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Clinical short communication

Sex-dependent characteristics of Neuro-Long-COVID: Data from a dedicated neurology ambulatory service

Marco Michelutti [a], Giovanni Furlanis [a], Alex Buoite Stella [a], Giulia Bellavita [a], Niccolò Frezza [a], Giovanna Torresin [a], Milos Ajčević [a,b], Paolo Manganotti [a,*]

[a] Clinical Unit of Neurology, Department of Medicine, Surgery and Health Sciences, University Hospital and Health Services of Trieste - ASUGI, University of Trieste, Strada di Fiume, 447, 34149, Trieste, Italy

[b] Department of Engineering and Architecture, University of Trieste, Via A. Valerio, 10, 34127 Trieste, Italy

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ABSTRACT

"Long-COVID" is a clinical entity that consists of persisting post-infectious symptoms that last for more than three months after the onset of the first acute COVID-19 symptoms. Among these, a cluster of neurological persisting symptoms defines Neuro-Long-COVID. While the debate about the pathogenesis of Long-COVID is still ongoing, sex differences have been individuated for both the acute and the chronic stage of the infection. We conducted a retrospective study describing sex differences in a large sample of patients with Neuro-Long-COVID. Demographic and clinical data were collected in a specifically designed Neuro-Long-Covid outpatient service. Our sample included 213 patients: 151 were females and 62 were males; the mean age was similar between females (53 y, standard deviation 14) and males (55 y, standard deviation 15); no significant differences was present between the demographic features across the two groups. Despite the prevalence of the specific chronic symptoms between male and females showed no significant differences, the total number of females accessing our service was higher than that of males, confirming the higher prevalence of Neuro-Long-COVID in female individuals. Conversely, a worse acute phase response in males rather than females was confirmed by a significant difference in the rates of acute respiratory symptoms ($p = 0.008$), dyspnea ($p = 0.018$), respiratory failure ($p = 0.010$) and the consequent need for ventilation ($p = 0.015$), together with other acute symptoms such as palpitations ($p = 0.049$), headache ($p = 0.001$) and joint pain ($p = 0.049$). Taken together, these findings offer a subgroup analysis based on sex-dependent characteristics, which can support a tailored-medicine approach.

1. Introduction

While the world enters a "post-pandemic" era, more and more people who were infected with COVID-19 are complaining about post-infectious symptoms collectively defined as "Long-COVID" [1].

As of January 2022, >293 million cases of Sars-Cov2 infection and 5.45 million deaths have been registered (according to the World Health Organization COVID-19 Dashboard). The clinical features of the COVID-19 acute respiratory syndrome have been extensively studied. However, there is a growing interest about the longer-term consequences of the infection. "Long-COVID" has been described as a variety of post SarsCov-2 infection symptoms lasting for more than three months after the onset of the first acute COVID-19 symptoms [1]. The most commonly reported symptoms are persistent shortness of breath, fatigue, hair loss, headache, autonomic disorders, anosmia/ageusia, and attention disorder [2–4]. Descriptions of other psychiatric and cognitive disorders are also common, with reports of neuropathies [5], altered mood, anxiety and "brain fog". "Brain fog" identifies self-reported minor memory impairments and deficits in focusing [6,7]. This cluster of symptoms has been recently covered by the umbrella-term of "Neuro-Long-COVID" [8,9].

Its pathogenetic factors are still a matter of ongoing debate: persistence of viral traces and trophism for organs other than lungs (including the central nervous system, CNS) with long-term tissue damage, reactivation of different pathogens, hypercoagulation, microbiome alterations have all being indicated as possible concurring explanations for Long-COVID [10,11]. Immune system dysfunctions in particular, such as abnormal inflammatory response or excessive autoimmune reactions elicited by the virus, possibly due to molecular mimicry, are thought to play a prominent role in this process [10,11].

Long-COVID has been observed to affect people differently on the

* Corresponding author.
E-mail address: pmanganotti@units.it (P. Manganotti).

