTSD) symptoms [26]. Pooled estimates from a large metanalysis study that reviewed 3094 abstracts suggested that 1 in 4 youth globally experienced clinically elevated depression symptoms and 1 in 5 youth experienced clinically elevated anxiety symptoms. These symptoms were higher in girls and in older children during the latter part of the pandemic [27]. There are limited studies carried out looking at other psychological conditions such as separation anxiety, social anxiety, and panic disorders. A Canadian study carried out amongst adolescents showed that rates of substance use were higher than expected with almost 20% indulging in substance use at least once a week. Thus, allocation of resources to address the dire mental health consequences and mitigate the long-term effects is much needed [28].

Dermatology

The cutaneous manifestations of COVID-19, its clinical presentation and course and outcomes differ in children compared to adults. A wide range of skin manifestations are seen in acute COVID-19 infection. Chilblain like lesions characterized by erythematous, edematous macules, nodules and sometimes ulcerated plaques on the dorsal surface of toes were demonstrated in adolescents [29]. Several hypotheses were postulated to explain the pathophysiology of chilblain lesions. This included virus induced type 1 interferonopathy which means that children with these lesions exhibit a strong Type I Interferons (IFN-1) response to attenuate the virus which can lead to microangiopathic changes leading to chilblains [30]. Another plausible explanation is the thrombosis/coagulopathy hypothesis due to elevated D-dimer levels that can lead to acral ischemia [31]. Thirdly vasculitis caused by the SARS-CoV-2 protein in the endothelial cells and eccrine glands can lead to these lesions [32]. Other skin manifestations seen during the acute phase of COVID-19 include erythema multiforme, urticarial rash. Case reports of children with the urticarial rash were mostly asymptomatic with respect to other symptoms of COVID-19. Another type of rash that occurs in the early stages of the disease, sometimes before the onset of other symptoms is vesicular exanthema [33]. Other forms of exanthems include maculopapular exanthems, pityriasis rosea-like eruptions and oral findings, among others. The pathogenesis of the urticarial rash was associated with bradykinin in the kinin- kallikrein system in conjunction with ACE-2 [34]. The pathogenesis of the vesicular rash is however unknown. A cutaneous and mucosal manifestation of MISC due to COVID -19 tends to be non-specific and mimics that of Kawasaki disease in children. These include non-exudative conjunctivitis, polymorphic rash, and perineal/facial desquamation [35,36].

Endocrinology

Emerging data has suggested that COVID-19 is a potential inducer of new onset Type-1 Diabetes Mellitus (T1DM) [37]. The basis behind this is coronavirus induced islet cell damage. The mechanism involves Beta cell destruction and release of sequestered islet cell antigens and activation of autoreactive T-cells that result in long term autoimmune

damage and subsequent T1DM. In addition to the decreased insulin release due to β-cell loss, proinflammatory mediators can result in functional defects like defective glucose mediated insulin release and delay in the conversion of proinsulin to insulin [38]. Multiple studies have reported that new onset T1DM triggered by COVID-19 present in Diabetic Ketoacidosis (DKA). A study carried out in UK reported children presenting severe DKA and significant hypokalemia leading to cardiac arrest [39]. The postulated pathogenesis for the hypokalemia is that SARS-CoV-2 reduces ACE-2 expression, leading to decreased degradation of angiotensin II, which can cause increased secretion of aldosterone and renal potassium loss [39].

Numerous studies although mostly in adults have been published on the effects of COVID-19 on lipid metabolism. A decrease in total cholesterol, LDL-C, HDL-C and apolipoprotein B and A-1 levels in patients with COVID-19 infections, similar to what is observed with other infections. Serum triglycerides levels were variable and lipoprotein a levels increased during COVID -19 infections. LDL-C and HDL-C inversely correlated with C-reactive protein levels.

COVID-19 has also been found to affect the gonads as there is ACE-2 expression in the testes, Leydig cells, Sertoli cells and the spermatogonia [40]. There are no studies carried out in the adolescent population however studies in young adults have shown reduction in testosterone levels. These studies should be interpreted bearing in mind that any viral infection can cause suppression of the hypothalamic-pituitary-gonadal axis. No studies have been carried out looking at reproductive system in females.

