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COVID-19 Symptoms Over Time: Comparing Long-Haulers to ME/CFS

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Abstract

Introduction: Our objective was to determine which symptoms among long-hauler COVID-19 patients change over time, and how their symptoms compare to another chronic illness group. 278 long-haulers completed two symptom questionnaires at one time point, with one recounting experiences from an average of 21.7 weeks prior.

Methods: We used a comparison group of 502 patients diagnosed with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). Participants completed a standardized symptom questionnaire and a list of additional CDC COVID-19 symptoms.

Results: Over time, the long-haulers reported an overall reduction of most symptoms including unrefreshing sleep and post-exertional malaise, but an intensification of neurocognitive symptoms. When compared to ME/CFS, the COVID-19 sample was initially more symptomatic for the immune and orthostatic domains but over time, the long-haulers evidenced significantly less severe symptoms than those with ME/CFS, except in the orthostatic domain. Among the COVID-19 long haulers, several neurocognitive symptoms got worse over time, whereas improvements occurred in most other areas.

Conclusions: These types of differential patterns of symptoms over time might contribute to helping better understand the pathophysiology of those reporting prolonged illness following COVID-19.

Keywords

Long-Haulers; COVID-19; SARS CoV-2 virus; Myalgic Encephalomyelitis/Chronic Fatigue Syndrome

Coronavirus disease 2019 (COVID-19) is caused by a highly transmissible[1] severe acute respiratory syndrome coronavirus 2 (SARS CoV-2) virus, which has been devastating for patients and societies, with a projected economic cost estimated to be 17 trillion dollars.[2] The death toll for this pandemic in the United States is over 250,000, with the highest rates among those who are elderly or with other chronic or immune disorders[3] as well as people of color.[4] This pandemic has also increased psychological distress in the general population,[5,6,7] which has been driven by uncertainty about the types and duration of

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symptoms, length of quarantine, requirements for social distancing, and disruption to social and daily routines.[8,9]

Islam, Cotler, and Jason[10] recently reviewed the literature regarding prior epidemics and infections and found a certain percentage of those infected have long-term complications including the development of severe fatigue. There are a growing number of media reports indicating post-infectious fatigue also is occurring with COVID-19. For example, lingering symptoms have been reported to include fatigue, muscle ache, cardiac issues, and rashes,[11] with others developing myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS)-like symptoms,[12] and still, other reporting exacerbating mold-related symptoms.[13] In one report, the Body Politic COVID-19 support group[14] collected data on over 600 COVID-19 patients experiencing symptoms for over two weeks. After 40 days, 91% of respondents had not recovered and 70% reported developing new symptoms at different stages of the illness. In a more formal study conducted by Davis and colleagues, it was determined that among COVID-19 patients who experienced symptoms six months after becoming ill, the most commonly occurring symptoms were fatigue, post-exertional malaise, and cognitive dysfunction.[15] There are also reports of patients developing Guillain-Barré,[16] Kawasaki disease, lung scarring, blood clots, renal failure, neurological complications,[17] and heart damage.[18] It is still unclear whether the severity of infection, lingering viral remnants, or possibly immune activation contribute to these later health problems.

Some have suggested 50 to 80% of COVID-19 patients will continue to have bothersome symptoms three months after contracting SARS CoV-2,[19,20] whereas more serious prolonged symptoms may be experienced by a smaller percentage (e.g., 10%[21]). There are two groups among these long-haulers, including those with identifiable biological damage to the lungs or heart and another group without any recognizable biological markers.

Researchers do not know whether symptoms among the long haulers increase, stay the same, or reduce over time, and whether such patterns occur for all symptoms or are differential. Determining this type of evidence can be enhanced by the use of standardized and validated instruments to measure symptoms at different time points in this illness. It is also unclear what the relationship of the long-hauler symptoms are to other illnesses such as ME/CFS. The current preliminary study examined symptoms experienced by long-haulers during the first two weeks and after time had elapsed to better understand which symptoms might get worse or improve over time. Also, to determine the relative severity of symptoms among the long-haulers, their symptoms were compared to another chronic illness group (i.e., ME/CFS).

Method

COVID-19 sample.

In August of 2020, the authors obtained IRB permission to distribute questionnaires to long-haulers, those who had self-reported not recovering from COVID-19. The questionnaires were posted on several social media sites, which are devoted to the exchange of information among long-haulers. Participants were asked to complete two symptom questionnaires at one time point, with one describing current symptoms and one recounting experiences

from an average of 21.7 weeks prior. The participants were not paid for filling out the questionnaires.

