REVIEW ARTICLE

COVID-19 Pediatric Problems: A Narrative Review

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Abstract

COVID-19 pediatric problems have been similar to those for adults, including medical, neurological, sensory and psychological conditions, although they have typically been less prevalent and severe. The lesser severity in children may relate to their less mature viral receptors, less dysregulation of immune responses, and a lesser incidence of pre-existing comorbid conditions. This narrative review is a summary of publications found on PubMed for 2019-2021 on the prevalence of infection and the characteristics of the clinical condition that has predominated for children (multisystem inflammatory syndrome typically presenting with fever and cough in 1-5% of children between the ages of 1 and 14). Most of the extra-pulmonary symptom literature has focused on neurological, sensory and psychological conditions including headaches and loss of smell and taste as well as skin problems. The research on psychological symptoms has noted helplessness, worry and fear as well as more serious problems including anxiety, depression, PTSD symptoms and suicidal ideation. These problems have been attributed to less exercise, separation from schools and peers, over-exposure to social media, already existing psychiatric disorders and chronic illnesses that have been exacerbated by COVID-19. Methodological limitations of the literature include small sample, cross-sectional studies assessing single variables in countries that experienced lockdowns early in the pandemic. And, sequelae or post-COVID problems have rarely been researched.

This narrative review was intended to be a brief overview of publications on medical, neurological, sensory and psychological problems that children and adolescents have experienced during COVID-19. The review is based on some of the larger sample studies and systematic reviews that appeared on PubMed for the years 2019-2021. The terms pediatrics, children, adolescents and COVID-19 were entered and the search yielded 173 papers. Inclusion criteria were peer-reviewed studies and systematic reviews. Case reports and non-English papers were excluded. Following these criteria, 57 papers were selected. The resulting review that reflects the current literature includes prevalence data, clinical characteristics and potential underlying mechanisms. Consistent with the aims of this review, the paper is divided into sections on medical, neurological, sensory and psychological conditions as well as COVID-19 sequelae.

Medical Conditions

The prevalence of COVID-19 in children has varied across countries as well as across the two-year pandemic period and across age groups in the samples studied. In an early report from China's Centers for Disease Control and Prevention, for example, children less than 10 years of age accounted for only 1% of COVID-19 cases (Wu et al, 2020). In a later report from U.S. Centers for Disease Control and Prevention (CDC), 5% of the confirmed cases were children, but the age range was wider (up to 18 years of age) (Sahu et al, 2020; US, 2020).

COVID-19 is not only less common in children than it is in adults but also typically less severe (Masokano et al, 2020). In a retrospective study on 2,141 children with COVID-19, for example, mild disease was noted in 43%, moderate in 21%, severe in 3% and critical in less than 1% (Dong et al, 2020). Approximately 9 to 15% of COVID-positive children remained asymptomatic and only mild to moderate severity was noted for those who were symptomatic. The reasons for the lesser severity in children are thought to relate to the less mature viral receptors in children, less dysregulation of immune responses, and a lesser incidence of pre-existing comorbid conditions in children versus adults (Rathore et al, 2020).

Pregnancy and neonatal outcomes

Transmission of the virus to infants is thought to be via respiratory droplets and direct contact with family members, although there is some limited evidence for vertical transmission through the placenta (Akhtar et al, 2020; Atcamora et al, 2020; Han et al, 2020; Hu et al, 2020; Patane et al, 2020; Pierce-Wiliiams, 2020). At least one study has reported a high incidence of fetal distress (30%) and preterm delivery (37%) in women with COVID- 19 (Zimmerman & Curtis, 2020). And, in another study, approximately 22% of newborns were born prematurely as compared to the U.S. average of 10% (Martin et al, 2019). Similarly, in a recent review, the Caesarean rates were as high as 85% and the rate of preterm delivery was 20% (Huntley et al, 2020). The authors concluded, like several others, that the pregnancy outcome data have frequently been limited to newborns of severely and critically ill mothers, and that the results seem to be related to "geographic patterns".

For those newborns and young infants who have become infected, the symptoms have typically been mild to moderate including cough, respiratory distress, fever and pneumonia (Buonenson et al, 2020; Panahi et al, 2020; Raba et al, 2020; Yoon et al, 2020; Yu et al, 2020). And they have typically recovered in one to two weeks, although long-term follow-up studies have not yet been reported.