COVID-19 has also been noted to blunt cortisol stress response. The pathogenesis behind this is the molecular mimicry between the COVID-19 virus and Adreno-corticotropic Hormone (ACTH). Thus antibodies produced against COVID-19 can destroy the body's circulating ACTH [41]. We do not have enough data on COVID-19 affecting the hypothalamic-pituitary axis. However other SARS virus has shown to cause either direct or immune mediated destruction of the hypothalamus and pituitary. Currently there are no data on possible direct or indirect effects of COVID-19 on thyroid function in children.

Respiratory

Multiple studies have described the implications of COVID-19 on the respiratory system following an acute episode of infection. The pathogenesis of COVID-19 infection in children can be divided into 3 phases. First phase being flu like illness with high viral load, followed by a critical phase with decreasing viral titers and an accelerated inflammatory response and thirdly, the recovery phase. Most children with COVID-19 have mild disease presentation, with asymptomatic infection reported in about 15%-42% of the pediatric population. Children with symptomatic infection usually present with one or more respiratory symptoms, which are like seasonal RSV infections, most frequently fever and cough [42]. Other respiratory symptoms include a runny nose, sore throat, and dyspnea. Besides the clinical respiratory symptoms post-infection, radiological investigations in acutely symptomatic hospitalized children have shown patchy opacities on chest X-rays and ground-glass opacities on chest Computed Tomography (CT) [43].

Ashkenazi-Hoffnung, et al. [44] described in detail abnormal respiratory symptoms in a subset of the pediatric population after a prospective study. Dyspnea is one of the most frequently reported symptoms among the long COVID-19 patients and was significantly associated with older patients who are about 11 years. More than half of the patient population reported impairment in daily activities due to symptoms. 45% of the patients had abnormal pulmonary function tests; these were compatible with mild obstructive patterns with low volumes of forced expiratory volume on spirometry and by air trapping on lung volume evaluation. Following bronchodilators in these patients, more than half exhibited reversibility of the obstructive defect. This study highlights the importance of pulmonary evaluation and the need for potential treatment with bronchodilators and inhaled corticosteroids in the long COVID- 19 patients. Ludvigsson did a case series reporting long COVID symptoms in 5 patients that were followed up until 6 months after the acute episode of COVID-19. All the patients reported dyspnea with a decrease in activity [45]. Dyspnea persisted in most patients and is usually associated with headache, sore throat and difficulty in concentrating directly affecting school performance.

In another interesting study Denina, et al. [46] organized a clinic in Turin to follow up on children affected by COVID-19. These patients were assessed at an average of 35 days from the time of diagnosis. A complete medical evaluation was done at the time of the visit including blood analysis, nasal swab and lung ultrasound. During the hospital admission, about 52% had pathological lung ultrasounds (62% showed a diffuse interstitial pattern, and 38% had both subpleural multiple consolidations and diffuse interstitial pattern). During the follow-up visits, a mild interstitial pattern was seen in 3 patients and multiple subpleural consolidations in the other 2 patients. The presence of clinical symptoms was not documented in this study. Given the radiation load for CT, this modality is not justified in the follow-up of for long COVID-19 patients. The use of lung ultrasound was documented in multiple studies (as described above) to assess both the acute and chronic effects of COVID-19. LUS has a high concordance with the gold standard for diagnosis and assessment of the severity of SARS-CoV-2 pneumonia, compared to CT chest [47,48].

La Regina, et al. [49] studied the use of lung ultrasound in patients with persistent symptoms after COVID-19 infection. In this study, some children, even after months of acute infection, have lung ultrasound artifacts such as B lines and showed an improvement with the passage of time from the acute episode. There were no differences in the clinical characteristics of the patients except for a difference in body mass index between patients with and without lung artifacts. Considering the safety with absence of radiation, low cost and its rapidity of the execution, lung ultrasound can represent an optimal method to follow children with previous COVID-19 infection. A prospective study with a larger sample size is needed to establish the causal relationship between long COVID-19 symptoms such as dyspnea and lung artifacts in the ultrasound. The long-term consequences of COVID-19 on the respiratory system have not been studied.

Cardiovascular system

Multisystem Inflammatory Syndrome in Children (MIS-C) secondary to COVID-19 infection is one of the major causes of admission in the intensive care unit during the pandemic period.

Multiple studies have been published about the different manifestations of the cardiovascular disease process [50-52]. Cardiovascular involvement in COVID-19 positive children is more predominant in healthy school-aged children and adolescents presenting with Kawasaki disease-like features and multiple organ failure. Although the respiratory tract is the primary target for SARS-CoV-2, the virus

produces myocardial injury through different mechanisms (either by direct myocardial damage by SARS-CoV2 virus entering cardiomyocytes through ACE 2 receptors or by systemic thromboembolism causing coronary damage) [53].

