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Long COVID Symptoms are Similar in Children and Adults: A Narrative Review

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Abstract

Long COVID-19 or the persistence of COVID-19 symptoms beyond four weeks has been recently recognized as a medical condition in children and adolescents. Only twelve studies could be found in the Long COVID literature on youth. This narrative review is a brief summary of some informative research on Long COVID in adults followed by a more detailed review of the studies on Long COVID in children and adolescents. Just as the prevalent COVID-19 acute infection symptoms are similar in adults and youth, so are the Long COVID symptoms including fatigue and dyspnea. Other persistent symptoms shared by the two age groups include headaches, muscle pain, memory loss and "brain fog" as well as similar patterns of brain PET hypometabolism. At this time, the symptoms have been less severe and persistent for youth versus adults. This may relate to their lesser severity of acute infection, in turn, related to less developed ACE-2 receptors and autonomic function or less frequent comorbidities. This research has several methodological limitations including non-representative samples that have typically been surveyed almost exclusively on physical symptoms at only one point in time and have not been compared to non-Long COVID control groups. Nonetheless, this sparse literature may inform potential diagnostic and preventative interventions.

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INTRODUCTION

A headline from the Wall Street Journal on August 22, 2021 reads "More children are hospitalized with COVID-19, and doctors fear it will get worse". The leading paragraph says "Hospitals in the south and west are treating more children with COVID-19 than ever and are preparing for worse yet to come. Cases there have jumped over the past six weeks as the highly contagious Delta variant spreads primarily among unvaccinated people. Children under age 12 aren't yet eligible to be vaccinated and vaccination rates for those between 12 and 17 remain relatively low according to data compiled by the American Academy of Pediatrics. Although children are much less likely than adults to develop severe COVID-19 or die from the virus, recent data from the Department of Health and Human Services show pediatric hospitalizations for COVID-19 are at the highest point since the agency began tracing them last year, driven by states that have been hit hard by the Delta variant. Children's hospitals are bracing for even more cases as schools reopen." And, on September 1, 2021, a CBS special focused on Long COVID in children and appealed to scientists to move beyond the study of Long COVID symptoms to the pathophysiology and treatment of Long COVID in children. Research on symptoms has typically preceded studies on pathophysiology and treatment and reflects the literature that is reviewed here.

Just as the youth of the world have been reputedly less frequently infected by COVID-19 and less severely affected, at least at this time, they have also been less frequently diagnosed as having Long COVID [1]. Long COVID has been defined as "post-acute COVID" for COVID-19 infection symptoms that persist for 4 to 12 weeks and "chronic COVID" for symptoms that persist for longer than 12 weeks [2]. Long COVID was first noted in adults shortly after the onset of the COVID pandemic and has only recently been recognized in children and adolescents [1]. Although it is now a diagnostic syndrome for youth, only twelve studies have appeared in the literature at this time. These include studies from Australia, Holland, Israel, Italy, Russia, Sweden, Switzerland, the UK and the US.

This narrative review is a brief summary of a random selection of 14 papers from the very extensive adult literature on Long COVID as a background for greater understanding of the more recent literature on Long COVID in youth (12 papers) that are reviewed in greater detail here. In this literature search, the terms Long COVID, Long Haul COVID and post-acute COVID-19 in children, adolescents and youth as well as Pediatric Long COVID were entered into PubMed and PsycINFO. Following exclusion criteria of case studies and foreign language papers, 12 studies were included in this review. Several commentaries appeared in this literature that were written by parents of children with Long COVID who were organizing attempts to inform pediatricians. These commentaries preceded the 12 studies that

have documented the Long COVID syndrome in children and adolescents and that are reviewed here.

Literature on Long COVID in Adults that Informs Long COVID in Youth

The term "Long Haul COVID" was first coined by a COVID survivor from Oregon, Amy Watson, who was inspired by a long haul trucker hat she happened to be wearing at the time [3]. The term came to be extensively used by fellow patients, media, government officials and the scientific community [3]. Interestingly, when long haul COVID was entered into PubMed for this narrative review, one third of the papers were studies on long haul truck drivers, one third on long haul airline pilots and one third on long haul COVID survivors. The term Long COVID was later introduced by a patient, Elisa Perego, an archaeologist at University College in London, as a hashtag on Twitter (May 2020), while describing her experience with continuing symptoms [4,5]. The first usage of the term has also been ascribed to an infectious disease professor describing 7 months of persistent COVID symptoms [6]. Based on the literature search for the current review, the term Long COVID has come to be more frequently used in publication titles, so that term is used here.

