

The Effect Of The Covid 19 Pandemic And Pandemic-Induced Isolation On The Standardized Minimental Test Result in Patients With Dementia

Demans Hastalarında Covid 19 Pandemisinin ve Pandemi Kaynaklı İzolasyonun Standardize Edilmiş Minimental Test Sonucuna Etkisi

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Abstract

Background: Social interaction is important to maintain healthy life for both old and young. However it is not more important for elderly. In this study, we aimed to evaluate the effect of COVID-19-related lockdown restrictions on cognitive functions in individuals with mild cognitive impairment (MCI) or Alzheimer's disease (AD) living in Balikesir city center and rural areas.

Methods: The study included people aged 50 years and older who were diagnosed with MCI or AD previous to lock down. The volunteers who lived in Balikesir city center were considered to be exposed to strict isolation during the COVID-19 pandemic while others who lived in villages were not. The Standardized Mini Mental State Examination scores (MMSE) of these two groups of patients obtained before and after the COVID-19 pandemic were compared.

Results: A total of 64 patients were included. Fifty of them had AD and thirty-six of these volunteers were kept in strict social isolation while the remaining 14 were not. Fourteen volunteers had MCI diagnosis. Ten of them lived in strict social isolation the other four were not. MMSE scores were significantly reduced among subjects diagnosed with AD in strict social isolation ($p < 0.001$). However there was no significant change in participants diagnosed with MCI during the lock down period (p value=0.132).

Conclusion: There is a statistically significant negative effect of pandemic-related strict social isolation on cognitive functioning of AD patients. MCI patients seemed unaffected however this result may be due to a small number of patients with MCI.

Keywords: Dementia, Mild cognitive impairment, Alzheimer's disease, COVID-19 infection, social isolation

Öz

Arka plan: Sosyal etkileşim hem yaşlılar hem de gençler için sağlıklı yaşamın sürdürülmesinde önemlidir. Ancak yaşlılar için daha da önemlidir. Bu çalışmada Balikesir şehir merkezi ve kırsal kesiminde yaşayan hafif bilişsel bozukluğu (MCI) veya Alzheimer hastalığı (AD) olan bireylerde, COVID-19 kaynaklı karantina kısıtlamalarının bilişsel işlevler üzerindeki etkisini değerlendirmeyi amaçladık.

Yöntemler: Çalışmaya, karantinaya alınmadan önce MCI veya AD tanısı konulan 50 yaş ve üzeri kişiler dahil edildi. Balikesir kent merkezinde yaşayan gönüllülerin Covid-19 salgını sırasında sıkı izolasyona maruz kaldığı, köylerde yaşayanların ise bu durumla karşılaşmadığı kabul edildi. Bu iki hasta grubunun, COVID-19 salgını öncesinde ve sonrasında elde edilen MMSE puanları karşılaştırıldı. .

Sonuç:Toplam 64 hasta dahil edildi. Bunlardan 50'sinde AD vardı ve bu gönüllülerden 36'sı sıkı sosyalizasyonda iken geri kalan 14'ü değildi. On dört gönüllünün MCI tanısı mevcuttu. Bunlardan 10'u sıkı sosyal izolasyona tabi iken kalan dördü sosyal izolasyonda değildi. Katı sosyal izolasyonda AD tanılı hastaların MMSE puanları anlamlı düzeyde azaldığı görüldü ($p<0,001$). Ancak karantina döneminde MCI tanılı hastalarda anlamlı bir değişiklik gözlenmedi ($p=0,132$).

Yorum: Pandemi kaynaklı sıkı sosyal izolasyonu Alzheimer hastalarının bilişsel işlevleri üzerinde istatistiksel olarak anlamlı bir olumsuz etkisi vardır. Her ne kadar MCI hastaları etkilenmemiş görünüyor da ancak bu sonuç MCI hasta sayısının az olmasından kaynaklanıyor olabilir.

Anahtar Kelimeler: Demans, Hafif bilişsel bozukluk, Alzheimer hastalığı, COVID-19 enfeksiyonu, sosyal izolasyon

Introduction

The population infected by COVID-19 has passed 60 million over a year worldwide (1). Our knowledge of the disorder related with COVID-19 infection has gradually increased. However, we do not have a specific antiviral treatment that is effective yet (2, 3). The main mortality reason of the infection is due to an unbalanced inflammatory response that damages the respiratory system quickly (4).

The growing evidences determined that the neurologic manifestation of COVID-19 infection is apparently a result of cytokine storm that is triggered by the virus itself, not due to its neuro-invasive feature (5). The acute deterioration in neuro-functional capabilities was mostly recognized among the severely ill COVID-19 cases (6). On the other hand, dizziness, anosmia, headache and altered consciousness are the most common reported neurological symptoms (7).

Cognitive decline may vary from healthy aging to minimal cognitive impairment (MCI) or Alzheimer's disease (AD). The gradual decrease in cognitive functions may be halted or reversed at some extend among even AD subjects (8). Physical activity and social contact may be as important as under-controlling high blood pressure or hypercholesterolemia for healthy neuro-cognitive functions (9). However, against all of the ethical discussions, lock-downs were crucial to stop the spread of COVID-19 virus at some point and widely announced by the governments worldwide (10,11).

