ORIGINAL RESEARCH

Neuropsychiatric Symptoms and Psychotropic Medication Use Following SARS-Cov-2 Infection Among Elderly Residents in Long-Term Care Facilities

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ABSTRACT

Background

SARS-CoV-2 infection can lead to persistent post-acute neuropsychiatric symptoms. Older adults with multimorbidity may be at increased risk of post-acute symptoms after COVID-19. The goals of the present study were to assess the associations of SARS-CoV-2 infection with neuropsychiatric symptoms and psychotropic medication prescription among older adults living in long-term care facilities.

Methods

Nursing home residents (n=111) participated in this three-month longitudinal study. Nurse ratings of neuropsychiatric symptoms were conducted at baseline and at the three-month follow-up. SARS-CoV-2 infection status and psychotropic medication prescription were extracted from a medical chart review.

Results

About 73.9% of participants were infected with SARS-CoV-2 on average 480.49 (SD= 228) days before study enrollment. There were no significant changes in neuropsychiatric symptoms during the study follow-up period. Participants with a SARS-CoV-2 infection had more agitation compared to those who were never infected. However, this effect disappeared after adjusting for age, sex, history of psychiatric disorder, neurocognitive status, and multimorbidity. Participants with SARS-CoV-2 had a higher number of psychotropic medication prescription. This effect was driven by increased use of antidepressants and antipsychotic medications.

Conclusion

Both acute and short-term neuropsychiatric symptoms associated with COVID-19 may contribute to long-term psychoactive polypharmacy among older adults living in long-term facilities.

Key words: neuropsychiatric symptoms, older adults, dementia, COVID-19, nursing homes

INTRODUCTION

SARS-CoV-2 can lead to sustained symptoms after the acute phase of the infection.(1) Neuropsychiatric symptoms are prevalent post-acute symptoms among patients with confirmed SARS-CoV-2 infection.(2) In a subset of COVID-19 patients, these post-acute symptoms can last for several months.(3) In a meta-analysis of longitudinal studies, depression, anxiety, and insomnia symptoms triggered by COVID-19 were observed up to 12 months post-infection.(4) Furthermore, in a two-year retrospective analysis of electronic medical records, patients with COVID-19 had increased risk for anxiety and mood disorders for one to two months post-infection, while risk for cognitive impairment and psychotic disorders increased over the following two years, compared to patients with other respiratory infections.(5) Notably, older adults are at increased

risk for persistent post-acute symptoms following COVID-19, compared to younger individuals.[6] Multimorbidity among older adults living in long-term care facilities may further increase this risk.[7]

Prior work highlights a high prevalence of neuropsychiatric symptoms among older adult residents in long-term care facilities during the COVID-19 pandemic.[8] In particular, agitation, depression, anxiety, and fatigue were some of the most common neuropsychiatric symptoms among nursing home residents during this period.[9] A number of studies also reported increases in psychotropic medication use in nursing homes during the COVID-19 pandemic.[10–12] Such increases in neuropsychiatric symptoms and psychotropic medication use may reflect the stress associated with the COVID-19 pandemic, the social and service delivery disruption during various confinement periods, or the consequence of the SARS-CoV-2 infection.[8]

To our knowledge, no prior studies have examined the contribution of SARS-CoV-2 infection on changes in neuropsychiatric functioning among older adults living in long-term care facilities. Accordingly, the goals of the present study were to assess the associations of SARS-CoV-2 infection with 1) neuropsychiatric symptoms several months after the initial infection; 2) changes in neuropsychiatric symptoms over time; and 3) psychotropic medication prescriptions among older adults living in long-term care facilities.

METHODS

Study Design and Procedures

In this longitudinal study, long-term care facility residents were initially assessed about two years after the onset of the COVID-19 in Canada, with a mean number of days since the WHO's declaration of the COVID-19 global pandemic = 695.60, SD= 86.76. A three-month longitudinal follow-up was conducted to assess the evolution of neuropsychiatric symptoms among older adult residents with and without a history of SARS-CoV-2 infection. A three-month follow-up period was selected given the WHO's proposed criteria for post-COVID condition.[13] Nurses rated the severity of participants' neuropsychiatric symptoms over the past two weeks at each assessment. Medical chart reviews were conducted to assess SARS-CoV-2 infection status and psychotropic medication prescription. Data collection occurred from August 2021 to February 2023. Participants, their caregivers, or their legal representatives provided consent prior to data collection. This study was approved by the local Research Ethics Board.

Participants

Inclusion criteria were adults ≥ 65 years of age residing in one of the six participating long-term care facilities from the Montreal West Island Integrated University Health and Social Services Centre. To be admitted to these long-term care facilities, individuals had to experience a significant loss of autonomy and require more than three hours of direct care per day. In the province of Quebec, residents from long-term care facilities were considered a priority group to receive mRNA COVID-19 vaccination. If they or their legal representative consented, they were eligible to have had received up to 3-4 doses of a COVID-19 vaccine prior to their study enrollment.