Multisystem Inflammatory Syndrome in Children (MIS-C)

The most common COVID-19-related medical conditions in children have been variously called Kawasaki syndrome and multisystem inflammatory syndrome (MIS-C).(Cui et al, 2020; deSouza et al, 2020; Kaushik et al, 2020; Meena et al, 2020; Yasuhara et al, 2020). In at least two reviews of the literature, the two syndromes were compared (Moreira, 2020; Pei et al, 2020). The results suggested that children with MIS-C were older than 5 years, had greater rates of cardiac involvement and more frequently required critical care. Although there has been some debate regarding the similarity of these syndromes, most of the recent literature has referred to this syndrome as MIS-C (Kone-Paut & Climaz, 2020).

MIS-C involves inflammation of different organs of unknown etiology. The most common symptoms are fever (50%) and cough (38%) (Wang et al, 2020). Other symptoms are shortness of breath, sore throat, rhinorrhea, conjunctivitis, fatigue and headache. Gastrointestinal symptoms, although less common than respiratory symptoms, include diarrhea, vomiting and abdominal pain (Rokkas et al, 2020; Wang et al, 2020). Other clinical indicators are elevated C-reactive protein, ferritin, pro-inflammatory cytokines including TNF (tumor necrosis factor as a sign of inflammation), interleukins-4, 6 & 10, and neutrophils as well as reduced lymphocytes (Rokkas et al, 2020).

In a recent report by the Center for Disease Control and Prevention (CDC, March 2021), most of those diagnosed as MIS-C were children and adolescents between the ages of one and 14 years with a median age of nine years, although MIS-C has also been reported for infants less than one year and in young adults at 20 years. Of these cases, 99% were diagnosed with COVID-19, more than half (59%) were male and 66% occurred in children who are Hispanic or Latino and Black, non-Hispanic, not unlike the ethnic distribution of COVID-19 in adults. Many symptoms have appeared in children and adolescents weeks after they were diagnosed with COVID-19 and sometimes when they had not had a prior COVID-19 infection. According to this CDC report, as the pandemic has progressed, increasing numbers of children and adolescents are becoming infected, possibly because of the reputedly stronger variants.

Just as in adults, children with pre-existing conditions (comorbidities) are more likely to require intensive care. For example, in a recent study, 83% of the pediatric sample (N= 48 children, 4-17 years of age) had pre-existing conditions including developmental delay/genetic anomalies (40%), immune disorders (23%), obesity (15%) as well as diabetes, seizure disorders and congenital heart disease (Shekerdemian et al, 2020). Other chronic illnesses that have been related to severity of MIS-C include asthma, kidney disease, liver disease and malnutrition.

Extra-pulmonary symptoms also have been noted in children during Covid-19. In a systematic review on 28 articles, for example, the decreasing order of frequency of extra-pulmonary symptoms was gastrointestinal, renal, cardiovascular, neurological, hematological, lymphatic, cutaneous, optic, ocular, olfactory and gustatory (Pousa et al, 2021). Most of the extra-pulmonary symptom literature has been focused on neurological, sensory and psychological conditions which are reviewed in the following sections.

Neurological Conditions

Neurological conditions have been less prevalent in children than respiratory problems, although the focus on respiratory problems may have resulted in overlooking neurological symptoms (Panda et al, 2020). In a systematic review of the literature, only 8% of children with COVID-19 showed neurological problems (Jieru et al, 2021). Of those children, 28% presented with headaches and 5% with more severe neurological symptoms including seizures, coma, encephalitis, demyelinating disorder and aseptic meningitis.

In another systematic review based on 21 studies (3,707 children), 17% showed neurological symptoms (Panda et al, 2020). The predominant nonspecific neurological conditions included headache, myalgia and fatigue. Only one percent showed definite neurological complications including encephalopathy, seizures and meningeal

signs. The authors suggested that direct neural invasion may have occurred in some cases, although disruption of the blood–brain barrier and neural–inflammation were suggested in others (Panda et al, 2020). The pathway the authors described was "direct invasion of the olfactory neural epithelium as it expresses the ACE–2 (angiotensin-converting enzyme 2) receptors, thereby causing inflammatory changes in the bilateral olfactory clefts".

Many of these children appeared to have neurological symptoms when first presenting, while the more severe neurological symptoms occurred in children with severe respiratory problems. The true prevalence of neurological conditions in children may not be reflected by these systematic reviews inasmuch as the original studies occurred primarily in countries that experienced COVID-19 early in the pandemic including China, Italy and France.