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basis of demographic features such as age, sex, and body mass index [12]. Sex differences have been described both for the acute stage of the infection and for Long-COVID. Males have been seen to be more susceptible to develop severe acute COVID-19 respiratory symptoms [13]. On the other hand, females have been described to experience Long-COVID more likely than males [12–18]. Some have hypothesized that this could be an artefact caused by a supposedly higher self-awareness for such symptoms in women [19]. Others suggest that the sex skew could be related to hormonal factors: these differences, in fact, have been reported to flatten for patients both older than 60 [12] and in the pediatric age [20].

Sex differences have already been described for post-COVID mood disorders [17,21], postural orthostatic hypotension [22], anxiety, sleep disturbances and subjective complains about memory impairment [17]. Nonetheless, due to the variability of Long-COVID characteristics and the heterogeneity of the samples, data are missing regarding the specific characteristics of people with Neuro-Long-COVID.

Therefore, the aim of this study was to describe the sex differences in Long-COVID characteristics observed in a specifically designed Neuro-Long-COVID ambulatory service. These data will hopefully offer more evidence on the existence of such differences and possibly provide a framework for future discussion on the etiopathogenetic mechanisms of Long-COVID, and Neuro-COVID in particular.

2. Methods

Participants who were referred to the Neuro-Long-COVID ambulatory service of the University Hospital of Trieste from the 1st January 2021 to the 1st October 2021 were screened for the presence of self-reported neurological symptoms in the post-acute COVID-19 period (diagnosis confirmed by SARS-CoV-2 nasopharyngeal swab). The neurological symptoms had to be present (persistent or ex-novo) at least after 4 weeks from acute COVID-19 symptoms manifestation.

Patients were excluded if the medical examination reported symptoms of no neurological relevance. All procedures were performed according to the declaration of Helsinki and the study was approved by the regional ethics board (CEUR FVG). Demographic characteristics were collected together with the presence of neurological, psychiatric, cardiovascular, respiratory, metabolic, neoplastic and endocrine comorbidities, obesity and both acute and chronic (i.e., lasting for more than three months) COVID-19 symptoms. Patients were screened to assess the presence of respiratory failure in the acute phase and they were asked whether they had previously displayed acute upper respiratory symptoms, fever, dyspnea, headache, myalgia or joint pain, hyposmia or anosmia, palpitations, diarrhea or gastrointestinal tract symptoms and fatigue. Additional acute phase data were collected for the requirement of ventilation and the received therapy: in particular, it was checked whether the patients were given corticosteroids, antibiotics, or heparine.

The presence of Long-COVID was extensively studied, screening for symptoms lasting for more than three months after the infection onset: the patients were investigated for the presence of persistent fatigue, respiratory symptoms, palpitations, gastrointestinal tract symptoms, myalgia or joint pain, tinnitus, vertigo, visual disturbances, persistent fever. The patients were especially investigated for the presence of persisting neurological symptoms, such as paresthesia, hyposmia or anosmia/ageusia, cognitive deficits, mood disturbances, headache, weakness, and insomnia. The examinator took into account the Long-Covid symptoms reported by the patient only in case these were not present before the infection.

Finally, the total count of symptoms, both for the acute and chronic phase, was reported for each patient, as a measure of the individual symptomatological burden.

2.1. Statistical analysis

Descriptive statistics, including medians (25th–75th percentile) for continuous variables and proportions (%) for categorical variables, have been used to summarize the results. Comparison between males and females was performed for each variable with the independent samples *t*-test for the continuous parameters and the chi-square test for proportions. Significance level was set for $p < 0.05$.

2.2. Data availability

The authors confirm that the presented data of this study are saved at the Clinical Unit of Neurology, Trieste University Hospital ASUGI, Italy. They are available upon reasonable request and according to the local institutional and ethics regulation.