Researchers of Long COVID in adults have mostly reviewed the prevalence of Long COVID including primary and secondary symptoms in samples from many different countries, a literature that is surprisingly consistent on the relative prevalence of the symptoms. In this literature, different demographic variables have also been identified as risk factors including gender and age. Other risk factors have included pre-existing conditions and comorbidities. And, less frequently, studies have appeared on potential underlying mechanisms. This section is divided accordingly by these topics.

Prevalence of Long COVID Symptoms in Adults

Long COVID first gained recognition among social support groups and later among medical and scientific communities. The formation of patient advocacy groups on various social media sites, for example Twitter, has been unique to the COVID- 19 pandemic. Long COVID surveys soon followed as the data for many of the prevalence studies reviewed here.

In one of the most comprehensive reviews of the adult Long COVID literature (67 original studies), about half of the studies were cohort (longitudinal), and half were cross-sectional [7]. Eleven per cent were focused on pathophysiology and 23% on management. But the majority of the studies (49%) were focused on signs and symptoms, as is typical of both the COVID-19 infection and the Long COVID literature [7]. Although the predominant symptoms were fatigue, dyspnea (labored breathing), arthralgia, sleep difficulties and chest pain, other long-term sequelae were also noted including cardiovascular, musculoskeletal, renal, neurological, sensory (olfactory, gustatory, cutaneous) and mental health symptoms.

The prevalence of Long COVID symptoms has varied significantly across countries and across assessment periods. The prevalence has also varied depending on whether the reports come from outpatients or hospital patients as well as the length of hospital stay with or without ICU treatment. For example, in India, the prevalence of Long COVID has been reported at 80% after two weeks but the percent of cases with persistent symptoms has been only 32% for outpatients as compared to 83% for hospitalized patients [4]. A decrease in persistent symptoms has been noted across time (at different assessment periods) in those with Long COVID, for example, 53% experienced the persistence of one symptom at greater than 12 days in the Faroe Islands, but only 33% at 1 to 2 months and 19% at 3 to 4 months [8]. And, the persistence varies by the number of symptoms. For example, In the UK, 86% prevalence has been reported but only for one symptom at one month follow-up [9]. Inconsistency has also been related to the type of data collection. In a review on hospital data from several countries, the five-week prevalence has been given at 22% and the 12-week prevalence at 10% [6]. However, survey data from several countries revealed a prevalence as great as 30 to 90% even as far out as 6 months, illustrating the variability across methodologies.

Variability has also been shown for the types of symptoms, although fatigue and dyspnea have been the most widely reported. As can be seen in table 1, the prevalent Long COVID symptoms vary across several countries including Italy [10], the US [11], France [12], China [13], England [9,14], Israel [15], and India [16], as well as a couple major reviews on fifteen studies [17] and 56 countries [18]. Based on the prevalence data

Table 1: Prevalence (% in parentheses) of Long COVID symptoms in adults (reference numbers in superscripts).

Country and Prevalence of Symptoms	
UK[19] (N=387)	London[14] (N=384)
-dyspnea (60)	-fatigue (69)
-myalgia (52)	-dyspnea (53)
-anxiety (48)	-cough (34)
-fatigue (40)	-depression (15)
-low mood (37)	Israel[26] (N=103)
-sleep disturbance (35)	-fatigue (22)
Italy[10] (N=143)	-smell (15)
-fatigue (53)	-taste (8)
-dyspnea (43)	-breathing (8)
-chest pain (22)	India[16]
U.S.[11] (N=274)	-fatigue (58)
-fatigue (71)	-headache (44)
-cough (61)	-attention(27)
-headache (61)	-dyspnea (24)
Paris[12] (N=120)	Review of 15 studies[18]
-fatigue (55)	-fatigue (58)
-dyspnea (42)	-headache (44)
-memory loss (34)	-attention disorder (27)
Wuhan[13] (N=1733)	-hair loss (25)
-fatigue (63)	-dyspnea (24)
-sleep disturbances (26)	56 countries[17]
-palpitations (9)	- fatigue (78)
-dizziness (6)	-cognitive dysfunction (55)

in table 1, the symptoms are primarily fatigue (ranging from 53% to 78% of patients with an average of 57%) and dyspnea (ranging from 8% to 53% with an average of 41%). Several other respiratory and cognitive symptoms have been reported, again with considerable variability as a function of the period of time between infection and follow-up assessment. This can be seen for the fatigue symptom that reportedly varied from 58% as assessed at 3 months in India to a markedly lower rate of 22% as measured at 6 months in Israel [15]. In the study from Israel, fever was the shortest duration symptom and taste and smell the longest lasting.