ME/CFS sample.

The ME/CFS sample was collected by the Solve ME/CFS Initiative (https://solvecfs.org). All participants were recruited by a physician and were previously diagnosed with ME/CFS by a specialist. Five hundred and two participants were included in the current study.

The study obtained IRB approval.

Measures

The DePaul symptom questionnaire. Participants across both datasets completed the DePaul Symptom Questionnaire (DSQ[22]), a 54-item self-report measure of ME/CFS symptomatology, demographics, medical, occupational, and social history. Participants with ME/CFS were asked to rate the frequency of each symptom over the past six months on a 5-point Likert scale with 0=none of the time, 1=a little of the time, 2=about half the time, 3=most of the time, and 4=all of the time. Likewise, participants were asked to rate the severity of each symptom over the past six months on a 5-point Likert scale with 0=symptom not present, 1=mild, 2=moderate, 3=severe, and 4=very severe. In contrast, those in the long-hauler group were asked to rate the DSQ symptoms as they were experienced during the first two weeks of their illness and at the current time point. All frequency and severity scores were standardized to a 100-point scale. Furthermore, the frequency and severity scores for each symptom were averaged to create one composite score per symptom. Author[23] reviewed research on the DSQ and found excellent psychometric properties. The DSQ has demonstrated strong reliability and validity[23,24] as well as the ability to accurately differentiate individuals with ME/CFS from individuals with other chronic illnesses.[25,26]

CDC symptoms.

The CDC lists several additional symptoms of COVID-19 on their website: https://www.cdc.gov/coronavirus/2019-ncov/downloads/COVID19-symptoms-24x36-en.pdf These items included: dry cough, loss of taste/smell, difficulty breathing, diarrhea, nose congestion, and loss of hair. As these items were not on the DSQ, they were added to the survey that was completed by the COVID-19 sample.

Results

Table 1 presents the demographic characteristics of the samples. There were significant differences between those in the COVID-19 and ME/CFS groups for age, gender, and race, and these variables were used as covariates in subsequent analyses (gender and race were dichotomized into male/female and white/nonwhite). The illness duration of the COVID-19 sample was a mean of 21.7 weeks, whereas, for the ME/CFS sample, 13% reported being ill since childhood and of the others, 85% had been ill for over two years (an interval scale was used with the ME/CFS sample so direct comparisons with the COVID-19 sample were

not possible). It was assumed that the duration of illness would vary between the two illness groups.

COVID-19 Long Hauler Symptomatology

Table 2 presents data on symptomatology at the start of the illness and currently for the COVID-19 sample. The highest domain scores at both testing points was for post-exertional malaise (PEM). Improvements in symptoms occurred over time for the sleep, PEM, immune, neuroendocrine, pain, gastrointestinal, and orthostatic domains. Within these 7 domains, 34 significant differences indicated a reduction in symptoms and only one symptom had a significant increase (sensitivity to alcohol). In contrast, the overall neurocognitive domain increased directionally over time. Within this domain, three symptoms significantly increased over time (i.e., trouble forming words, difficult focusing, absent mindedness) and two significantly decreased over time (i.e., trouble paying attention, sensitivity to smells). Comparable results were found with the CDC symptoms, which significantly reduced over time for the overall score as well as for loss of taste/smell, difficulty breathing, diarrhea, and nose congestion; however, significant increase over time was found for loss of hair.

COVID-19 and ME/CFS

In addition, Table 2 also contrasts those in the ME/CFS group to those in the two time points for the COVID-19 group. At the initial time point, the COVID-19 group was significantly more impaired than the ME/CFS group for the immune and orthostatic domains, whereas the ME/CFS group was significantly more impaired for the gastrointestinal and neurocognitive domains. Within the specific symptoms at the initial time point, for 18 symptoms, the COVID-19 group was significantly higher, whereas for 17 other symptoms, the ME/CFS group was significantly higher (11 of these scores were within the neurocognitive domain).

When contrasting the current COVID-19 symptoms with the ME/CFS group, the ME/CFS group was significantly more symptomatic for every domain except orthostatic. When examining specific symptoms, the ME/CFS group was significantly more impaired on 39 symptoms, whereas the COVID-19 group was significantly more impaired on only 3 symptoms within the orthostatic domain (chest pain, shortness of breath, and irregular heartbeat).