During the acute phase, the patients usually present with cardiogenic shock, ECG alterations, (prolonged PR interval and ST-T wave changes on ECG), myocardial dysfunction (left ventricular systolic and diastolic function), and coronary artery abnormalities. There were a few cases reported with myocarditis, pulmonary hypertension, and cardiac arrhythmias [54].

Other changes include elevated cardiac biomarkers and pericardial effusion. Although several papers have been published about the short-term effects of COVID-19 on cardiovascular system, the long-term effects have not been established. Easy fatigability is one of the most common symptoms in post covid patients [55]. Breckel, et al. [56] described in their study that 87% of the patient population complained about new onset fatigue. About 35% of the patients complained about thoracic pain, 18% had cardiac palpitations, and 3% had dizziness. A prospective study published in December 2021 studied the effects of long COVID-19 on a small set of the population (about 90 children) [45]. During the follow-up, 71% of the patient population reported fatigue, 31.1% had chest pain and 8.9% had palpitations during the follow-up visit 4 months after the primary infection. Recently, exercise intolerance and walking intolerance were noticed in patients with COVID during the long-term follow-up [57].

Long term cardiovascular outcomes were analyzed by Chakraborty and his team in patients affected with MIS-C secondary to COVID-19. It was a single study with a sample size of 80 patients and was followed up until 1 year from discharge. Almost half the patients had elevated BNP and troponin during the admission at the hospital, but there were no patients with elevated cardiac biomarkers at the 4-6 months and during 12 months follow-up. Prolonged PR interval was noticed in very few patients at the follow up but there were no ST-T wave changes. About 34% presented with systolic dysfunction during the peak illness, but it was completely resolved in all the patients during the follow-up. Mitral regurgitation and pericardial effusion were noticed in a few patients during the peak illness, but later during the follow up, it was not present. Coronary artery abnormalities were noticed in 14 patients at the time of peak illness but during the follow up it was resolved in all but one patient (giant coronary aneurysm present) [58].

Dove, et al. [59] studied cardiac magnetic resonance findings performed at about 3-4 months after the diagnosis of MIS-C and found that patients had decreased left ventricular ejection fraction, residual valvular regurgitation and residual coronary artery dilation. But none of the patients met the modified Lake Louise criteria for myocarditis. Capone and her team did a longitudinal 6-month study of all children admitted and treated for MIS-C. Patients were followed up until 6 months' post-admission, and those with coronary aneurysms were closely followed up [60]. Almost all patients had normalization of systolic function, recovery of coronary abnormalities and no inflammation or scarring noticed on cardiac Magnetic Resonance Imaging (MRI). One interesting finding is the persistent diastolic dysfunction in the follow-up studies, but larger prospective study is needed to determine the association. Clinical symptoms like easy fatigability, palpitations, chest pain and dizziness can all lead to poor grading in the school reports. Although the imaging findings were not significant during the follow-up, a prospective randomized controlled study is needed to establish the importance of cardiovascular effects in long COVID-19 patients.

Hematological

Thrombocytopenia during the acute phase of COVID-19 infection or during MIS-C is a well-established finding [61]. There have been only a handful reported cases of isolated Immune Thrombocytopenia (ITP) occurring 2-4 weeks post-acute COVID infection which was not associated with MIS-C (no other systemic involvement) [62-65]. Xu, et al. [66] established a few mechanisms of COVID associated ITP. These include firstly, cytokine storm that abolishes hematopoiesis and hence decreases platelet count, secondly the virus directly infecting the hematopoietic stem cells and causing dysfunction, thirdly, viral induced autoantibodies causing platelet destruction and lastly, lung injury caused by the virus that activates platelets causing microthrombi and thus causing thrombocytopenia by increased platelet consumption. The most common presenting symptoms in these reported cases were petechiae, epistaxis and bruising a few weeks after a COVID-19 infection. Platelet count ranged from 4k-20k in these cases and most of the patients who were symptomatic treated with Intravenous immune globulin (IVIG) or steroids.