3. Results

The patients who were referred to the Neuro-Long-COVID neurology ambulatory service of the University Hospital of Trieste in the study period were 225, of which 12 were excluded due to symptoms other than neurological involvement (6 for respiratory symptoms, 6 for rheumatological symptoms). Two-hundred-thirteen patients were included in the final analysis. Among these patients, 151 were females (73%) while 62 were males (29%). The age of the patients ranged from 16 to 87 (females 53 +/− 14; males 55 +/− 15; $p = 0.355$).

Among the pre-existent comorbidities, females were characterized by lower prevalence of cardiovascular (23.0% vs 41.9%; $p = 0.009$) and metabolic disease (23.2% vs 40.3%; $p = 0.013$), and a higher prevalence of endocrine disease (21.2% vs 4.8%; $p = 0.003$) compared to males (See Table 1).

During the acute phase of SARS-COV-2 infection, compared to males, females presented more upper respiratory symptoms (47% vs 27.4%; $p = 0.008$), myalgia/joint pain (45.7% vs 30.6%; $p = 0.043$), palpitations (6.0% vs 0.0%; $p = 0.049$), while presented less frequent dyspnea (29.8% vs 46.8%; $p = 0.018$), which resulted in less acute respiratory failure (8.6% vs 21.0%; $p = 0.010$) and consequent ventilation (8.6% vs 21%; $p = 0.015$). Requirement of ventilation (8.6% vs 21.0%, $p = 0.015$) and antibiotics (22.5% vs 37.1%, $p = 0.038$) for their treatment was less frequent in females than in males (See Table 2).

The most frequently reported Long-COVID symptoms were cognitive deficits, persistent asthenia and persistent hyposmia or anosmia (45%, 36% and 33% of the total cases, respectively).

Considering the Long-COVID symptoms, none of those reported showed a significant difference between females and males, although a tendency for a higher prevalence of headache was found in females (14.6% vs 3.2%; $p = 0.080$) (See Table 3).

As a measure of the individual symptomatological burden, the number of the different symptoms was also counted for each patient, both symptoms of the acute and the Long-COVID phase. No significant difference was found for the mean of both the acute and the Long-COVID phase symptoms.

Table 1
A Participants' demographics and pre-infection clinical characteristics in females (n = 151) and males (n = 62) reporting Long COVID symptoms. Data are presented as prevalence and frequency.

Characteristics	Females	Males	Sig.
	n = 151	n = 62	
Neurological Comorbidities	65 (42.8%)	18 (29.5%)	0.072
Psychiatric Comorbidities	15 (9.9%)	6 (9.5%)	0.936
Cardiovascular Comorbidities	35 (23.0%)	26 (41.9%)	**0.009***
Respiratory Comorbidities	14 (9.0%)	11 (17.7%)	0.086
Metabolic Comorbidities	35 (23.2%)	25 (40.3%)	**0.013***
Neoplastic Comorbidities	11 (7.3%)	8 (12.9%)	0.199
Endocrine Comorbidities	32 (21.2%)	3 (4.8%)	**0.003***
Obesity	10 (6.6%)	6 (9.7%)	0.455

* : Significant ($p < 0.05$) value (Sig.) for intergroup comparison.

Table 2
Partecipants' acute phase infection features. Data are presented as prevalence and frequency.

Characteristics	Females	Males	Sig.
	n = 151	n = 62	
Acute Upper Respiratory Symptoms	71 (47.0%)	17 (27.4%)	**0.008***
Acute Dyspnea	45 (29.8%)	29 (46.8%)	**0.018***
Acute Fever	109 (72.2%)	42 (67.8%)	0.517
Acute Headache	60 (39.7%)	10 (16.1%)	**0.001***
Acute Myalgia/Joint Pain	69 (45.7%)	19 (30.6%)	**0.043***
Acute Hyposmia/Anosmia	69 (45.7%)	24 (38.7%)	0.35
Acute Palpitations	9 (6.0%)	0 (0.0%)	**0.049***
Acute Gastrointestinal Tract Symptoms	36 (23.8%)	9 (14.5%)	0.13
Acute Fatigue	59 (39.0%)	21 (33.8%)	0.476
Acute Respiratory Failure	13 (8.6%)	13 (21%)	**0.010***
Ventilation	13 (8.6%)	13 (21%)	**0.015***

* **:** Significant ($p < 0.05$) value (Sig.) for intergroup comparison.