Discussion

The current study found for most symptoms, the COVID-19 long-haulers did significantly improve over an average 21.7 week period of time. Only 5 symptoms worsened over time and they included sensitivity to alcohol, trouble forming words, difficulty focusing, absent mindedness, and loss of hair. Of interest was that 3 of these symptoms were within the neurocognitive domain. Therefore, one of the current study's primary findings is several neurocognitive symptoms within the COVID-19 group did get worse over time, whereas improvements occurred in most other areas. This is of importance so that clinicians and researchers might have a better idea of this differential pattern of symptoms over time, and it might also help understand aspects of the pathophysiology of this illness.

COVID-19 Long-haulers and ME/CFS

These findings do match findings from the Body Politic COVID-19 support group,[14] where cognitive problems seemed to be the most challenging and problematic for these individuals. It is still unclear the reason for the neurocognitive impairment, with some speculating small parts of the virus remain in their bodies or the immune systems continues to overreact after the infection. However, recent research suggests patients do not have strongly elevated levels of inflammatory proteins.[27,20] Still, these types of neurocognitive problems that are intensifying over time in some long-haulers might provide investigators with insights into other possible central nervous system pathology in patients, such as that found in patients with ME/CFS.[28]

Also of importance, when the COVID-19 sample was compared to those with ME/CFS, during the initial few weeks of the illness, their symptomatology had different patterns, with a comparable number of significantly higher and lower symptoms. The COVID-19 long-haulers were more impaired than the ME/CFS group for many symptoms within the immune and orthostatic domains were. However, the ME/CFS group had significantly worse scores for most of the neurocognitive symptoms. As noted above, it is within this symptom category that over time the most impairment in COVID-19 symptoms occurred.

When the ME/CFS group was compared to the current COVID-19 long-haulers status, the ME/CFS group was more symptomatic in all domains, except for the orthostatic domain, with the following items being more problematic in the COVID-19 cohort: irregular heartbeat, chest pain, and shortness of breath. These types of findings are supported by investigations such as Puntmann et al.,[29] who found cardiac involvement in 78% of COVID-19 patients and ongoing myocardial inflammation in 60%. While COVID-19 does not appear to attack the heart, the heart might have to work harder to pump oxygenated blood through the body causing heart damage.

Limitations

There are several limitations in the current study, such as patients with ME/CFS were sick a longer period of time, and it is unclear how their ME/CFS symptomology would compare to the COVID-19 group during the early period of their illness. In addition, whether symptoms of the COVID-19 group persist will need to wait for longer-term evaluation of the COVID-19 group. It is possible that some in the COVID-19 group will continue to improve over time, whereas some might persist in their symptoms or get worse, and those that persist or get worse might over time more closely match the symptoms of the ME/CFS group. Our study also did not differentiate between those COVID-19 long-haulers that do and do not have identifiable organ impairments in their lungs or heart. The data are based on self-reports and have limitations regarding recall bias for the beginning of the COVID-19 illness. There were few people of color in the samples and this also limits generalizations of the findings. Finally, this article focused on symptomatology, but there is also a need to better understand family members, health care personnel, and co-workers' reactions to these changing symptom patterns, and if these individuals expect a relatively quick resolution of COVID-19. It is possible that similar to ME/CFS, reactions from these individuals as well as not recovering quickly when they expect to could be demoralizing for the patients.

Summary

In summary, much has been written within the media about those who have not recovered from COVID-19, and the reports have generally been anecdotal and lacked the use of questionnaires with adequate psychometric properties. In the current study, a valid assessment instrument was used to compare long hauler symptoms during the first weeks of illness versus the current time, after several months have elapsed. What is now clear is that most symptoms do lessen over time, however, there are some symptoms within the neurocognitive domain that seem to be intensifying. Furthermore, when the long hauler symptomatology is compared to another fatiguing chronic illness (ME/CFS), it is clear that most symptoms of the long haulers are less intense, but in some orthostatic domains, increases are noted. We believe the medical community can use such finding regarding the fact that most symptoms will slowly reduce, but the symptoms within the orthostatic domain, involving circulatory issues as well as neurocognitive areas, need to be more closely monitored.

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Table 1.