Sensory Disorders

Although smell and taste dysfunction could be considered neurological conditions, they are reviewed here under sensory disorders as they are distinct COVID-19 syndromes at least in adults, and they have been increasingly reported in children and adolescents. In a systematic review and meta-analysis on smell and taste disorders during COVID-19, the prevalence of loss of smell in adults was 48%, loss of taste was 42%, and loss of smell and taste combined was 35% (Ibekwe et al, 2020). These authors categorized their findings at the different levels of dysfunction as anosmia for total loss of smell, hyposmia for partial loss and dysosmia for distorted smell (and the comparable categories for loss of taste including ageusia, hypogeusia and dysgeusia). These data were derived from 13

countries including the UK, France and Italy (Ibekwe et al, 2020). The authors suggested that these disorders could occur by one of three or all three mechanisms including: "1) by inflammation of respiratory and olfactory mucosa and breaking the barrier between mucosa and olfactory sensory neurons; 2) by direct attack on the olfactory receptors; and/or 3) penetration through the cribiform plate to the olfactory bulb and ultimately to the olfactory cortex in the temporal lobe."

In an overview of smell and taste problems in children, 19% tested positive for these disorders (Erdede et al, 2020). Other authors have reported greater prevalence at 30% (Mannheim et al, 2020) and 37% (Qiu et al, 2020). However, most of these studies were self-report surveys. When a more objective test was given (a mix of eugenol, ethanol and vinegar on swabs held 1 to 2 centimeters from the nostril), only 10% of those who had normal subjective olfaction showed abnormal responses (Qiu et al, 2020). It is notable that 54% of these occurred in mild cases of COVID-19 infection, 37% in moderate cases and 17 % in severe cases of COVID-19, suggesting that these disorders are less apparent as COVID-19 symptoms increase. Another group suggested that these may be transient disorders or persist after respiratory symptoms have resolved, as in "long-haul" symptoms (Mak et al, 2020).

The increasing prevalence of sensory symptoms especially in asymptomatic and mild COVID-19 infection and the later appearance of these symptoms following recovery from COVID-19 has suggested that this syndrome may be an early marker as well as a sequelae syndrome of COVID-19 (Mak et al, 2020). These possibilities are perhaps not surprising given that the transmission of COVID-19 is thought to happen via the olfactory system, and smell and taste are processed by the olfactory and gustatory cranial nerves that are located in the temporal

lobe. Surprisingly, the data reported in these studies and systematic reviews do not appear to be informed by previous studies linking these syndromes as early markers of other diseases including Parkinson's and Alzheimer's, highlighting the need to use the more objective, culture-specific smell and taste tests in addition to self-report measures (see Field 2015 for a review).

Contrary to earlier data suggesting self-reporting as being more sensitive, objective sensory testing methods have revealed a greater prevalence of olfactory loss in COVID-19 positive patients when compared to subjective methods. In a recent systematic review and meta-analysis, for example, olfactory loss ranged from 5 to 98% (McKenzie et al, 2020). In that review, 77% of cases were identified by objective methods, while only 44% were identified by subjective methods. Recovery was noted in approximately 30 days. In another systematic review on 18 studies, significantly different prevalence was noted as a function of the severity of the disease, with 47% of symptomatic patients showing loss of smell and/or taste as compared to 31% in severe cases of symptomatic patients, while as many as 67% were noted in mild to moderately symptomatic cases (Borsetto et al, 2020). The loss of smell and taste preceded the COVID symptoms in 20% of cases and was concomitant in 28% of cases (Borsetto et al, 2020).The significant prevalence of loss of smell and taste has suggested that at least the loss of smell would be a sensitive early diagnostic marker for COVID-19 disease (Rake et al, 2020).

Cutaneous markers have also been noted in children (Lee et al, 2020). Some have suggested that these markers may be even more prevalent in children than in adults (Larenas-Linnemann et al, 2020). In a three part series, skin symptoms have been described in children experiencing COVID-19 (Andina et al, 2020). In part one of the series, the first and most widespread skin problem in children during COVID-19 was chilblain-like lesions (Andina et al, 2020). These have been called "COVID-toes" which are purple, painful, typically bilateral and feature prominent inflammation. In part two of the series, erythema, multiforme, and urticaria were described as less common symptoms (Andina et al, 2020). In the third part, histological findings were reviewed (Andina et al, 2020).