The symptoms have been clustered by some researchers including cluster A being myalgia and fatigue, B being low mood and anxiety as well as sleep disturbances and C being memory impairment, attention deficit and cognitive impairment [19]. The persistence of Long COVID symptoms was not related to the severity of the acute illness in this study [19]. Unfortunately, given that most of the published research is based on cross-sectional studies, the relationship between severity of acute infection and the occurrence of Long COVID as well as the persistence of Long COVID symptoms typically cannot be determined.

Those with breakthrough COVID, which has been defined as a positive RT-PCR assay (repeat reverse-transcriptase-polymerase chain reaction) 11 or more days after the second vaccine, have also experienced persistent effects [20]. Although most of the breakthrough cases have been asymptomatic or mild, as many as 10 to 30% of those who have experienced breakthrough COVID have had persistent symptoms [20]. And, 19% have been reported to have symptoms beyond six weeks [20]. Those with breakthrough Long COVID have had symptoms that are similar to those who were infected prior to vaccinations including respiratory symptoms (36%) [20]. Myalgia (28%) and loss of smell or taste (28%) have also been reported for Long COVID breakthrough cases, although the data are very limited at this time [20].

Surprisingly, although psychological problems like depression, anxiety and post-traumatic stress disorder are typically associated with breathing problems, myalgia, and confusion, they have been rarely mentioned as symptoms of Long COVID [21]. As an exception, data from a Multi Center European study suggest that depression was occurring in 29% of folks with Long COVID, anxiety in 34% and PTSD also in 34% [4].

Long COVID symptoms are similar to those of the Gulf War Syndrome and the post 9/11 syndrome [19], and as in these syndromes, if the Long COVID symptoms persisted, they would meet the criteria for a chronic fatigue syndrome diagnosis [19]. These symptoms include post-exertion fatigue, cognitive difficulties, sleep disturbances and chronic pain. Other Long COVID symptoms that have been cited as similar to those of chronic fatigue syndrome include psychiatric, neuroendocrine, autonomic and immune dysfunction [6]. And, a conservative criterion that has been suggested for a chronic fatigue diagnosis has been "profound fatigue" greater than 50% daily for greater than 6 months [13]. The etiology of chronic fatigue syndrome remains obscure, but viral triggers have been noted [19] (Table 2).

Table 2: Prevalence (%in parentheses) of Long COVID symptoms in youth (reference numbers in superscripts).

Country and Prevalence of Symptoms	
Holland[1] (N=89)	Russia[29] (N=518)
-fatigue (87)	-fatigue (11)
-dyspnea (55)	-sleep disturbances (7)
-difficulty concentrating (45)	-smell & taste dysfunction (6)
-headaches (38)	-multiple symptoms (8)
-memory loss (13)	
-brain fog (2)	
Tel Aviv[32] (N=90)	
-fatigue (71)	
-dyspnea (50)	
-myalgia (46)	
-sleep disturbance (33)	
-chest pain (31)	
-headache (29)	
-smell & taste dysfunction (26)	
Rome[28] (N=129)	
-insomnia (19)	
-respiratory problems (15)	
-fatigue (11)	
-muscle pain (10)	
-joint pain (7)	
-difficulty concentrating (10)	

Although sensory symptoms including cutaneous, olfactory and gustatory symptoms were prominent in Acute COVID, they have rarely been mentioned in Long COVID. An exception again is the Multi Center European study in which residual olfactory and gustatory dysfunction were revealed in 54% and 23% of Long COVID individuals respectively and 24% exhibited both olfactory and gustatory dysfunction [4]. In contrast, persistent loss of smell and taste was noted at a lesser prevalence of 8% in a review on Long COVID studies [6].