Table 3
Participants' Long-COVID clinical features. Data are presented as prevalence and frequency.

Characteristics	Females	Males	Sig.
	n = 151	n = 62	
Persistent Fatigue	55 (36.4%)	22 (35.5%)	0.961
Persistent Respiratory Symptoms	37 (24.5%)	17 (27.4%)	0.611
Persistent Tinnitus	4 (2.6%)	2 (3.2%)	0.802
Persistent Vertigo	7 (4.6%)	3 (4.8%)	0.93
Persistent Headache	22 (14.6%)	2 (3.2%)	0.08
Persistent Visual Disturbances	5 (3.3%)	5 (8%)	0.129
Persistent Fever	4 (2.6%)	0 (0%)	0.199
Persistent Paresthesia	15 (10.1%)	10 (16.1%)	0.244
Persistent Myalgia/Joint Pain	37 (35.5%)	15 (24.2%)	0.989
Persistent Hyposmia/Anosmia	50 (33.1%)	20 (32.2%)	0.964
Persistent Palpitations	5 (3.3%)	2 (3.2%)	0.99
Persistent Gastrointestinal Tract Symptoms	6 (3.9%)	1 (1.6%)	0.389
Persistent Cognitive Deficits	70 (46.3%)	25 (40.3%)	0.476
Persistent Insomnia	24 (15.9%)	10 (16.1%)	0.833
Persistent Weakness	5 (3.3%)	2 (3.2%)	0.987
Persistent Mood Disturbances	12 (7.9%)	6 (9.6%)	0.66

4. Discussion

This study compared a group of males with one female patients reporting Long-COVID symptoms in a specifically dedicated neurology ambulatory service for Long-COVID syndrome.

The distribution of the Long-COVID symptoms and their frequencies in the two groups did not differ significantly, although a tendency for a higher prevalence of headache was found in females. Although in the general population headache is more common in females [23] and therefore this might contribute to higher prevalence observed in our study, growing evidence indicates that a specific headache pattern might be related to the Long-COVID syndrome [24]. As such, this specific headache subtype may be expected to be more common in females with Long-COVID symptoms.

Previous studies found heterogeneous results. However, data were collected from self-reports [12] or virtual appointments [17] rather than through an objective clinical examination. In addition, neurological deficits were not specifically investigated [25] and lacked of a precise timeframe in the inclusion criteria for the onset of the symptoms described [21].

The intensity or duration of Long-COVID symptoms have been suggested not to be correlated with neither the burden of the symptoms at the onset nor the requirement for hospitalization in intensive care units [26–28].

Our findings are in line with previous observations supporting that acute phase characteristics may not influence the development of Long-COVID symptoms. Yet, this study only relied on individuals who referred to our neurology ambulatory service and it cannot be generalized to the whole population.

The number of female patients accessing our outpatient service was three times higher than the number of male patients, despite the latter being characterized by a more severe acute SARS-COV2 infection and a higher prevalence of cardiovascular and metabolic comorbidities. Although the relative frequencies in the Long-Covid symptoms did not differ significantly in our sample, this global higher number of females patients suggests that Long-Covid might be subject to a sex-dependent response. This needs to be confirmed in a larger sample of patients.

Some factors have been hypothesized to explain the observed sex-dependent responses to the acute phase of the infection and Long-COVID syndrome development.

Sex-dependent expression of the angiotensing-converting-enzyme 2 (ACE2) receptor and the transmembrane protease serine 2 (TMPRSS2), which are targeted by the virus to access the body, may help explaining worse clinical outcomes in the acute phase of the infection in males [29]. Genetic factors related to the immune responses of females, such as stronger IFN1 activity and higher expression of TLR7 (a common sensor of viruses which is located on chromosome X) have also been indicated among the possible reasons for a better immune-inflammatory response in females [13,30,31]. In addition, a stronger immune response can be observed in females due to the difference in the sex hormones expression [19,32]. Although this factors may suggest females being characterized by a less severe acute infection, they may put them at a higher risk of developing Long-COVID syndrome [33].

