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Original Research

Neuropsychiatric Effects of COVID-19 Pandemic on Alzheimer's Disease: A Comparative Study of Total and Partial Lockdown

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Abstract

Objectives: Coronavirus disease 2019 (COVID-19)-related lockdown may have a negative effect on the neuropsychiatric status of Alzheimer's disease (AD) cases. In this study, it was aimed to find future implications by evaluating the neuropsychiatric conditions of AD cases during total and partial lockdown periods.

Methods: It is a prospective, cross-sectional, and multicenter study that includes AD cases which have been followed for at least 1 year by outpatient clinics from different regions of Turkey. Sociodemographic data, comorbidities, mobility, existence of social interactions, clinical dementia rating (CDR) scale, and neuropsychiatric inventory (NPI) for total and partial lockdown were questioned by the caregivers with the help of case files of the patients.

Results: A total of 302 AD cases were enrolled to the study (mean age: 78±8 years, mean duration of education: 5.8±9 years). The total comorbidity ratio was found to be 84%, with the most frequent comorbidity being hypertension. The mean NPI score was 22.9±21 in total lockdown and 17.7±15 in partial lockdown, which is statistically significantly different. When lockdown periods

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were compared with the total scores of NPI scores according to gender, existence of social interactions, mobility, and comorbidities were found higher in the total lockdown than the partial lockdown. When switching from total lockdown to partial lockdown, the presence of comorbidities, mobility, and CDR were found to be factors that had a significant effect on NPI scores. In regression analysis, CDR score was found as the most effective parameter on the neuropsychiatric status of AD cases for both lockdown periods.

Conclusion: When lockdown-related restrictions were reduced, the neuropsychological conditions of AD cases were significantly improved. Lockdown rules should be considered with these data in mind.

Keywords: Alzheimer's disease, Coronavirus, Lockdown, Neuropsychiatric status, Pandemic

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In December 2019, an outbreak of pneumonia with unknown origin began and it rapidly spread overall the world. This disease was named as coronavirus disease 2019 (COVID-19).[1]

COVID-19 has more severe negative effects on older people, especially those who have comorbidities including hypertension, cardiovascular disease, and diabetes mellitus. Patients who have Alzheimer's disease (AD) also have an additional risk for infection, because of the difficulties in following prevention and social isolation rules.[2] Furthermore, lockdown-related social isolation may affect their cognitive and psychiatric status negatively.[3] Neuropsychiatric findings of AD patients progress with cognitive decline and agitation, psychosis, aggression, sleep disturbance, anxiety, and increased irritability.[4-6]

In Turkey, the first case of COVID-19 was confirmed on March 11, 2020. People over 65 were under total lockdown at whole country from March 21 until June. Thus, their mobilization and social interactions were restricted during this period. On June 1, enforced quarantine restrictions were relaxed and were combined with strict rules of hygiene (partial lockdown period).

"Total lockdown" here refers to people's restriction of movement except for those movements deemed as "necessary" such as doctor's appointment, obtaining food from shops within walking distance. A general curfew was in place and intercity travel was prohibited. In partial lockdown, permission was given to go out into the neighborhood during limited hours.[7]

Studies showed that nearly 50% of dementia patients have some degree of depression[8] and around 20–30% of them have a major depressive disorder.[9,10] It has been suggested that about 25%–71% of them experience anxiety. Moreover, psychosis is estimated to occur among as many as 50% of patients with dementia.[11] These high levels of neuropsychiatric symptoms will naturally increase in patients with AD who are forced to live indoors. Therefore, it is important to evaluate the neuropsychiatric findings of AD patients that may arise as a result of being restricted to living indoors.

This study aimed to investigate the neuropsychiatric effects that can be seen in AD patients during the total and partial lockdown periods of the COVID-19 pandemic.