Although physiological/biochemical profiles have also been identified in Long COVID, they have rarely been assessed because most of the data have been collected by survey. In the cross-sectional study from London, for example, 38% were noted to have abnormal chest radiographs suggesting lung fibrosis [14] And a 30% increase was noted in D-dimer (protein fragment following a dissolved blood clot) and a 10% increase in C-reactive protein [14]. High levels of C-reactive protein and D-dimer have been noted in at least one other study along with elevated IL-6 and ferritin as well as thrombocytopenia and lymphopenia [4].

Risk Factors for Long COVID in Adults

Although a review of Long COVID studies suggested that no gender, race or age differences were noted in the recovery time for persistent symptoms [4], at least one other review has suggested that being female was a risk factor for Long COVID. Other risk factors identified in this review included having more than five early symptoms of Long COVID, early dyspnea and specific

biomarkers including elevated D-dimer, C-reactive protein and lymphocyte counts. These risk factors are consistent with those of another review including female gender, comorbidities and having more than 5 symptoms [21], Pathophysiological findings were also listed in this review including organ damage, chronic inflammation, post intensive care syndrome, drug side effects and psychological issues including PTSD [22].

In still another review, female gender has been cited as a risk factor as well as having more than five symptoms during the first week of infection and being middle-age (50-60 years) [4]. Underlying comorbidities were also specified in this review as being risk factors for Long COVID including diabetes, hypertension, obesity, cardiovascular disease, smoking, chronic alcohol use and chronic kidney disease. Disease severity, length of intensive care unit stay and assisted ventilation were also given as risk factors.

Comorbidities have also been prevalent in a cross-sectional study from London including hypertension (42%), diabetes (27%), asthma or COPD (18%), kidney disease (11%) and heart disease (10%) [14]. The level of care was given in this study as a risk factor including oxygen alone (59%), ICU care (15%) and intubation (7%). In this sample, greater risk occurred for males and 43% of the samples were minority groups including Blacks and Asians [14].

Potential Underlying Mechanisms for Long COVID in Adults

As has been noted, ACE-2 receptors are widely expressed in endothelial cells, lining many tissues/organs throughout the body [3]. The COVID virus not only attaches to the ACE-2 receptors but also can cross the blood brain barrier by trans-synaptic transfer via the optic and olfactory nerve channels which then can bind to the ACE-2 receptors and a cytokine storm results [23].

The autonomic nervous system has been implicated in several studies. Orthostatic intolerance (sympathetic activation upon standing) has been observed in a number of studies [2,3,5,22]. Postural orthostatic tachycardia syndrome (POTS), a form of orthostatic intolerance, has been noted to lead to many of the Long COVID symptoms including vertigo, irregular pulse, chest pain, headache, difficulty concentrating, muscle ache, nausea, fatigue and sleep disturbances [5,6]. Sympathetic activation induces pro-inflammatory cytokine release [2,3,5,22]. Viral infections can trigger autonomic dysfunction, cytokine storms and hyperinflammation [3]. Composite Autonomic Symptom -31 scores have been elevated in Long COVID [3]. And vagal stimulation results in an anti-inflammatory response, suggesting therapeutic targets in the autonomic nervous system [2,3].

Tissue damage in the lung, brain and heart and inflammation from viral persistence, autonomic dysregulation and auto-immunity may contribute to the persistence of symptoms. The same respiratory symptoms have dominated both the acute and Long COVID phases including exercise dyspnea and fatigue as the most common complaints and the persistent abnormal markers of inflammation [21].

The frequently cited "brain fog" has been an umbrella term for the constellation of cognitive dysfunction symptoms that persist including confusion, short-term memory loss, dizziness and inability to concentrate [4]. This syndrome has been thought to be secondary to hypoxia and mitochondrial dysfunction that leads to micro-structural brain damage [4].

Limitations of this Literature

Several limitations of this literature can be noted including the prevalent data collection by survey. This is not only limited by the questionable reliability of self-reports but also by the virtual reports of symptoms that cannot be quantified for severity or validated by physiological measures and biological markers [19]. The significant variability across countries in the timing of assessments and the types of surveys as well as the operational definition of Long COVID has limited the use of meta-analyses for validation of the results from multiple studies.