In this observational study, we aimed to investigate the impact of the strict lock-downs on the cognitive functions among the people that were diagnosed with MCI or Alzheimer's disease.

Material- Method

This retrospective observational clinical study included people who were aged 50 years and older with the diagnoses MCI or AD previous to lock down in Balıkesir Province. The volunteers who lived in Balıkesir city center were considered to exposed to strict isolation during the COVID-19 pandemic while others who lived in villages did not. Because the participants

who lived in the city center could not socialize with anyone but their immediate family members . They had to stay at home unless they require medical help. However in rural areas which meant villages in which inhabitants were not isolated as the city dwellers. They could go out to the orchards or farms, could speak the neighbors over the fence So that we think those people who lived in city center and villages constituted two different groups according to exposure of strict social isolation. MMSE of these two groups of patients obtained before and after the COVID-19 pandemic were compared (12).All of the participants who admitted to the neurology out-patient clinic at Balıkesir University Medical Faculty Hospital for a follow up visit on September and October 2020 were included into the study. The physical examinations and MMSE were all performed by a single neurologist (13). The investigator was unaware of the pre-COVID-19 MMSE results while she was performing the post-COVID-19 ones. The forced social isolation that we studied on lasted almost 3.5 months (from March 21st, 2020 to July 1st, 2020) in Turkey (9,14).

The participants who were diagnosed with COVID-19 infection or recently hospitalized for any reason during the study period were excluded from the study. The ones without a MMSE_before COVID-19 pandemic at the same health center and the participants with any possible cause that may alter the cognitive function (e.g. vitamin B12 deficiency, hypothyroidism, systemic infections like pneumonia or urinary system infections) were excluded from the study. The subjects with an active cerebrovascular disease or any other neurological disorder which may result in cognitive impairment including delirium or new-onset major depressive disorder history in the last six months were also excluded from the study. The subjects with prominent visual or hearing impairments were not included in to the study as well.

The demographic features of the cases such as gender and age, laboratory analyses were obtained from the hospital's digital archive. All procedures performed in studies involving human participants were in accordance with the ethical standards of the Institutional Research Ethics Committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The ethical approval of the study was obtained from the Ethics committee of Balıkesir University Faculty of Medicine. (Date: 14/10/2020, Decision Number: 2020 / 172).

Statistics

Statistical analyses were performed by using SPSS 23.0 (IBM Corp., US). Data were presented as median with minimum and maximum because the values were not statistically normal distributed based on Kolmogorov- Smirnov test. Kruskal- Wallis test and Mann-Whitney U test for post-hoc analysis were conducted for the non-parametric variables to analyze the difference between groups. For categorical values Chi-square test was used to compare the groups. $P<0.05$ was accepted for statistical significance.

Results

In our study, 64 patients were included, 50 of whom were diagnosed with AD and 14 with MCI. There was no difference in age between the groups; the mean age was 69.7(55-80) in MCI and 70.3(51-87) in AD. Thirty two (64%) of the volunteers diagnosed with AD were female, while there were 3 (21.4%) female volunteers diagnosed with MCI (Table 1). Participants with AD were divided into two groups according to the presence or absence of social isolation. Both groups were similar in terms of gender and age distribution ($p = 0.377$ and $p = 0.440$, respectively). The socially isolated MCI group and the non-isolated groups were also similar in terms of gender and age distribution ($p=0.330$ and $p=0.064$, respectively).

Table 1. Baseline demographic features of the subjects included into the current study.

	MCI N: 14)	AD: (N: 50)	P value
Sex, male, N (%)	11 (78.6)	18 (36)	0.005
Sex, female, N (%)	3 (21.4)	32 (64)	0.005
Age, median, years old (min-max)	69.7 (55- 80)	70.3 (51- 87)	0.802
MMSE, median (min- max) (pre-COVID)	26.5 (23- 29)	16 (5- 27)	<0.001
MMSE, median (min- max) (post-COVID)	26 (23- 28)	15 (3- 24)	<0.001

As seen in Table 2, social isolation had a significant effect on the reduction of MMSE in the AD group compared to the MCI group.

Table 2. The decline in MMSE in MCI and AD groups according to the presence of social isolation.

	Presence social isolation N (%)	MMSE median (min-max) (pre-COVID)	MMSE media (min-max) (post-COVID)	P
MCI Number: 14	Yes, 10 (71.4)	26.5 (24- 29)	26 (23- 28)	0.132
	No, 4 (28.6)	26.5 (23- 28)	26.5 (23- 28)	NA
AD Number: 50	Yes, 36 (72)	17.5 (8- 21)	15 (8-21)	<0.001
	No, 14 (28)	15.5 (5- 27)	14.5 (3-24)	0.026

On the other hand, although the decrease in MMSE was seen even in the group without social isolation, both the amount of decrease in MMSE and the percentage decrease in MMSE were more pronounced in the socially isolated group (Table 3).

Table 3. The impact of social isolation on the decline of MMSE among Alzheimer's disease group.