Methods

Study Design and Participants

This study is a prospective, cross-sectional multicenter study with AD cases at outpatient clinics. The participants were from different regions of Turkey and were being "followed" for at least 1 year. All data obtained were provided by the caregiver's answers during the examination of patients at the end of May for total lockdown and at the end of August for partial lockdown. The patient's primary caregivers were asked to respond to a number of sociodemographic questions, such as duration of education, comorbidities, existence of social interactions (patients with/without visitors), mobility (mobile or immobile), and medications. Furthermore, hypertension, diabetes mellitus, heart disease, cerebrovascular disease, cancer, kidney failure, chronic obstructive pulmonary disease, and hypothyroidism were explored as comorbidities in the files of dementia outpatient clinic patients. Patients who were able to walk outside the home at least once every week before the lockdown were considered mobile. Patients who were unable to go for a walk were immobile. Immobile patients with primary psychiatric disease and for orthopedic reasons were not included in the study group.

In addition, their clinical dementia rating (CDR) scale was evaluated and neuropsychiatric inventory (NPI) questionnaires were applied. None of the patients included in the study had COVID-19 during the data collection period.

Patients were classified according to years of education (illiterates, 1–5 years, 6–12 years, and ≥13 years). Age of patients was evaluated into four categories (55–70 years, 71–80 years, 81–90 years, and ≥90 years).

AD diagnosis was made according to National Institute of Neurological and Communicative Disorders and Stroke-AD and Related Disorders Association (NINCDS-ADRDA) criteria.[12] Information about the research was given to the caregivers of all patients. The study protocol and ethical procedures were approved by the ethics board of our institution. Patients or their legal guardians provided informed signed consent. The Ethics Committee acceptance number is 2020/900/54.

Instruments of Measurement

The NPI

NPI is a valid and reliable tool in the Turkish language[13] and it is commonly used for the evaluation of behavioral changes in neuropsychiatric practice. NPI is used to evaluate 12 behavioral areas that are commonly affected in patients with dementia. These 12 behavioral areas include delusions, hallucinations, agitation, depression, anxiety, euphoria, apathy, disinhibition, irritability, aberrant motor behavior, night-time behavior, appetite, and eating disorder. If one of the answers is "yes," then the frequency and severity of these behaviors are also questioned. The maximum score is 144 and high scores indicate poor neuropsychiatric conditions.[14]

The CDR Scale

CDR scale includes six domains: Memory, orientation, judgment and problem-solving, community affairs, home and hobbies, and personal care. Data were collected through semi-structured interviews and each area was scored on a 5-point scale.[15] In determining the stage of the disease, the most important domain is memory and other domains are secondary. If the scores from three different domains are the same as the memory score, then the patient is given that score. If the three secondary domains are given a greater score than the primary memory score, then the CDR score is given regarding secondary categories. If three secondary domains are given lower scores than the primary memory score, then the CDR score is given regarding the memory score. Staging of dementia is based on memory and secondary domains: 0 (no dementia), 0.5 (questionable dementia), 1 (mild dementia), 2 (moderate dementia), or 3 (severe dementia).[16]

Statistical Analysis

Statistical analysis was performed using SPSS version 16.0 (IBM, Chicago, IL, USA). Descriptive statistics were applied to demographic and questionnaire data. The results were explained as the mean±standard deviation (SD) for quantitative data and percentage for categorical data. NPI scores, gender, existence of social interactions, mobility, and CDR score of the patients for total and partial lockdown were compared with a repetitive two-way ANOVA test. Correlation analyses of other parametric variables were performed with the Pearson correlation coefficient. A multiple linear regression analysis was used to predict the factors affecting NPI score in total and partial lockdown. P≤0.05 is statistically significant.

Results

A total of 302 AD cases (n: 184 females/118 males; mean age: 78±8 years, mean duration of education: 5.8±9 years) were enrolled to the study. The total comorbidity ratio was found to be 84%, with the most frequent comorbidity being hypertension. All comorbidities are shown in Figure 1.

The NPI score was detected as X = 22.9±21 in total lockdown and as X = 17.7±15 in partial lockdown and F value was calculated as F (1,301) = 265,16 p<0.05.

When lockdown periods were compared with the total scores of NPI according to age stage, education level, mobility, comorbidities, and CDR were found higher in the total lockdown than the partial lockdown (Fig. 2). The impact of age was found to be statistically significant when we compared the NPI scores between total lockdown and partial lockdown. NPI scores were higher in both lockdown periods in elderly decades compared to other decades. In the partial lockdown period, NPI scores were significantly lower in all age decades (Table 1).