Measures

Neuropsychiatric symptoms were assessed using the Neuropsychiatric Inventory (NPI)– Nursing Home version.[14] The NPI is a nurse-rated instrument assessing the frequency and severity of neuropsychiatric symptoms in the past two weeks in 12 domains of behavioural disturbances including delusions, hallucinations, dysphoria, anxiety, agitation/ aggression, euphoria, disinhibition, irritability/lability, apathy, aberrant motor activity, night-time behavior disturbances, as well as appetite and eating abnormalities. Recent works suggest that a 5-factor structure provides the best fit to the NPI score.[15] In addition to the total score of the scale, scores for the agitation (agitation, irritability, aberrant motor activity), affective (dysphoria, anxiety), psychotic (delusions, hallucination), disinhibition (disinhibition, euphoria), and apathy (apathy) factors were computed.

SARS-CoV-2 infection was assessed during routine care. From March 2020 to December 2021, SARS-CoV-2 testing was done using reverse transcription-polymerase chain reaction (RT-PCR) in the designated, regional, clinically certified diagnostic microbiology laboratory. From December 2021 to December 2022, lateral flow antigenic tests were used as the initial testing method for symptomatic residents. Test results were collected from the participant's medical records to determine SARS-CoV-2 infection and reinfection status at each assessment. A positive SARS-CoV-2 infection status was defined as having a RT-PCR confirmed SARS-CoV-2 infection at any time prior or during the study period.

Medical history and sociodemographic characteristics were obtained via medical chart review. Information on age, sex, history of cardiovascular disorder, hypertension, diabetes, obesity, chronic pulmonary disease, cancer, and psychiatric disorders were extracted. Multimorbidity was defined as presenting three or more comorbid chronic medical conditions.[16] History of psychiatric disorder was defined as having a past diagnosis of a psychotic, mood, or anxiety disorder. A medication review was conducted at study enrolment to assess whether the participants had current prescriptions for benzodiazepine, antipsychotic, or antidepressant medications.

Statistical Analysis

Repeated measure analysis of variance (ANOVA) was conducted to assess whether SARS-CoV-2 infection status influenced change in neuropsychiatric symptoms during the three-month follow-up period. MANOVA tested whether SARS-CoV-2 status was associated with mean levels of neuropsychiatric symptoms across time. ANOVA evaluated the association between SARS-CoV-2 infection status and psychotropic medication prescriptions. Logistic regressions evaluated the association of SARS-CoV-2 infection status with specific psychotropic medication types. In sensitivity analyses,

the following covariates were added to the models: age, sex, neurocognitive disorder, history of psychiatric disorder and multimorbidity. All analyses were conducted with SPSS v. 28.0 (IBM Corp).

RESULTS

Participants Characteristics

Participants (n = 111) had a mean age of 82.25 (SD = 11.57), ranging from 52–101. About 69.4% were females, 66.4% had a neurocognitive disorder, 50.5% had a history of psychiatric disorder, and 28.2% had multimorbidity. The mean number of COVID-19 vaccine doses was 2.97 (SD = 1.03), ranging from 0 to 4. About 4.5% of participants had not received COVID-19 vaccination, and 22.5% had not received their first booster at study enrolment.

Prevalence of SARS-CoV-2 Infection

About 73.9% of participants were infected with SARS-CoV-2. Of those, 8.11% had a re-infection, including 3.6% during the study follow-up period. The mean number of days since the first infection at study enrollment was 480.49 (SD = 228). All but two participants were infected prior to receiving COVID-19 mRNA vaccination. SARS-CoV-2 infection status was not related to neurocognitive disorder status (χ^2 = .04, p = .84), history of psychiatric illness (χ^2 = 1.24, p = .27), or multimorbidity (χ^2 = .19, p = .66. However, males (χ^2 = 12.49, p < .001) and younger participants (F = 3.67, p = .06) were more likely to be infected with SARS-CoV-2, compared to females and older participants.

Impact of Infection on Neuropsychiatric Symptoms

Within-person repeated measure ANOVA tested whether SARS-CoV-2 status was associated with changes in neuropsychiatric symptoms over time. Using the NPI total scores at baseline (M = 9.50 SD = 10.28) and at the three-month follow-up assessment (M = 11.68, SD = 15.31), there was no significant change in neuropsychiatric symptoms over time (F [1, 98] = .29; p = .59; partial η^2 = .003. Furthermore, SARS-CoV-2 infection status did not moderate change in neuropsychiatric symptoms over time (F [1, 98] = 1.35; p = .25; partial η^2 = .014).