Anemia is one of the commonly reported hematological manifestations of MIS-C. These have now been a few cases of autoimmune hemolytic anemia reported during an acute covid infection (isolated anemia with or without ITP and no other symptoms of MIS-C) [67-69]. Cold agglutinin disease has a common occurrence in the adult population; however, it was very rare in children. But many cases of COVID-19 triggered Acute Immune Hemolytic Anemia (AIHA) have been shown to manifest as cold agglutinin disease, some mixed with warm antibodies as well. Children present with symptoms such as pallor, jaundice with laboratory findings showing evidence of hemolysis. Some cases have shown only warm antibodies (IgG^+), some mixed warm (IgG^+ and $C3d^+$) and some exclusively cold agglutinins ($C3d^+$). Most of the patients responded to steroids (pulse methylprednisolone followed by a steroid taper) as a first line treatment. Few other cases needed the addition of IVIG as a second line treatment 68. Few cases have reported the occurrence of Evan's syndrome where anemia and thrombocytopenia have both occurred in the setting of COVID infection. Lymphopenia is one of the most common laboratory findings in children with COVID [70]. Various mechanisms have been postulated that contribute to COVID induced lymphopenia. COVID-19 virus brings about a cytokine storm that brings about an increase in IL-6 and TNF-α which have a cytotoxic effect on the T cells and Natural Killer (NK) cells [71]. The virus brings about an exhaustion of $CD4^+$ as well as $CD8^+$ T cells as evidenced by a decrease in Programmed Cell Death Protein 1 (PD-1) and T cell immunoglobulin and mucin domain (Tim-3) the two markers of T cell exhaustion [72]. Lastly some of the genes involved in T cell activation such as MAP2K7 and SOS1 are downregulated during an acute COVID infection. An interesting point to note is that all the above-mentioned hematological abnormalities are generally seen in adults with moderate to severe COVID infection. However, in children they appear even with minimal symptoms of COVID infection.

Early in the pandemic many adult patients were noticed to have evidence of venous thromboembolism with laboratory findings suggestive of a high D-dimer and fibrinogen, low platelets and prolongation of PT [73]. Whitworth et al conducted a large multicenter study to evaluate the incidence of thrombosis in children hospitalized with COVID. They found the highest incidence was in patients with MIS-C followed by those with acute COVID and lastly minimal in asymptomatic patients. This was also the first pediatric study to demonstrate a co-relation with the incidence of thromboembolism and raised D-Dimer;

a finding well established in the adult population [74]. International Society on Thrombosis and Hemostasis (ISTH) also published an abstract citing the incidence of thrombosis in children during acute COVID infection and MIS-C. Deep vein thrombosis was the most common finding, followed by superficial thrombosis, pulmonary embolism and very rarely arterial ischemic stroke and cerebral venous sinus thrombosis. It was reported that prolonged Prothrombin Time (PT) was more evident in children with acute COVID infection whereas elevated D-Dimer was noticed in patients with MIS-C. ISTH has recommended that in patients who are hospitalized with COVID who either have a high D-dimer or risk factors for the development of Venous thromboembolism (VTE), should be anticoagulated for the duration of hospitalization with Low-Molecular-Weight Heparin (LMWH) (preferred) [75]. It is a well-known fact that malignancy is a pro-thrombotic state. Hence, it has been reported that many children with malignancies especially leukemia have a higher predisposition to develop VTE post-acute COVID infection. It is postulated that many chemotherapy agents like peg asparginase used in the induction phase may increase their risk as well [76].

Oncology

Patients with co-morbidities have a higher risk of COVID-19 complications as compared to the general population. Hence, it goes without saying that children with malignancies form a subset of the most vulnerable pediatric population. Johnston et al performed an observational study that highlighted those older patients with hematological malignancies, patients who are neutropenic and those with other co-morbidities were the ones who were at the highest risk of severe COVID-19 sequelae [77]. Greaves hypothesis states that there are two hits in leukemogenesis such as the primary mutations in utero lead to the formation of pre-leukemic clone. There then has to be a secondary mutation which many times are driven by environmental factors that leads to overt leukemia [78,79]. These have been a few cases of children with acute COVID-19 infections presenting a few weeks later with anorexia, bone pain, fatigue with hematological laboratory abnormalities that ended up being diagnosed as leukemia. This postulated that COVID infection may be a second hit leading to the development of leukemia [80,81]. There are no published studies about the association of long COVID presenting as hematological/oncologic systemic involvement as all the above-mentioned manifestations were reported either during an acute COVID infection or as an involvement of MIS-C. There also have been no reported associations to date of any solid tumor malignancies and its link to COVID-19.