The presence of comorbidities and the mobility rate was found to be the factors that impact the NPI scores after transition from the total to partial lockdown (Table 1). Patients with chronic disease had statistically significantly higher NPI scores during both lockout periods than those without

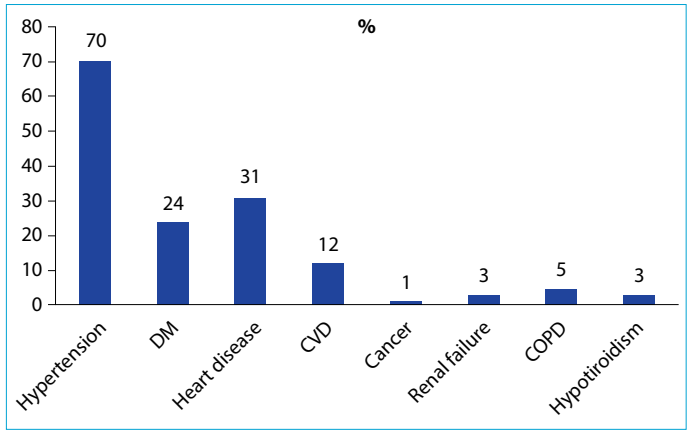

Figure 1. The frequency of comorbidities. DM: Diabetes mellitus, CVD: Cerebrovascular disease, and COPD: Chronic obstructive pulmonary disease.