In a systematic review of the literature, skin problems were said to derive from immune dysregulation in the pediatric-age group (Larenas-Linnemann et al, 2020). The authors suggested that the underlying mechanisms for these may be viral-induced skin damage, vasculitis-like reactions and/or indirect injury from inflammatory reactions. Surprisingly, although skin conditions are said to be more common in children than adults, fewer studies have appeared in the COVID literature on the prevalence and symptoms of skin problems in children than adults, and the literature is also more sparse on skin conditions than it is for smell and taste dysfunction in children and adolescents.

Psychological Problems

Psychological problems appear to be all-pervasive, affecting children and adolescents not only diagnosed with a COVID-19 infection but also in the pediatric population at large during the pandemic. Psychological problems that have been noted during COVID-19 in adults have also been reported for pediatric samples. These have included anxiety, depression, PTSD symptoms, sleep problems and fatigue (Lee et al, 2020). In a recent COVID-19 survey, anxiety was noted in 87% of an adult sample, depression which

is typically comorbid with anxiety was noted in 70% of the sample, 65% had PTSD symptoms, 91% reported sleep disturbances and 85% were experiencing fatigue (Field et al, 2021).These problems were less prevalent in a Chinese sample Including anxiety (45%), depression (43%), and PTSD (32%) (Liu et al, 2020). The contrasts in these prevalence rates highlight the geographic and pandemic-timing differences, with the latter lower rates being noted earlier in the pandemic.

Most of the data on psychological problems in children during COVID-19 are derived from non-infected children and adolescents who were experiencing these problems during quarantines/lockdowns. In one sample, helplessness was noted in 66%, worry in 69% and fear in 61% of children and adolescents (Saurabh & Ranjan,2020). More serious psychological conditions including anxiety, depression and PTSD symptoms have also been noted among children and adolescents during COVID-19 (Yue et al, 2019).In this survey study from China, for example, 2% of children experienced moderate anxiety, 2% experienced depression and 3% met the diagnostic criteria for PTSD. (Yue et al, 2019). The prevalence was also low for their parents at 1% for anxiety, 4% for moderate depression and 4% for PTSD. These prevalence figures seem unusually low, but they are based on self-report, suggesting that the participants may have been under-reporting for "social desirability" or "faking good" reasons. The findings also suggested that excessive media exposure was a risk factor for anxiety and PTSD in the children (Yue et al, 2019). And, surprisingly, in contrast, social media exposure was a positive factor against anxiety and depression in their parents. However, the media exposure measure was explicitly for news media.

In another survey study from China, an online questionnaire was given to adolescents during a lockdown including depression, anxiety and demographic scales (Chen et al, 2020). Of this sample, 12% were experiencing depression, 19% had high anxiety scores and 7% had both high depression and anxiety scores. A logistic regression analysis suggested that female adolescents had a greater risk for depression and anxiety, and older adolescents were more depressed than younger ones. In addition, adolescents "left at home on weekdays without a companion" were more likely to be depressed and anxious. Exercise was associated with less depression and anxiety, as has been the case for adults during COVID-19 (see Field et al, 2021 for a review).

Suicidal ideation has increased during COVID-19 even during non-lockdown periods, especially in adolescents with depression symptoms, as has been noted in at least 6 publications. For example, in an historical chart review study comparing psychiatric hospitalizations during 2019 and 2020, the prevalence of suicidal ideation in adolescents (mean age=15 years) increased from 16 to 25% during the early COVID-19 period (Thompson et al, 2021). The primary problems cited by the adolescents were worry about contracting the virus, missing special events, having limited contact with others and being unable to leave home. As the authors suggested, these were more acute cases of suicidal ideation given that the adolescents were willing to be in a congregate living facility during COVID-19. However, this study was limited to being a small sample (N=142), cross-sectional, retrospective study.

These problems have been attributed to several underlying factors including less activity (exercise) during quarantines/lockdowns, separation from schools and peers, over- exposure to social media, and touch deprivation (Field et al,

2021). And many of the problems have been associated with already existing psychiatric disorders and chronic illnesses with the symptoms being exacerbated by COVID-19 (Caffo et al, 2020).