Sociodemographic information for participants with COVID-19 and ME/CFS

Demographic	COVID Sample (*N* = 278)	ME/CFS Sample (*N* = 502)
	***M* (SD)**	***M* (SD)**
Age (years)	45.37 (20.98)	54.79 (12.03) *
Illness Duration (weeks)	21.69 (07.09)	-
	% (*n*)	% (*n*)
Gender		
Male	14.00 (39)	23.10 (112) *
Female	84.20 (234)	76.90 (372)
Nonbinary	01.80 (05)	00.00 (0)
Race		
White/Caucasian	87.00 (241)	97.70 (471) *
Other	09.70 (27)	01.50 (07)
Asian/Pacific Islander	02.50 (07)	00.20 (01)
Black/African American	00.70 (02)	00.40 (02)
Latinx	07.10 (20)	02.70 (13)
Region of Origin		
North America	79.00 (215)	100.00 (502)
Europe	19.90 (54)	-
Asia/Pacific Island	00.70 (02)	-
Africa	00.40 (01)	-

* signifies $p < .01$

Table 2.

DSQ scores for COVID-19 participants during initial and current phases alongside ME/CFS participants

Domain/Symptom	COVID Sample[1] (*N* = 278)		ME/CFS Sample[2] (*N* = 502)
	Initial	Current	
	M (*SD*)	*M* (*SD*)	*M* (*SD*)
Sleep	**55.37 (24.91)**	**47.91 (23.88)**	55.44 (19.56)[b]
Unrefreshing Sleep	**70.56 (31.60)**	**62.10 (31.05)**	74.43 (21.89) [ab]
Needing to Nap	**63.98 (34.61)**	**48.16 (32.69)**	53.12 (29.68)[ab]
Difficulty Falling Asleep	**47.42 (34.70)**	**42.37 (33.63)**	50.60 (30.32)[ab]
Difficulty Staying Asleep	49.37 (34.71)	45.86 (33.21)	53.26 (29.40)[b]
Waking up Early	**45.46 (34.39)**	**41.10 (33.70)**	45.72 (29.93)
Sleep All Day	**18.48 (28.51)**	**11.15 (22.91)**	13.02 (23.07)[a]
PEM	**68.06 (28.89)**	**61.26 (25.97)**	64.78 (20.00)[b]
Heavy Feeling	**67.08 (38.60)**	**57.97 (35.12)**	64.52 (29.16)[b]
Mental Fatigue	**67.84 (33.91)**	**60.34 (29.78)**	62.23 (25.09)[b]
Minimum Exercise	71.83 (33.12)	68.89 (30.01)	68.91 (24.65)
Feeling Drained	**73.64 (31.61)**	**65.56 (30.35)**	64.02 (24.87)[a]
Fatigue	**75.27 (28.29)**	**67.27 (28.30)**	75.10 (18.99)[b]
Muscle Weakness	**52.70 (36.86)**	**47.12 (33.70)**	53.93 (28.08)[b]
Neurocognitive	37.90 (26.05)	39.42 (23.35)	46.42 (18.86)[ab]
Difficulty Remembering	48.11 (33.37)	51.80 (30.27)	58.73 (25.83)[ab]
Trouble Paying Attention	55.67 (34.51)	54.09 (30.59)	61.00 (26.74)[ab]
Trouble Forming Words	**43.48 (34.64)**	**49.78 (30.92)**	55.48 (25.58)[ab]
Difficulty Understanding	36.15 (32.59)	37.05 (31.42)	42.46 (25.93)[ab]
Difficulty Focusing	**47.53 (35.42)**	**53.42 (31.84)**	58.14 (27.45)[ab]
Slowness of Thought	46.22 (35.22)	49.60 (30.70)	52.14 (26.58)[ab]
Sensitivity to Noise	33.45 (36.63)	30.80 (31.68)	51.89 (28.60)[ab]
Sensitivity to Light	33.26 (34.38)	31.47 (32.78)	44.95 (31.01)[ab]
Sensitivity to Smells	**24.06 (32.49)**	**20.05 (29.31)**	37.90 (32.11)[ab]
Unable to Focus Vision	40.83 (33.72)	42.63 (31.32)	42.60 (26.12)
Loss of Depth Perception	15.96 (28.04)	15.33 (27.56)	18.38 (25.65)[b]
Twitching	22.12 (27.77)	23.79 (27.44)	28.14 (22.89)[ab]
Absent Mindedness	**45.59 (35.43)**	**52.62 (31.71)**	51.94 (27.48)[a]
Immune	**43.83 (22.90)**	**19.80 (17.93)**	27.71 (16.68)[ab]
Sore Throats	**42.85 (33.27)**	**26.12 (27.77)**	30.19 (22.41)[ab]
Lymph Nodes	**30.94 (33.24)**	**18.71 (26.31)**	29.68 (26.45)[b]
Fever	**38.36 (31.71)**	**11.24 (21.81)**	12.15 (18.08)[a]
High Temperature	**48.38 (30.43)**	**21.81 (26.16)**	22.78 (24.27)[a]
Flu	**58.72 (33.26)**	**21.09 (27.61)**	43.63 (26.00)[ab]