Given the lack of change in neuropsychiatric symptoms over time, exploratory analyses were conducted to examine whether SARS-CoV-2 infection would be associated with specific neuropsychiatric symptoms. A MANOVA evaluated whether SARS-CoV-2 status was associated with mean levels of the 5 factors from the NPI. There was a statistically significant difference in neuropsychiatric symptoms based on a SARS-CoV-2 status (F [5, 94] = 3.16, p = .01; Wilks' λ = 0.86, partial η^2 = .14). SARS-CoV-2 infection was associated with greater agitation symptoms (F [1, 99] = 4.82; p = .03; partial η^2 = .047), but was not related to affective symptoms ((F [1, 99] = .50; p = .48; partial η^2 = .005), psychotic symptoms (F [1, 99] = .08; ^{p} = .79; partial η^2 = .001), disinhibition (F [1, 99] = .06; p = .81; partial η^2 = .001), or apathy (F [1, 99] = 1.19; p = .28; partial η^2 = .012). However, after adjusting for age, sex, history of psychiatric disorder, neurocognitive status, and multimorbidity, SARS-CoV-2 infection was no longer independently associated with agitation symptoms (F [1, 99] = .95; p = .31; partial η^2 = .011). Figure 1 depicts change in neuropsychiatric symptoms as a function of SARS-CoV-2 status.

Association of Infection with Psychotropic Medication Prescription

Participants were prescribed on average 1.53 (SD = 97) psychotropic medications, with 53.3% of residents having a prescription of antidepressants, 47.7% of antipsychotics, and 51.8% of benzodiazepines. About 17.4% of participants had prescriptions of the three classes of psychotropic medication, while 17.4% had no prescriptions. Participants with a history of SARS-CoV-2 infection had a higher number of psychotropic medication prescriptions, compared to SARS-CoV-2- participants (F [1,107] = 5.12, p = .03). Specifically, SARS-CoV-2+ participants were more likely to have a prescription for antidepressants (χ^2 = .8.01, p = .05) and antipsychotics χ^2 = 4.58, p = .03), but not for benzodiazepines (χ^2 = .42, p = .51). After adjustment for age, sex, neurocognitive disorder, history of psychiatric disorder, and multimorbidity, antidepressants prescription was independently associated with SARS-CoV-2 status (OR = 3. 47 [95%CI = 1.04-11.49], p = .03), but not antipsychotics (OR = 2.21 [95% CI = .78-6.25], p = .13) or benzodiazepines (OR = .62 [95% CI = .23-1.64], p = .33).

DISCUSSION

This study examined the neuropsychiatric sequelae of SARS-CoV-2 infection among older adults living in long-term care facilities. Although residents with a prior SARS-CoV-2

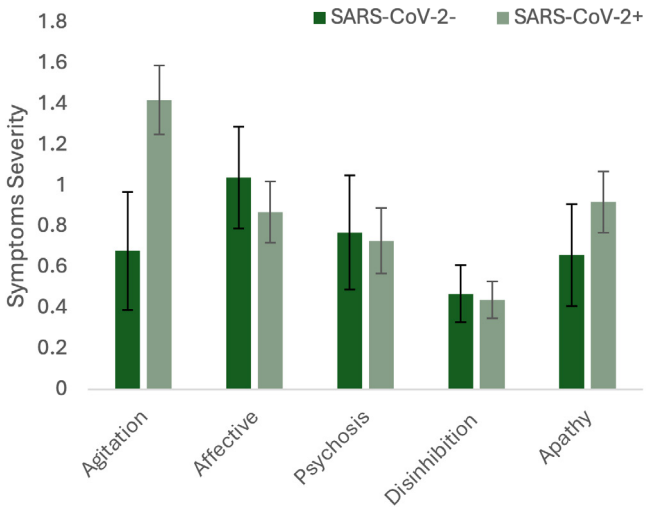

FIGURE 1. Neuropsychiatric symptoms as a function of SARS-CoV-2 status: the average score across the two time points is depicted for each factor of the Neuropsychiatric Inventory; error bars represent standard errors of the mean

infection had a slight increase in nurse-rated agitation behaviors at an average of 480.49 (SD= 228) days post infection, this effect was no longer significant after accounting for potential confounders, including age, sex, history of psychiatric disorder, neurocognitive status, and multimorbidity. However, SARS-CoV-2 infection was associated with a greater number of psychotropic medication prescriptions, in particular antidepressant medication. These results suggest that COVID-19 may promote psychotropic medication prescription that contributes to polypharmacy in frail older adults living in a long-term care facility.