Alzheimer's disease (N: 50)	Without social isolation, N: 14	With social isolation, N: 36	P value
The amount of decrease in MMSE median (min- max)	0.5 (0.0- 2.0)	2.2 (-1.0- 8.0)	0.007
The percentage decrease in MMSE median (min- max)	%4.0 (0.0- 18.1)	%14.5 (5.2- 58.3)	0.011

Discussion

Choline esterase inhibitors such as rivastigmine, donepezil and galantamine have been used for treating AD. Memantine which is an N-methyl-D-aspartate (NMDA) receptor antagonist is also used for AD treatment. However, their effects are very limited. So that supportive treatment and preventive measures are immensely important. (15). The cognitive impairment could be recognized almost 18 years before the exact AD diagnosis (16). AD, which presents with a gradual cognitive and functional decline, is affecting almost 24 million people all around the world, by a doubling rate every five years following the age of 65 (17). Patients with cognitive decline tend to develop some significant, life-altering behavioral and physiological symptoms as the severity of the underlying disease increases (18). Therefore, after the diagnosis of cognitive decline, regardless of the severity, the main aim of the treatment is to slowing down the decline in cognitive and functional features. Unfortunately, all of the attempts to protect the cognitive functions of those vulnerable subjects were put in jeopardy with COVID-19 pandemia restrictions. In this study, we were able to show the impact of a strict social isolation on a further cognitive deterioration of the subjects with AD. We could not find any other explanation for the alteration in MMSE score in AD patients with social isolation. As expected from the nature of AD, decline in MMSE score was also more prominent among -socially isolated AD subjects (Table 2).

The neuro-invasive character of COVID-19 and its' unbalanced immunologic activation were already determined (5). However, the social impact of the strict isolation has not been studied adequately. It was recently reported how much it could harm the mood of the general population (19). To protect the cognitive functions of the society, it is highly recommended to be physically isolated, but socially active. To maintain a daily routine, getting involved with technology to keep being socially active and doing regular exercises were widely suggested to reduce the harmful effect of social isolation (9, 20). However, as expected, as the severity of cognitive impairment increases, the capabilities of the people to follow those recommendations decrease. Furthermore, there is growing evidence regarding with an increasing rate of dementia seen after delirium (21). We should take it account that delirium is reported in almost one fourth of the COVID-19 infected patients (4- 7).

In order to show the likelihood of the cognitive decline under social isolation orders we mostly focused on the elderly patients with the diagnosis of MCI or AD who were not infected by COVID-19 virus clinically. It was not a surprise to find that the AD patients were affected from those restriction orders. More importantly, this harmful effect showed itself only after six months of social isolation and there was no other possible cause. Another issue is the severity of cognitive function. We may speculate that the less the cognitive defect the less the deterioration due to social isolation. However our MCI group is very small to reach this conclusion. Stratification of elderly people according to their mental status would be more informative in larger scale.

In the literature, it previously showed that social isolation was not only resulted in behavioral and physiological alteration in human, but also it increased anxiety level and impaired the cognitive functions in animal models (22). An important amount of data was collected during the mandatory quarantine practices due to SARS, MERS or H1N1 infections previously. Emotional exhaustion, anger, burnout, social insecurity, insomnia and eating disorders were not rare (23- 25). Furthermore, impaired ventral hippocampus, reduced volume of prefrontal cortex, altered corticosteroid response to stress due to the affected hypothalamic- pituitary- adrenal axis were defined in animal models (26, 27).

The recent studies shows the negative effects of strict social isolation on the psychosocial well being of individuals and society (28).

During the Covid-19 pandemic people had difficulty to keep cognitive functional capacity due reduced social interactions and reduced environmental stimuli.

The concerns about the possibility of contracting COVID-19 also caused serious problems. Our study presents informative data about the negative effects of strict social isolation on cognitive functionality of AD patients. Although the numbers are limited it suggests that the cognitive functions of MCI patients' cognitive functions were not seriously harmed during the lock down period.

The recent studies which searched the effects of pandemic over the patients and care givers did not directly addressed the cognitive function. However caregivers reported cognitive decline in 60% of patients(29).To overcome the restrictive measures deleterious effects use of technological devices are suggested. Implementing devices and educated caregiver into the everyday life of the patients especially in nursing homes might have some benefits.(30).

Limitations and future prospects

The MMSE is not sensitive enough to detect minor changes and have some other handicaps (31). In our opinion, the lack of a decrease in MMSE seen in MCI group could have been a result of the small number of subjects or the use of MMSE. We strongly encourage the other researchers to focus on this unique group too. Although the personal history of the included patients was negative for overt COVID-19 infection they did not have serologic confirmation. We did not use any index to assess the degree of social engagement of the subjects. Basically, the patients who lived in the countryside were accepted as not socially isolated group, because the social isolation restrictions were not effective in those regions. On the other hand, the volunteers who lived in the crowded cities were deeply exposed to the limitations. None of our cases were in long-term care facility or nursing home residents. Most of the subjects in the study were living with their immediate family members, and minority of them was residing with only their own partners.

The large size of pandemic caught the world unprepared. However the experiences may shed a light for future.

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