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LETTERS TO THE EDITOR

Gender issues during the times of COVID-19 pandemic

Introduction

In this letter to the editor, the Task Force on Gender and Diversity Issues in Neurology founded under the auspices of the European Academy of Neurology (EAN) addresses various gender issues that are arising during the COVID-19 pandemic. These issues concern different aspects, spanning from gender disparities in the healthcare workforce to gender differences amongst patients suffering from COVID-19, risk factors, occurrence of neurological complications and (outcomes of) management. Due to the continuous flow of COVID-19 related papers this review cannot be comprehensive. We attempted to select the most relevant literature on this topic.

Gender disparities amongst healthcare providers

The global healthcare systems have a very high female gender workforce representation in all positions: from hospital aids and social workers to nurses and doctors [1] The double bind of professional roles and family and social roles is often a burden of females.

Family caregiving is also predominantly provided by women, although the role of men is gradually increasing, in particular in countries with an extensive social infrastructure [2] The COVID-19 pandemic has increased already existing gender inequality in the labour force with troubling consequences. Since women compose the majority of the health workforce they are more at risk of contracting SARS-CoV-2 given their prolonged close contact with patients. Based on data derived from the US COVID-19-Associated Hospitalization Surveillance Network (COVID-NET), nursing related occupations accounted for the largest proportion of COVID-19 hospitalized cases amongst healthcare professionals during 1 March to 31 May 2020 [3] These data highlight the importance of strict adherence to prevention measures including the availability of personal protective equipment.

The high physical and mental demands of caring for COVID-19 patients in hospitals and long-term care facilities have taken their toll, as shown by the high sick leave percentage amongst healthcare professionals worldwide and the high prevalence of burnout amongst Japanese front-line female workers [4] Of note, the virus might not be the only reason for the steep increase in sickness absence. It may also be due to underlying causes, such as staff shortages, pre-existing workplace gender bias and inequities [5,6] A recent review on articles concerning the identification of potential variables that influence mental health well-being during the COVID-19 pandemic in a broad array of women in healthcare showed that organizational factors were an important cause of stress and burnout [6] Resource adequacy related reasons (lack of protective personal equipment or staff shortages) and human resource related safety concerns (fear of getting infected with COVID-19 and thus putting family members at risk) were also major drivers of stress and burnout [6]

Thus, there is an urgent need to further analyse and evaluate gender issues in the health and social sector workforce during this pandemic.

Gender differences in patients with COVID-19

A study from the UK on 10,926 COVID-19 related deaths showed that age and male sex are risk factors for worse outcomes in COVID-19, with those aged 80 years and older having a 20 times higher risk compared with those aged 50–59 years and males having a higher risk than females (hazard ratio 1.59) [7] These gender differences are probably due to gender-specific behaviours, genetic and hormonal factors, and sex differences in biological pathways related to SARS-CoV-2 infection [8] Men are more likely to show smoking and alcohol consumption behaviours and have higher age-adjusted rates of pre-existing comorbidities associated with poor COVID-19 prognosis, including hypertension, cardiovascular disease and chronic obstructive pulmonary disease [8] Haitao et al. have synthesized the scarce evidence regarding the proposed cellular and molecular markers of COVID-19 severity by sex, and found amongst other things strong evidence that oestrogen exerts significant anti-inflammatory responses and that low levels of testosterone in elderly men have been associated with upregulation of inflammatory markers and possible increased risk of lung damage and increased need for assisted ventilation [8]

A systematic review and meta-analysis of clinical characteristics, risk factors and outcomes of 212 studies originating from 11 countries/regions and involving 281,461 individuals with laboratory-confirmed COVID-19 (most of them from the United States) showed that there was a mean age of 46.7 years and equal representation of males and females. The majority of studies included in the meta-analysis were hospital-based and/or tertiary-care-center-based studies. The pooled proportion of patients admitted to intensive care units was 10.96% (95% confidence interval [CI] 6.6–17.6), the overall pooled mortality was 5.6% (95%

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CI 4.2–7.5) and overall 22.9% (95% CI 13.3–36.5) of COVID-19 patients had severe disease. Amongst those with severe disease (defined by World Health Organization criteria for severe pneumonia), the pooled mean age was 60 years (compared with 44.6 years for those without severe disease) and more than half (61%) were male [9] Immunosuppression, diabetes and malignancy were most strongly associated with severe COVID-19, whereas older age, male gender, diabetes and hypertension were associated with higher mortality. Obesity or body mass index was not included in this analysis.