Surprisingly, interventions have not appeared in this literature, although some have been suggested. These have included stretching, acupressure and massage as well as exercise therapy [6]. These would be expected to diminish autonomic dysfunction via stimulating pressure receptors under the skin and, in turn, increasing vagal activity [24]. Increased vagal activity would be expected to reduce stress hormones (cortisol) and save natural killer cells that ward off viral cells [24]. The increase in natural killer cells and activity following massage data do not appear in the Long COVID literature but have been documented for HIV both in adolescents [25], and adults [26]. Further, antidepressants including serotonin reuptake inhibitors may decrease inflammatory markers associated with Long COVID [6]. Despite the limitations of the literature on Long COVID in adults, those data will hopefully inform the research and interventions for Long COVID in youth.

Long COVID in Youth

The review of literature on Long COVID in youth can be similarly divided into sections on prevalence, symptoms and limitations. Although the degree to which the adult literature has informed the youth studies is not known, significant similarities can be noted for these two age groups (developmental periods) both in terms of prevalence and symptoms. Like the adult literature, the research on Long COVID in children and adolescents has suggested that the primary symptoms that persist beyond 4 to 12 weeks include fatigue and dyspnea. Unlike adult Long COVID, however, the prevalence of Long COVID in children and adolescents is not as great and the symptoms are not exacerbated by comorbidities that are also not as prevalent.

Prevalence of Long COVID in Children and Adolescents

Just as support groups were instrumental in identifying Long COVID in adults, parent groups became founding members of Long COVID Kids in England, for example, which is now comprised of 2200 parents [27]. The Office for National Statistics in England suggests that 12 to 15% of children have Long COVID symptoms lasting five weeks or more [27]. Unfortunately, a major concern is that parents are afraid of having their children "branded" with the stigma of Munchausen Syndrome by Proxy [27]. Although a significant literature has been accumulating on COVID-19 in children and adolescents [see 23 for a review], research on Long COVID in youth is very scant.

The most common Long COVID symptoms in youth, like those in adults, are fatigue, dyspnea, headache, abdominal pain, dizziness and muscle pain [27]. Several psychological problems are associated with these including anxiety, OCD and volatile mood changes that accompany the neuro-inflammatory process [27]. It is surprising then that physicians in the UK have attributed the psychological symptoms to lockdown or homeschooling effects [27].

In a sample from Rome (N=129 children), caregivers were interviewed about their child's symptoms [28]. Fifty-three per cent of children had one symptom at greater than 4 months, 36% had one or two symptoms and 23% had more than three symptoms. Forty-three per cent were impaired during their daily activities by fatigue, muscle and joint pain, headache, respiratory problems and palpitations. Forty-two per cent completely recovered. This was not only a small sample but was also only representative of a single center. And, over-reporting may have occurred due to interviewer probes of the caregivers. As might be expected, an assessment at eight months in Russia [29] yielded half the prevalence of persistent symptoms that occurred at four months in the previous study from Rome [28]. In the study from Russia (N=518), 24% had persistent symptoms out at eight months [29].

An unusually low prevalence was reported at 4% for 1 symptom at greater than one week in a study from Switzerland [30]. In this study, schools were selected randomly and symptom questionnaires were given to parents. This survey research was limited not only by potential recall bias of the parental report but also by the small number of seropositive children. In addition, no information was given on the time of infection or the symptom severity, suggesting possible misclassification of the children.

In contrast, the prevalence was high in a study from Australia that was based on electronic medical records [31]. In this follow-up at 3 to 6 months, 64% were symptomatic. The median age of the sample (N=171) was very young (M=3 years). Disease severity was based on World Health Organization criteria. The prevalence of mild disease was 58% and moderate disease was 5%. The hospitalization rate was 8% and 36% were asymptomatic. The results of this research are not generalizable given that the sample was significantly younger than the age range of the other samples and that the data collection was not comparable to that of other studies as they were derived from electronic medical records rather than the typical surveys of parental reports.

The variability noted in the prevalence across these studies relates in part to the different ages assessed. Other variable factors are the severity of the initial infection (which was unknown in most cases), the different methodological approaches (clinical assessment versus self or parent report), and the definition of cases (diagnosed versus suspected). Nonetheless, the data from several studies from different parts of the world highlight the prevalence of Long COVID in children and adolescents.