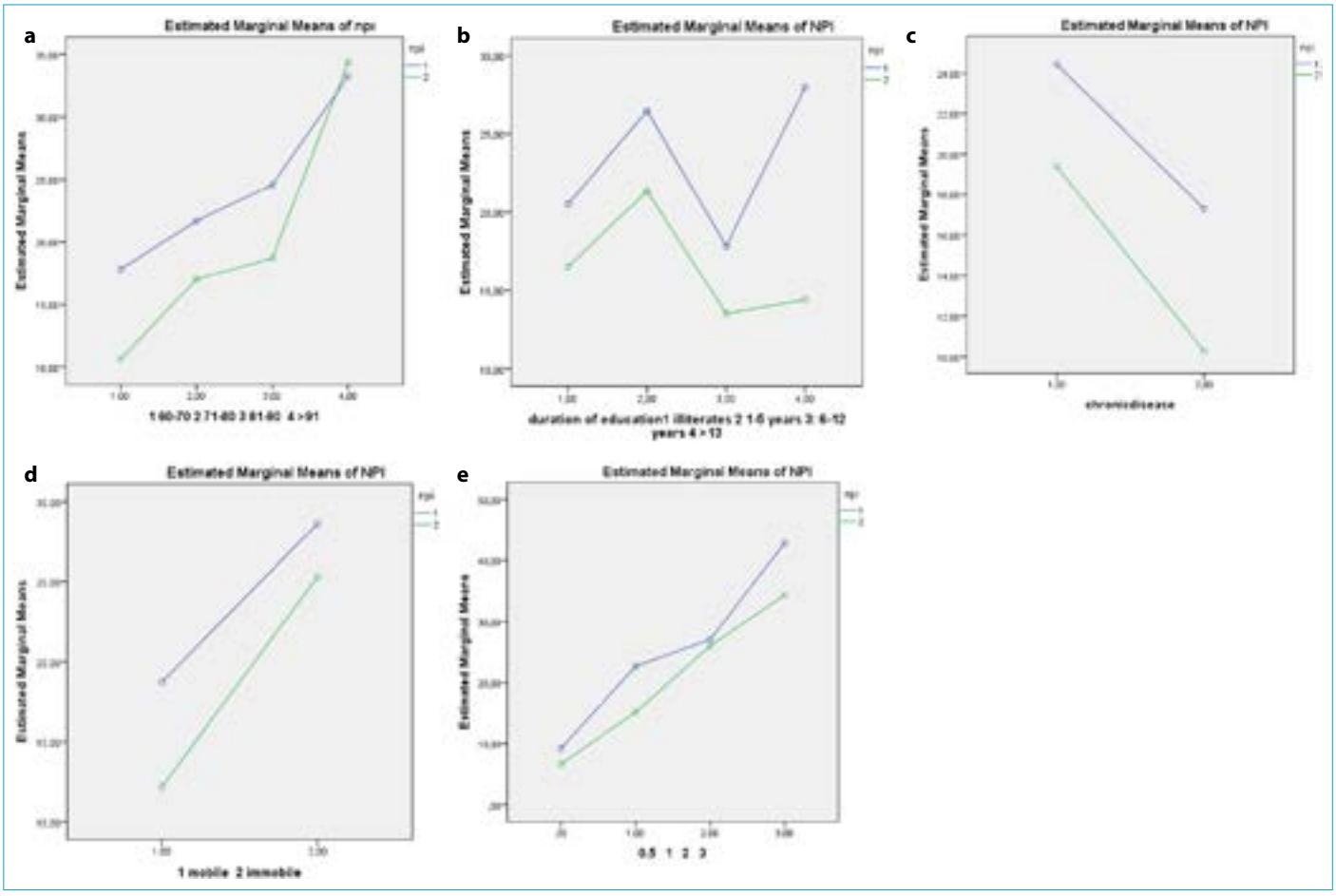

Figure 2. Relationship between NPI 1 - 2 scores and other risk factors. When NPI total scores were compared according to age stage during quarantine periods, a statistically significant difference was found between the ages of 60-90 and >90 years **(a)**. NP2 was found to be signifi-cantly lower in those with an education level above 13 years; however, there was a borderline statistical difference **(b)**. The NP1 scores of the group with comorbidities were found to be significantly higher **(c)**. When mobile and immobile patients were compared in terms of NP scores, NP1 scores were found to be significantly higher **(d)**. CDR scores were significantly effective on NP scores **(e)**.

NPI 1: The score of neuropsychiatric inventory in total lockdown; NPI 2: The score of neuropsychiatric inventory in partial lockdown; CDR: clinical dementia rating.

chronic disease. NPI scores decreased considerably during the shift to partial lockdown in both groups with and without comorbidities. Similarly, the NPI scores of those who remained immobilized during both lockdown periods were much higher. During the shift to partial lockdown, the NPI scores of both mobile and immobile patients decreased significantly (Table 1).

According to CDR scale, 71 participants were clustered in Stage 0.5; 132 participants were participants in Stage 1; 61 were in Stage 2; and 38 participants were Stage in 3. The total NPI score increased parallel to the dementia severity level according to the CDR scale. In the total lockdown period, the NPI score was higher for all stages of dementia than the partial lockdown period.

After transition from total lockdown to partial lockdown, CDR was found to be an effective factor on NPI scores (Table 1). In the correlation analysis, it was found that the total NPI scores increased only with age in the total lockdown period ($r = 0.18$; $p=0.007$); in the partial lockdown, NPI scores were correlated with age ($r = 0.21$; $p=0.001$) and decreased with duration of education ($r = –0.13$; $p=0.04$).

Each item of NPI was found higher in the total lockdown when compared to the partial lockdown. Higher scores were found in night-time behavior, depression, and delusion in total lockdown period, while high scores in the partial lockdown period were observed in night-time behavior, depression, and appetite, respectively (Table 2).

Pharmacotherapy of AD cases consisted of 71% cholinesterase inhibitors (donepezil and rivastigmine) and 39% glutamate antagonist (memantine). Thirty percent of patients received antidepressants and 34% received antipsychotic drugs. Statistical analysis could not be made between drug use and neuropsychiatric status due to polypharmacy.