Neurological complications of COVID-19

There is a host of publications on neurological complications of the COVID-19 infection. The percentage of neurological symptoms amongst the COVID-19 affected individuals varies widely (4.2%–87.3%) [10,11] This can be ascribed to several methodological limitations [12] Therefore, Pezzini and Padovani caution against inferring any specific causal links between SARS-CoV-2 and neurological symptoms [12]

The EAN core COVID-19 Task Force performed a multi-centre survey on neurological symptoms in SARS-CoV-2 patients of whom about half were polymerase chain reaction confirmed. The 2343 participants (82% were neurologists, mostly from Europe and in particular Italy) observed at least one neurological symptom in their patients (especially myalgia, headache, anosmia and ageusia). Seventy-five per cent of the survey respondents were of the opinion that it was associated with the COVID-19 disease. No differences in gender were detected [13]

A study composed of 1420 laboratory confirmed patients (962 females, 436 healthcare workers which is 30.7 % of the cohort) from 18 European hospitals focused on mild to moderate COVID-19 infection of which fewer than 10% required hospitalization [14] The most frequent symptoms were headache (70.3%), loss of smell (70.2%), nasal obstruction (67.8%), cough (63.2%), asthenia (63.3%), myalgia (62.5%), rhinorrhoea (60.1%), gustatory dysfunction (54.2%) and sore throat (52.9%). Loss of smell, headache, nasal obstruction, throat pain and fatigue were more prevalent in females ($p < 0.001$), whereas males more frequently suffered from cough and fever ($p < 0.001$) [14]

In an American study composed of 509 hospitalized COVID-19 patients, neurological manifestations were present at COVID-19 onset in 215 patients (42.2%), at hospital admission in 319 patients (62.7%) and at any time during the disease course in 419 patients (82.3%) [15] The most frequent neurological manifestations were myalgias (228, 44.8%), headaches (192, 37.7%), encephalopathy meaning an altered mental status, depressed level of consciousness or delirium (162, 31.8%), dizziness (151, 29.7%), dysgeusia (81, 15.9%) and anosmia (58, 11.4%). Males had significantly more often any neurological manifestation (55.1%) compared to women (44.9%), without specification of the nature of the symptoms and signs, except for encephalopathy which was more common in males [15]

Various systematic reviews focusing on neurological manifestations in patients with COVID-19 have been performed. One systematic review and meta-analysis described neurological manifestations in patients with COVID-19 (analysis of 41 out of 298 eligible articles) [16] The meta-analysis separately addressed six case series and 15 case reports focusing on specific neurological symptoms. All but one were retrospective in nature and originating from China. Five out of six papers found a frequency of smell and taste impairment ranging from 35.7% to 85.6% and from 33.3% to 88.8%, respectively. Frequencies differed amongst males and females, but there were no consistent trends. Another case series included in the meta-analysis showed data on 214 hospitalized patients (40.7% males) from the early days of the pandemic in Wuhan. Seventy-eight patients (36.4%) with neurological manifestations were reported. In particular, the patients with severe disease (41.1% according to their respiratory status) had acute cerebrovascular diseases (5.7%), impaired consciousness (14.8%) and skeletal muscle injury (19.3%) [17] Far more females were affected with COVID-19, although a severe disease course was equally distributed amongst the sexes. The authors put in a word of caution since all data were abstracted from the electronic medical records and therefore not all patients with certain neurological symptoms might be captured. That might explain the low frequency of smell and taste impairment (5.1% and 5.6%, respectively).