Domain/Symptom	COVID Sample[1] (*N* = 278)		ME/CFS Sample[2] (*N* = 502)
	Initial	Current	
	M (*SD*)	*M* (*SD*)	*M* (*SD*)
Neuroendocrine	**37.39 (24.01)**	**21.97 (16.87)**	28.50 (15.60)[b]
Cold Limbs	**33.14 (33.12)**	**25.99 (28.76)**	46.22 (28.39)[ab]
Chills	**46.84 (31.03)**	**19.69 (24.31)**	27.66 (22.66)[ab]
Feeling hot/cold	**50.22 (31.44)**	**34.26 (28.93)**	40.49 (26.93)[ab]
Night Sweats	**42.99 (32.96)**	**23.70 (28.66)**	30.75 (27.41)[ab]
Sweating Hands	**11.38 (21.78)**	**06.56 (16.41)**	09.46 (18.94)[b]
Weight Change	**41.70 (35.16)**	**27.93 (33.51)**	30.23 (31.72)[a]
Loss of Appetite	**44.47 (33.81)**	**26.30 (28.68)**	20.84 (22.33)[a]
Low Temperature	**19.33 (25.37)**	**11.11 (18.93)**	22.39 (25.70)[b]
Pain	**50.56 (25.50)**	**44.39 (23.30)**	49.49 (18.62)[b]
Muscle Pain	**59.26 (32.35)**	**49.64 (30.87)**	61.95 (26.22)[b]
Headaches	**58.27 (33.57)**	**46.90 (31.07)**	43.43 (24.77)[a]
Eye Pain	25.76 (32.22)	23.25 (28.89)	24.88 (26.15)
Soreness	**65.73 (35.78)**	**60.03 (31.65)**	67.06 (23.38)[b]
Joint Pain	43.97 (35.92)	42.18 (34.25)	50.17 (31.01)[ab]
Gastrointestinal	**27.41 (22.05)**	**24.38 (19.13)**	34.45 (20.28)[ab]
Bloating	29.86 (32.58)	28.24 (31.00)	38.90 (27.92)[ab]
Bladder Issues	17.31 (29.05)	15.87 (27.05)	31.77 (31.03)[ab]
Sensitivity to Alcohol	**17.15 (32.81)**	**21.19 (34.46)**	29.28 (33.59)[ab]
Stomach Pain	**36.78 (33.14)**	**28.33 (29.30)**	33.67 (25.89)[b]
Irregular Bowels	**35.48 (35.40)**	**28.42 (32.21)**	38.42 (31.28)[b]
Orthostatic	**46.01 (24.50)**	**34.49 (20.63)**	29.15 (17.03)[ab]
Nausea	**35.16 (32.39)**	**24.37 (27.51)**	27.05 (23.42)[ab]
Chest Pain	**54.41 (33.68)**	**37.46 (29.25)**	20.54 (22.53)[ab]
Feeling Unsteady	**42.63 (35.08)**	**33.39 (30.29)**	37.43 (26.74)[b]
Shortness of Breath	**61.96 (33.78)**	**42.90 (28.04)**	32.47 (25.84)[ab]
Dizziness	**39.61 (32.49)**	**30.98 (29.16)**	32.84 (25.49)[ab]
Irregular heartbeat	**42.18 (35.09)**	**37.99 (29.61)**	24.60 (24.42)[ab]
CDC	**37.06 (18.84)**	**24.31 (17.88)**	-
Dry Cough	**34.58 (27.26)**	**21.93 (27.20)**	-
Loss of Taste/Smell	**38.26 (40.22)**	**19.40 (32.11)**	-
Difficulty Breathing	**56.16 (34.25)**	**32.38 (28.13)**	-
Diarrhea	**35.79 (33.66)**	**22.78 (28.81)**	-
Nose Congestion	**31.38 (31.05)**	**21.53 (25.14)**	-
Loss of Hair	**14.39 (27.69)**	**26.47 (34.98)**	-

[1]For the COVID-19 sample, significant differences between symptoms at the start of the illness and currently are in bold using paired t-tests at the $p < .01$ level.

[2]Superscript “a” indicates differences between the ME/CFS and COVID-19 groups at the initial time point, whereas superscript “b” indicates differences at the current time point; independent t-tests were used at the $p < .01$ level.