In multiple regression analysis, the most effective factor

Table 1. Evaluation of the effect of other factors on NPI in total and partial lockdown with two way Anova.

	n	The score of NPI (total lockdown) Mean±SD	The score of NPI (partial lockdown) Mean±SD	F	p	Eta-squared (η2)
Gender						
Female	184	23±21	16±14	F (1,300)	.78	.00
Male	118	22±21	19±17	.077		
Age						
60-70	52	17±16	11±10	F (1,298)	.003	.04
71-80	111	21±20	17±16	4.857		
81-90	117	24±23	18±17			
>90	22	33±22	34±26			
Duration of education						
Illiterates	82	19±18	16±15	F (1,298)	.056	.02
1-5 years	128	27±23′	22±21′	2.55		
6-12 years	62	18±17′	13±12′			
≥13	30	24±19	14±13			
Existence of social interaction						
With visitors	133	24±21	16±14	F (1,300)	.88	.00
Without visitors	169	22±20	19±17	.023		
Existence of comorbidity						
With comorbidities	249	24±23	19±17	F (1,294)	.019	.01
No comorbidities	53	17±14	10±8	5.589		
Mobility of patient						
Mobile	172	18±16	12±11	F (1,299)	.0001	.06
Immobile	130	28±25	25±22	22.046		
CDR						
0.5	71	9±8	7±5	F (1,298)	.0001	.18
1	132	22±21	15±12	22.446		
2	61	27±22	26±22			
3	38	42±23	34±21			

NPI: Neuropsychiatric inventory.

Table 2. Comparison in mean item points of neuropsychiatric inventory (NPI) during total and partial lockdown periods. p-value ≤ 0.05 is statistically significant

NPI Item	The score of NPI (Total lockdown)		The score of NPI (Partial lockdown)	
	Mean±SD	≥1 (%)	Mean±SD	≥1 (%)
Delusions	2.7±3	49	1.4±3	51
Hallucinations	2.3±3	60	1.5±2	49
Agitation/Agression	2.1±3	61	1.1±2	48
Dysphoria/Depression	3±3	60	1.9±2	64
Anxiety	2.5±3	49	1.3±1	51
Euphoria/Elation	0.3±0.9	24	0.4±1	25
Apathy/Indifference	2.3±3	40	1.5±2	39
Disinhibition	1.4±2	35	0.9±2	36
Irritability/Lability	1.8±3	40	1±2	39
Aberrant Motor	0.8±1	30	0.5±2	28
Nighttime Behavior	4±3	61	2.5±3	65
Appetite /Eating	2.6±3	46	1.6±2	50
Total	22.9±21		17.7±15	

on NPI during the total lockdown period was found to be CDR when compared with other parameters such as age, comorbidities, and mobility (Table 3). During partial lockdown period, mobility was also found to be efficient besides CDR score.

Discussion

In this study, the aim was to investigate the neuropsychological effects of total and partial lockdown in patients with AD during the COVID-19 pandemic. In our study, advanced age, the existence of comorbid conditions, mobility, and CDR were the most influential factors on NPI ratings during the transition from a total confinement to a partial lockdown. The influence of visitor presence, gender, and education level was not significant.

In the previous studies, it was found that men were less affected than women in the lockdown period. Cultural differences might be responsible for this.[17] In our study, no neuropsychiatric differences were found between men and women – both in the total and in the partial lockdown periods.

Considering the psychological effects of lockdown, it was found that a high level of education provides some protection against anxiety and depression.[18] Our study showed that AD patients with a high education level had milder negative neuropsychiatric findings during the partial lockdown period. However, there was no relationship between education level and neuropsychiatric findings during total lockdown. This finding might be related to the decrease of restrictions in the partial lockdown period. In addition, more educated AD patients might have an opportunity to improve their lifestyle in partial lockdown.

The benefits of physical activity are known to be achieved by stimulating muscle contraction, reducing systemic inflammation, oxidative stress, sarcopenia, and frailty. Social and physical restrictions have been found to cause negative results, especially in elderly populations with comorbid diseases.[19,20] In our study, it was found that patients with comorbidity and immobility in both partial and total lockdown periods were neuropsychologically worse than other patients.

Sepúlveda-Loyola et al. found that socially active older women had fewer disabilities and fewer comorbidities.[21] In the COVID-19 pandemic, it has been determined that physical activity and exercise are an effective treatment for both mental and physical health in most chronic diseases, especially cardiovascular diseases.[22] In our study, the effectiveness of mobility and comorbidity on neuropsychiatric symptoms in dementia patients during the pandemic period was studied. These two factors were significant factors in neuropsychiatric findings during both lockdown periods, and their positive effects were more significant during the transition to partial lockdown.