Gastrointestinal

GI symptoms were thought to be the earliest manifesting symptoms even prior to respiratory symptoms in many children [82]. The SARS-CoV-2 virus enters the host cell via binding to the angiotensin converting enzyme 2 (ACE-2) which is found in abundance on the epithelial cells in the small intestine and found in some numbers in the crypt cells of the colon which likely contribute to the emergence of gastrointestinal symptoms by the virus [83].

Diarrhea, nausea, vomiting, anorexia, abdominal pain, acute appendicitis, ileocolitis were some of the frequently reported symptoms whereas mesenteric adenitis, protein losing enteropathy were some of the rarely reported gastrointestinal (GI) symptoms during an acute COVID infection. Diarrhea was the most commonly occurring symptom as well as one of the earliest manifestation [84]. Appendicitis has been widely reported in patients with acute COVID infection with patients presenting with vomiting, abdominal pain and CT findings of dilated fluid filled appendix with inflammation; treated with antibiotics and appendectomy [85]. A single center study in the UK reported 8 patients (6 of whom were COVID polymerase chain reaction positive) who presented with fever, abdominal pain, vomiting and diarrhea with their ultrasound finding consistent of terminal ileitis. However, due to the strong previously known co-relation of acute appendicitis and COVID; a CT was done in all the cases that depicted changes consistent with acute appendicitis [86]. It is well known that intussusception is often preceded by a viral illness [87]. There have been a handful of cases of intussusception being the only systemic manifestation in infants or younger children who were COVID PCR positive and were treated with broad-spectrum antibiotics and air enema [88].

MIS-C is characterized by numerous GI manifestations; in fact, just as in acute COVID infection, many pediatric studies are now reporting that GI symptoms are more prominent than respiratory symptoms in patients with MIS-C as well. Vomiting, diarrhea, constipation, adenitis were some of the symptoms reported alongside increased inflammatory markers and a positive COVID antibody. Ultrasound findings in such patients included cholecystitis, gall bladder sludge, hepatomegaly, mesenteric adenitis [89]. Amongst the multiple GI symptoms that are linked to COVID-19; nausea, vomiting, and abdominal pain are reported to be long COVID symptoms persisting for the many weeks after an acute infection.

DISCUSSION

Neonatal

One of the systematic reviews reported that most of the children born to mothers with COVID-19 were healthy newborns with a 1-minute and 5-minute appearance, pulse, grimace, activity, and respiration score of 8 and 9 respectively. Most of the neonates had a negative nasopharyngeal nucleic acid testing for SARS-CoV-2. A handful of newborns were critically ill with disseminated intravascular coagulation (DIC), septic shock and pneumonia [90]. Another review of 26 observational studies published that most of the neonates who tested positive for COVID-19 were either asymptomatic or had a mild respiratory illness [91]. Contrary to what was seen earlier, a large prospective multinational study showed that COVID-19 in pregnancy was associated with significant neonatal morbidity. Newborns of affected mothers had a longer NICU stay >7 days as well as had a higher Severe Neonatal Morbidity Index (SNMI) which took into consideration complications like bronchopulmonary dysplasia, hypoxic ischemic encephalopathy, sepsis, intraventricular hemorrhage, necrotizing enterocolitis etc. [92]. Acute SARS-COV-2 infection in neonates mostly manifests as feeding difficulties and other gastrointestinal symptoms. Neonatal MIS-C constitutes only 4% of the total MIS-C cases that have been reported in children [93]. Studies have shown that neonatal MIS-C can be secondary to maternal transfer of antibodies eliciting an immune response in the neonates, Symptoms observed were mostly cardiac conduction abnormalities, respiratory symptoms, feeding intolerance associated with high inflammatory markers. Rare cases of neonatal thrombosis have also been reported. Most of the cases required treatment with steroids and IVIG [94,95]. The long-term effects of COVID-19 on the neurodevelopmental outcomes of these children affected by acute COVID or MIS-C are yet to be studied.

CONCLUSION

In summary, COVID-19 in children presents with a myriad of systemic manifestations. The prognosis in children is excellent for the most part; however, some children with comorbidities have been reported to be critically ill. Most of the systemic manifestations in children are associated with acute COVID or MIS-C. A few recent studies have established long COVID symptoms (mostly cardiovascular and neurological) in the pediatric population. There still are many questions and associations that need to be answered and hence future prospective studies are warranted.

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