Prevalence of Long COVID Symptoms

Primary Symptoms: The Long COVID symptoms that are prevalent in youth are similar to the adult Long COVID symptoms, the primary ones being fatigue and dyspnea. The difference is that, like the acute infections, Long COVID has not been as severe for children as it has been for adults [1,32,33], possibly because of the lesser prevalence of comorbidities in children [31,34]. As can be seen in table 2, the prevalence of symptoms in youth is as variable as the prevalence of a Long COVID diagnosis. It would appear that the earlier the assessment of Long COVID (the closer in time to the acute infection), the greater the prevalence of symptoms, as in the adult literature. For example, the samples from Holland [1]and TelAviv [32], were assessed as early as one month. And the prevalence of fatigue was high at 87% and 71% respectively. In contrast, the samples from Rome [28], and Russia [29], were seen later at 4-8 months when the prevalence of fatigue was at a low of 11% in both places.

When a more subjective assessment was made on impairment of daily activity, the estimates were also variable, but they don't reflect differences in timing of assessments. For the sample from Holland 36% were said to have "severe limits in daily function [1], for the TelAviv sample, 57% were said to have "impairment in daily activity"[32] and for the sample from Rome, 43% were said to be "impaired during daily activity"[28].

Secondary Symptoms

Also, as can be seen in table 2, the cluster of secondary symptoms varied across the different samples with that from Holland suggesting prevalent cognitive symptoms including difficulty concentrating, headaches, memory loss and "brain fog" [1]. In Rome, the secondary symptoms mostly involved muscle and joint pain, although difficulty concentrating was also a prevalent secondary symptom [28]. In the sample from Tel Aviv, the symptoms were not only pain and cognitive symptoms but also sensory symptoms including olfactory and gustatory dysfunction [32]. And, in at least two other samples, smell and taste dysfunction were noted [29,34], and skin rash was reported in at least two studies [35,36].

In the study that reported smell and taste dysfunction in 15% of the sample, these problems only occurred in children older than 11 years and more often in males than females [34]. And, for some unknown reason, olfactory dysfunction was noted for every odorant except cinnamon, mint and jasmine. It only lasted for two weeks which was surprising given that 95% of adults who have olfactory dysfunction only regained their sense of smell after several weeks [15].

Skin rash was one of many symptoms in a study from Sweden [35]. These included fatigue, dyspnea, heart palpitations, chest pain, headache, concentration difficulties, muscle weakness, dizziness, sore throat, sleep problems and remitting fever. In addition, the children showed a high pulse rate on exertion and an inability to perform physical activities. And, this was one of the only research groups that reported depression in the children [35]. Despite this lengthy list of symptoms, which might have derived from the parents meeting on an internet-based social media forum and their encouraging listing of symptoms, no comorbidities were noted except for asthma and allergies in one child. Several parents reported having Long COVID themselves and suggested that their children may have "shared genetic or environmental traits" [35]. These data are tentative given the small sample size and the absence of clinical tests to rule out differential diagnoses.

In the study showing a rash and /or mucositis in 47% of children and adolescents, those with a rash had fewer respiratory symptoms, lower C-reactive protein and ferritin levels as well as a less severe course [36]. Sensory dysfunction (taste and smell) and skin problems have been more prevalent in both adults and children with less severe respiratory symptoms. The greater prevalence of sensory symptoms in mild COVID-19 infection and Long COVID suggests that this dysfunction may be an early marker as well as a sequelae syndrome of COVID-19 [36]. This is not surprising given that COVID-19 is thought to be transmitted via the olfactory system, and smell and taste are processed by the olfactory and gustatory cranial nerves in the temporal lobe, as is tactile stimulation that may have related to itchy skin and skin rash.

Clinical Assessments

Clinical assessments were performed on the Tel Aviv sample [32], the sample from Russia [29] and the U.S. sample [36]. In the Tel Aviv study, structured interviews were conducted by pediatricians and physical exams were also given as well as blood tests, EKGs, radiographs, pulmonary function tests, echocardiograms, bronchodilator response testing and cardiac MRIs [32]. The prevalent symptoms for this sample were fatigue and dyspnea, not unlike the adult data. And a novel finding was obstructive sleep apnea. Forty-five per cent were said to have abnormal cardiorespiratory function and the values were below threshold for all of the children who were given the exercise stress tests. Elevated levels of creatinine phosphokinase and ferritin were also noted. These results are tentative because, as in most Long COVID studies, no baseline pre-COVID data were collected and, once again, the sample size was limited. The data are consistent, however, with those from a study from Italy showing altered inflammatory markers (ferritin, fibrinogen and D- dimmer, IgG) in children with Long COVID [37], also as in adult studies [4].