In a study conducted with dementia patients during the COVID-19 pandemic in Italy, it was stated that the lockdown has negative effects on behavior and mood in mild-to-moderate dementias, but not in very advanced dementias.[23] In our study, we have found that neuropsychiatric deterioration of the severe group was higher than the mild and moderate groups according to CDR. However, even in these patients, significant neuropsychiatric improvements were observed when switching to partial lockdown. Increasing caring opportunities may decrease caregiver anxiety and this positive situation may reflect on their patients' life during the partial lockdown period.

An increase in psychological symptoms was noted in 1/3 of cognitively normal individuals in lockdown.[24] Sepúlveda-Loyola et al. evaluated 10 descriptive cross-sectional studies during the pandemic period. It was found that the most affected parameters were sleep disturbance and depression in a comprehensive group formed using the information of 20,069 people, including the elderly.[19] In addition, the rate of depression was reported to be 47% and the anxiety rate 8–49% in the previous pandemics.[25,26] In the general population, it was found that the COVID-19 lockdown was associated with changes in quantity and quality of sleep, deprivation in night-time sleep, shifts in the sleep cycle, and depressive symptoms.[27] A study by

Table 3. Summary of regression analysis for variables predicting neuropsychiatric inventory score (NPI). Dependent variable: NPI total and partial lockdown scores are R2=0.15 and R2=0.20, respectively

	B	SD	β		B	SD	β
NPI (total lockdown)	11.09	7.14		NPI (partial lockdown)	0.27	6.3	
Age stage	1.48	1.20	0.05	Age stage	2.62	1.44	0.09
Comorbitidies	-6.53	3.7	-0.09	Comorbitidies	-7.28	3.30	-0.11
Mobility	1.24	1.02	0.02	Mobility	5.29	2.64	0.11
CDR	10.78	1.79	0.35	CDR	9.17	1.59	0.33

SD: standard deviation; CDR: Clinical Dementia Rating.

Lara et al. showed that the most frequent neuropsychiatric symptoms in patients with dementia were agitation, apathy, and aberrant motor activity during the 5 weeks of lockdown.[28]

NPI, the terms "depression" and "dysphoria" are used when the patient looks unhappy or speaks unwilling. Night-time behavior is described as waking frequently, wandering, feeling anxiety at night, getting up early in the morning, and sleeping excessively during the day.[14] Our results suggested that the most affected parameters of the neuropsychiatric profile were dysphoria/depression and night-time behavior. The results of our study, which include AD patients, are similar to the results of studies including the general population.

In the study of Van Maurik et al., half of the caregivers stated that cognitive decline accelerated in 53% of their patients. However, more than half of the caregivers had a high caregiver burden.[29] Assessment of cognitive decline will not be objective as caregiver burden increases. In addition, cognitive decline can be masked by neuropsychiatric findings.

The pandemic causes social isolation during the lockdown. Different types of physical exercise programs on online platforms showed positive results.[30] Balance, coordination, mobility, and cognitive exercises are especially important for these patients. In the future, it will be necessary to perform online exercise modalities appropriate to the severity of the dementia and to the physical capacity of AD patients.[22]

One of the limitations of our study was that it does not contain an evaluation of caregivers. The Turkish version of the NPI was filled out by the caregivers for the total and partial lockdown periods in the outpatient clinic.

Conclusion

Despite the restrictions, a more intensive social and physical activity in patients during the partial lockdown period positively affected the neuropsychiatric status.

Partial removal of severe restrictions in partial lockdown had a positive effect on patients in terms of neuropsychiatry. The role of physical activity and social interaction in this should not be denied.

In a lockdown period, personalized support programs on online platforms should be organized and maintained for the needs both of patients and caregivers.

Disclosures

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Ethics Committee Approval: The study protocol and ethical procedures were approved by the ethics board of our institution. Patients or their legal guardians provided informed signed consent. The Ethics Committee acceptance number is 2020/900/54.

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