Using a nurse-rated neuropsychiatric assessment, older adult residents who had a SARS-CoV-2 infection reported more agitation compared to those who had never been infected by the coronavirus. However, this difference was no longer significant after accounting for key confounding factors. This contrasts with other reviews highlighting protracted neuropsychiatric symptoms in a subset of individuals after a SARS-COV-2 infection.[3] However, in line with the present findings, no difference in psychiatric disorders was observed between COVID-19 and non-COVID-19 patients in a study using electronic medical records of hospitalized geriatric patients in Sweden.[17] A survivor bias or the high uptake of vaccine boosters may have attenuated COVID-19 post-acute neuropsychiatric symptoms in the present sample.[18]

A number of studies have documented an increase in psychotropic medication use in long-term care facilities. In a study of 747 nursing home residents, a significant increase in antipsychotic medication use was noted during the COVID-19 pandemic compared to the pre-pandemic period,[11] despite unchanged prevalence of neuropsychiatric symptoms.. A similar increase in antipsychotic prescription use was noted in Canadian nursing homes.[19,20] Other studies noted that antidepressant medication prescription showed the greatest increase among nursing home residents during the COVID-19 pandemic.[10] However, these prior studies did not tease apart the impact of the confinement measures from the effects of SARS-CoV-2 infection. The present results indicate that, in spite of the non-significant changes in neuropsychiatric symptoms, residents who had a SARS-CoV-2 infection had a greater number of psychotropic medication prescription, particularly antidepressant and antipsychotic medication, compared to SARS-CoV-2 naïve residents.

SARS-CoV-2 infection might have triggered acute delirium, agitation, and mood-like symptoms.[21] Antipsychotic medications are often used as a first-line approach for managing neuropsychiatric symptoms associated with infection-related delirium states and agitation. Antidepressant medication may have been used to treat apathy symptoms frequently seen during the COVID-19 pandemic.[8] The psychotropic medication prescription in response to acute or short-term neuropsychiatric symptoms associated with SARS-CoV-2 are unlikely to undergo deprescription, particularly in the context of ongoing pandemic-related health service provision challenges seen in long-term care facilities. The acute infection symptoms may then lead to long-term polypharmacy among these frail older adults individuals. Importantly, psychoactive polypharmacy is associated with increased risk for falls, impaired cognition, stroke, and death among older adults.[22–24]

In the present sample, psychoactive polypharmacy, defined as three or more psychotropic medication, was present in 17.4% of the residents. This prevalence, consistent with other long-term facilities in Canada,[25] highlights the need for deprescribing strategies and the use of nonpharmacological strategies to deal with neuropsychiatric symptoms in residents of long-term care facilities.[26] The Optimizing Practices, Use, Care, and Services-Antipsychotics (OPUS-AP) study in Quebec showed that deprescribing was successful in 85.5% of residents.[27] The present study suggest that it might be prudent to reassess the need for psychotropic medication prescribed in response to acute SARS-CoV-2 symptoms among older adults residing in nursing homes.

These results have to be interpreted in light of the study limitations. At each wave of the COVID-19 pandemic, the number of residents without SARS-CoV-2 infection diminished cumulatively. As a result, our non-infected group was relatively small (n = 28), potentially limiting our ability to detect significant differences between groups in neuropsychiatric symptoms. Furthermore, given that data were collected on average 16 months following SARS-CoV-2 infection, this study might not have captured short-term changes in neuropsychiatric functioning post-infection. Also, the number of residents with repeated SARS-CoV-2 infections was too small to draw meaningful conclusions on the impact of repeated reinfections on neuropsychiatric symptoms. Furthermore, although the study included a longitudinal assessment in neuropsychiatric symptoms, changes in psychotropic medication and frequency of medication use were not assessed. Particularly, it was not possible to determine whether the psychotropic medication prescription was received after the SARS-CoV-2 infection or whether the use of *pro re nata* medication increased following COVID-19.

CONCLUSION

SARS-CoV-2 infection was associated with increased psychotropic medication prescription in older adult residents living in long-term facilities. A SARS-CoV-2 infection may contribute to psychoactive polypharmacy in nursing homes. Clinicians should reassess the need for psychotropic medication prescribed following a SARS-CoV-2 infection, and implement deprescribing strategies when appropriate.

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CONFLICT OF INTEREST DISCLOSURES

We have read and understood the *Canadian Geriatrics Journal*'s policy on conflicts of interest disclosure and declare the following interests: DCV has received clinical trial support from Cidara Therapeutics, CSL Behring, and Janssen Pharmaceuticals; has served on advisory boards for CSL Behring, Novartis Canada, and UCB Biosciences; has received speaker honoraria from CSL Behring and Merck Canada; and has a patent application pending (Electronic Filing System ID: 40101099) and a report of invention to McGill University (Track code: D2021-0043), both unrelated to this work. All other authors declare no competing interests.

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