In the only study that included a control group, cardiovascular function was compared in children COVID-19 (N=121) and children without COVID (N=95) matched on age, weight and body mass index [38]. Thirty-seven percent of the COVID-19 group had Long COVID symptoms at least one month following infection including chest and back pain, dizziness, headache, palpitation, fatigue, shortness of breath, loss of balance, and coughing. Based on electrocardiography and echocardiography results, the groups differed on systolic blood pressure suggesting cardiovascular involvement for the Long COVID group. Unfortunately, the inclusion of a non-COVID control group cannot inform the etiology of long COVID or why some children and adolescents have persistent symptoms and others do not.

Similar patterns of brain PET hypometabolism have been reported for both pediatric and adult patients with Long COVID [33]. This pattern involving bilateral medial temporal lobes, brainstem, cerebellum and the right olfactory gyrus was noted at 5 months post-infection in children. The pattern was independent of age and initial severity and was suggested to be a biomarker by its authors [33]. These data were not surprising inasmuch as the COVID-19 virus is thought to be transmitted via the olfactory system and to involve the olfactory and gustatory cranial nerves in the temporal lobe.

Risk Factors

The cardiovascular and brain PET data just reviewed are suggestive of risk factors. However, it's not clear whether Long COVID and the appropriate control group (COVID-19 without persistent symptoms) would differ on these measures. Risk factors for Long COVID have been difficult to determine due to the lack of baseline data on severity of infection and related symptoms. Only one research group cited risk factors for Long COVID in children but these were not COVID-19 factors [29]. They were a history of allergic disease and age. The odds ratios were 2.74 for children 6-11 years-old and 2.68 for 12-18 year-olds. As in adults, another risk factor was multi-system involvement (multiple symptoms) [29]. The absence of longitudinal data has made it impossible to determine risk factors for Long COVID.

Methodological Limitations

This research on Long COVID in youth appears to have been responsive to the appeal given to researchers in Nature magazine entitled "Long COVID and Kids: Scientists race to find answers" [39], and the recent significant press about this syndrome. However, the research is sparse and has methodological problems. They include, among many, the limited sample sizes, the different methodological approaches (clinical assessment versus self or parent report), the variable definition of cases (diagnosed versus suspected), the variation in time of assessment following infection and the variability of measures such that meta-analyses have not been possible. Differential diagnostic testing is needed to rule out comorbid inflammatory or autoimmune conditions. And, in most studies, the infection severity was not assessed based on World Health Organization or National Institutes of Health criteria.

Most of the studies are cross-sectional so that causality or directionality of effects cannot be determined. The absence of baseline data from COVID-19 infection to the Long COVID period makes it impossible to determine the relationship between the severity of acute infection and the existence and persistence of Long COVID. The absence of control groups, for example, a COVID-19 infected but without persistent symptoms group, also makes it difficult to address etiology of Long COVID. Although at least one study involved a control group, unfortunately the control group was a non-COVID group which is not an optimal control group for a Long COVID group. In that sense, it doesn't allow speculation on why some, for example, as many as 53% in the sample from Rome, had persistent symptoms beyond 4 months, while others do not have persistent symptoms. This prevalence as well as that in other countries has highlighted the need for interventions that continue beyond the period of infection. Surprisingly, intervention studies could not be found in the Long COVID literature on youth.

Although several references were made to the similarity between Long COVID symptoms in the youth and adults, the severity of symptoms in the youth was apparently less than in adults, likely because of the less severe infections and the relative absence of comorbidities in the children. The almost exclusive focus on symptoms in the research on Long COVID in youth, not unlike that on adults, is another limitation of this literature. And, surprisingly, although anxiety and depression have been noted to accompany COVID-19 infection [23], psychological problems

were rarely mentioned and were not assessed in this research. Hopefully, future research will expand this literature not only to include assessments of the emotional and mental health of those with persistent symptoms but also to assess differences between those with and those without persistent COVID-19 symptoms. Despite these methodological limitations, the limited literature highlights the importance of exploring the etiology and potential interventions for youth with Long COVID.

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