Sequelae (Also Called "Long COVID" or "Long-Haul COVID")

Only 68 studies on sequelae of COVID-19 were found in the vast literature on COVID-19 (78,000 papers) as of March 12 2021. Of these, only three were on pediatric samples. In the first of the pediatric studies, pulmonary fibrosis was noted 30 days post-discharge in 50% of the very small sample (N=14) (Zhang & Huang, 2020). In a larger sample (N=126), anosmia and dysgeusia were noted in 15% of the sample (Conchero-Guisan, 2021). Although the screening test used in this study was designed for children older than six years of age, these problems were only noted in children greater than 11 years and more often in males than females. The dysfunction occurred for every odorant except cinnamon, mint and Jasmine. This dysfunction only lasted less than two weeks which was surprising inasmuch as 95% of adults who have olfactory dysfunction have only regained their sense of smell after several weeks and sometimes as long as six months. The authors suggested that this dysregulation of smell happened in less developed ACE-2 receptors in nasal mucosa. In a third study, 47% of children and adolescents with MIS- C had a rash and/or mucositis (Young et al, 2021). Those with a rash had fewer respiratory symptoms, lower C-reactive protein and ferritin levels as well as a less severe course. Again, sensory dysfunction (taste and smell) as well as skin problems have typically been associated with less severe respiratory symptoms and sometimes have preceded less severe infection and

sometimes emerged only as sequelae to COVID-19 infection.

Several other sequelae need to be studied in children, as has been suggested by studies on adult samples. In addition to smell and taste dysfunction and rash, which have been frequently noted in adults, other problems have also persisted. In one study (N=234 completed in November 2020), smell and taste dysfunction occurred in 14% of the sample, fatigue also in 14%, problems with activities of daily living in 8% and "brain fog" in 2% (Logue et al, 2021).These were noted six months after discharge for COVID-19 and persisted for 30% in older adults and for those with hypertension and diabetes. A greater prevalence was noted for smell dysfunction (54%), taste (38%) and rash (13%) in a study that also noted audio-vestibular symptoms in COVID-19 adults (Gallus et al, 2021). These sequelae included 8% hearing loss, 4% tinnitus, 8% dizziness, 2% vertigo and 8% imbalance. Although tinnitus was persistent in 50% of the sample, the other problems were transitory.

The only psychological sequelae that have been reported for COVID-19 are post-traumatic stress symptoms and post-traumatic stress syndrome. These have been noted in 20% of an adult sample at four months post discharge (Bellan et al, 2021). In this sample (N=248), lung impairment was also noted in 50% of the sample, functional impairment in 54% and limited mobility in 22%. These symptoms might be expected to contribute to PTSD, although they are likely comorbid.

Surprisingly, none of the studies on sequelae have mentioned chronic fatigue and psychological problems (other than PTSD) being persistent. A study on previous COVID epidemics including SARS (severe acute respiratory syndrome that started in China) and MERS (Middle East respiratory

syndrome that started in Saudi Arabia) suggested that following SARS, 44% had chronic fatigue syndrome, PTSD, anxiety and depression (O'Sullivan et al, 2020). And one year after MERS, 48% had chronic fatigue and 27% had anxiety, depression and PTSD. Given the similarities of these COVID viruses to COVID-19, it is reasonable to assume similar significant sequelae following COVID-19.

Methodological Limitations

Several methodological limitations characterize these studies including small samples and the resulting lack of statistical power, self–report data, lack of compliance (e.g. 64% non-compliance in the Bellan et al study), attrition, single location of the study, and a focus on single versus multiple variables. Further, comparisons between studies have been virtually impossible given the different times of data collection in different countries at different stages of the pandemic. In addition, different measures have been used with relative differences in their objectivity. Longitudinal studies are needed on larger samples across the lockdown and non-lockdown periods of COVID-19.

Nonetheless, just as studies from previous epidemics (SARS and MERS) have informed the potential sequelae of COVID-19 infection, the adult studies have suggested potential long-haul problems for pediatric problems following COVID-19. Further,

even the scant literature on the sequelae of pediatric problems can inform interventions to prevent or ameliorate those already noted for COVID-19 in adults.

Conclusions

This narrative review suggests that although COVID-19 pediatric problems have been similar to those for adults, including medical, neurological, sensory and psychological conditions, they have typically been less prevalent and severe. An overview of the recent literature has highlighted the prevalence and clinical characteristics of pediatric infection (multisystem inflammatory syndrome) as well as the neurological and sensory problems of headaches, loss of smell and taste and skin conditions that have occurred. Fewer publications have appeared on psychological problems including anxiety, depression, PTSD symptoms and suicidal ideation in youth. These problems have been attributed to less activity, separation from schools and peers, touch deprivation, over-exposure to social media, already existing psychiatric disorders and chronic illnesses, although the potential underlying factors have rarely been studied. Methodological limitations of the literature also include small sample, cross-sectional studies that have focused primarily on prevalence and symptoms without exploring contributory factors that could help inform intervention research to reduce the symptoms and sequelae associated with COVID-19 pediatric problems.

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