The existence of a "female effect" in the pathogenesis of Long-COVID has been recently debated [19,32]. The fact that more women than males accessed our outpatient service could reveal higher awareness in females when it comes to one's own body and its alterations compared to males [19]. However, this is unlikely to be due solely to gender-related psychological factors. [19]. The role of sex hormones in determining stronger immune responses has been described [31,34]. This is reflected by higher rates of autoimmune diseases in females as opposed to males [33]. In Long-COVID syndrome, it can be hypothesized that traces of the SARS-COV-2 lingering in multiple organs such as in the kidneys, the heart, the liver, the gastrointestinal tract or the brain could chronically activate an inflammatory cascade, leading to a disruption of the central nervous system activity, as observed in "brain fog" [35]. This mechanism may be similar to those elicited by Lyme disease, another post-infectious disease with a predominance of female cases [36], and the Chikungunya virus [37]. Higher levels of cytokines have been reported in females as opposed to males for Lyme disease [38]. *Borrelia Burgdorferi* antigens have also been described to spread into different tissues in the body, leading to low-grade chronic inflammation [39].

A similar pattern has been also described in other conditions such as Chronic Fatigue Syndrome (CFS), whose etiology is regarded as post-infectious [40].

Long-COVID hyperinflammatory syndrome have been reported both in children and adults [13]. However, a correlation between Long-COVID symptoms and higher levels of inflammatory biomarkers measured months after the infection onset is still debated [41] [42]).

Our study had some limitations. Firstly, this study was a monocentric and included data from only one neurology ambulatory service. This may have impacted the limited sample size, the study population, which came from the same area. On the other hand, the clinical evaluation was always performed by the same neurologist, leading to a consistent assessment. We did not include instrumental or blood tests.

Secondly, symptoms were subjectively reported by the patients and some of them could not be objectively assessed (given headache). Thus, due to global reporting of all neuro-Long-COVID symptoms, some instrumental data are missing for specific conditions. Finally, in this study we do not present data from the general population or from patients who were infected by SARS-COV2 but did not develop Long-COVID syndrome.

Future studies should consider follow-up visit to include the analysis

of Long-COVID resolution and duration in males and females. To give a better pathophysiological insight which may explain sex differences in Long-COVID prevalence, future studies should investigate the relationship between different symptoms and instrumental data including hormonal and inflammatory patterns.

5. Conclusion

In conclusion, our study was conducted on a large number of homogeneous patients, included on the basis of well-defined clinical features who underwent an in-person thorough examination by a neurologist in a specifically designed Neuro-Long-COVID outpatient service.

We observed a predominance of females attending the service for neuro Long-COVID symptoms, without significant differences in symptoms distribution between males and females.

Based on the above observations, a health care professional working in such services should expect an overall higher presentation of females complaining persistent cognitive deficits, paresthesia, vertigo, tinnitus, headache, hyposmia or anosmia, mood disturbances and insomnia. From the practical viewpoint, future outpatient services for Long-COVID, and especially Neuro-Long-COVID disturbances, should be tailored to the specific features of female patients.

All authors contributed to the study conception and design. Data were collected by Giovanni Furlanis, MD, Niccolò Frezza, MD, Giulia Bellavita, MD and Giovanna Torresin, MD. Data analysis was performed by Alex Buoite Stella, PhD, Giovanni Furlanis, MD and Marco Michelutti, MD. The first draft of the manuscript was written by Marco Michelutti, MD and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Ethics approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the Bioethics Committee of the Medical University of Trieste.

Consent to participate

Informed consent was obtained from all individual participants included in the study.

Consent to Publish

The participants have consented to the submission of the study to the journal.

Data availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Declaration of Competing Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article. Figures are original and not previously published.

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