Interpretation of the results of a systematic review which analysed 64 out of total of 2353 studies, mostly from China, might also require some caution. The studies included 11,687 COVID-19 adult patients (5568 females and 6114 males) [18] The authors reported that COVID-19 patients showed central nervous system symptoms, including headache (8.6%), dizziness (5.9%) and impaired consciousness (1.9%). However, the frequencies were much lower compared to those provided by other authors [14–16].

A recent systematic review which attempted to capture only studies focusing on specific neurological manifestations (92 out of 1387 eligible publications were assessed) also reported headache, dizziness, taste and smell dysfunctions, or impaired consciousness as the most frequently reported neurological symptoms in COVID-19 patients, each observed in more than five of the analysed studies and with an overall frequency of greater than 4% of the populations [19]

Summarizing these results, smell and taste impairment is found to be a frequent feature in mildly affected patients, whereas other neurological manifestations such as headache, dizziness and impaired consciousness seem to be associated with severe disease. Whether there is predominantly male involvement as is generally the case amongst COVID-19 infected patients cannot be confirmed. Unfortunately, possible gender disparities have often not been analysed. It might well be that systematic databases, such as the EAN COVID-19 Registry (ENERGY, https://wwweanorg/ean/eancore-covid-19), will help to further analyse the occurrence of neurological manifestations and the possible impact of gender [20]

There are some reports of involvement of the peripheral nervous system, that is, Guillain–Barré syndrome cases or Miller–Fisher syndrome concomitantly with the COVID-19 spread, suggesting a

pathogenic link [21,22] However, a study from the UK did not find epidemiological or phenotypic clues of SARS-CoV-2 being causative of Guillain–Barré syndrome [23]

Finally, long-COVID should be mentioned, which affects about 10% of individuals lasting for more than 28 days following a COVID-19 infection. The symptoms (fatigue, headache, dyspnoea, inability to concentrate and myalgia) show similarities with those associated with chronic fatigue syndrome. Those experiencing long-COVID were consistently older and more often female [24] Long-COVID-19 or post-COVID-19 neurological syndrome has as yet not been extensively researched.

Gender balance in clinical trials

Gender issues also play a role in the design of clinical trials. There are several factors why there may be gender differences in the design of trials. These factors can impact the eventual performance and acceptance of the novel drug [25] One of the factors is that women of childbearing age are usually excluded. However, pregnant or breastfeeding women were eligible for the randomized controlled trial investigating the efficacy of dexamethasone on the 28-day mortality in patients who were hospitalized with COVID-19 [26]

Both the Food and Drug Administration and European Medicines Agency have recommended the inclusion of sufficient numbers of subjects of both sexes in clinical trials, possibly at percentages adequate in representing the prevalence rates within the general population. In addition, the National Institutes of Health has adopted a code for the inclusion of both genders and ethnic minorities within clinical trials [27] A recent paper has investigated the inclusion of sex and/or gender data in currently registered COVID-19 studies on ClinicalTrials.gov [28] The authors found that only 416 (16.7%) of the 2484 registered SARS-CoV-2/COVID-19 trials mention sex/gender as a recruitment criterion, and only 103 (4.1%) allude to sex/gender in the description of the analysis phase. None of the 11 clinical trials published in scientific journals on June 2020 reported sex-disaggregated results.

Conclusion

Gender inequality during the COVID-19 crisis has been well recognized. Although in this paper our focus has been directed towards gender issues in patient care in general and neurology in particular, we would like to conclude with a quote from a United Nations development programme report that 'understanding gender-differentiated impacts of the COVID-19 crisis through sex-disaggregated data is fundamental to design policy responses that reduce vulnerable conditions and strengthen women's agency, placing gender equality at their centre' [29]

KEYWORDS

COVID-19, diversity, gender, neurology, workforce

CONFLICT OF INTEREST

Drs Ferretti, Giovannoni, Gouider and Moro report personal fees from sources outside the submitted work. The other authors have no conflict of interest to report.

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