

## THE PREVALENCE OF DEPRESSION IN DEMENTIA SYNDROME

Sanja Tomasović<sup>1,2</sup>, Josip Sremec<sup>1</sup>, Jelena Koščak Lukač<sup>1</sup>, Marija Sedlić & Nataša Klepac<sup>3</sup>

<sup>1</sup>Department of Neurology, University Hospital "Sveti Duh", Zagreb, Croatia

<sup>2</sup>Medical School Josip Juraj Strossmayer University of Osijek, Osijek, Croatia

<sup>3</sup>Department of Neurology, University Hospital Centre Zagreb, Medical School University of Zagreb, Zagreb, Croatia

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### SUMMARY

**Background:** It is estimated that up to 90% of patients with dementia are affected by behavioral and psychiatric symptoms during the course of the disease. The aim of this study was to investigate the prevalence of depression in dementia and mild cognitive impairment (MCI), the use of benzodiazepines and antidepressants among them and the impact of former education on their cognitive decline.

**Subjects and methods:** In the study we have enrolled 100 patients with clinical diagnoses of either MCI or dementia, as was established by a single cognitive neurology subspecialist. All patients were assessed during their regular outpatient follow-ups in the University Clinical Center Zagreb, Croatia, in the period between November 2019 and March 2020. Using the patients' medical history the demographic data, disease characteristics, history of other diseases, use of medications, Mini-Mental State Examination (MMSE) and the data on radiological brain examinations were obtained. The statistical tests were used depending on the distribution of variables.

**Results:** In total, there were 34 patients diagnosed with dementia and 66 diagnosed with MCI. The diagnosis of depression before the onset of dementia or MCI was established in 11% and it has developed in further 20% after cognitive deterioration, which represents an increase of 81.81%. The total prevalence of depression in the study group is thus 31%. The proportion of patients taking benzodiazepines was 26% and antidepressants 17%. The MMSE scores were significantly lower in patients with Alzheimer's disease than in patients with vascular MCI or dementia. Generally, MMSE values correlated significantly with the duration of education.

**Conclusions:** Depression is a frequent accompanying disease of dementia that aggravates already complex clinical picture and greatly diminishes the quality of life of the patient. It is important to monitor changes in a patient's cognitive decline and presence of psychiatric symptoms in order to give medical professionals a better chance to alleviate the complex issues that arise during the management of this specter of diseases.

**Key words:** dementia - Alzheimer's disease - mild cognitive impairment - depression

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### INTRODUCTION

Dementia is a disease characterized by cognitive decline. It is assumed that by 2030 the number of people with dementia will reach 75 million. In 2015, the estimated economic cost of dementia was 818 billion dollars per year globally or 1.1% of global gross domestic product (World Health Organization 2017). Due to its rising prevalence and high economic cost, dementia represents a public health priority (Tomasović et al. 2016).

Psychiatric and behavioral symptoms are common among patients with dementia. It is estimated that up to 90% of patients with dementia are affected by behavioral and psychiatric symptoms during the course of the disease. These symptoms include hallucinations, delusions, agitation, aggression, depression, apathy and anxiety (Cerejeira et al. 2012). A study by Lyketsos et al. (2002) shows that apathy, depression and aggression are four-time more common in patients with dementia. Symptoms usually appear as episodes; some of them are found early in the course of the disease and some of them, such as hallucinations, delusions and aberrant motor behavior, appear in later stages (Lyketsos et al. 2000).

Lyketos et al. (2000) found that the most frequent psychiatric symptoms among patients with dementia are apathy (27%) followed by depression (24%), aggression and anxiety (24%). Patients with Alzheimer's dementia are less likely to have depression, but they commonly have apathy and they more often manifest delusions (Zhao et al. 2016). Delusions and hallucinations in Alzheimer's disease also predict cognitive and functional decline (Scarmeas et al. 2005). Psychiatric syndromes are less common in mild cognitive impairment than in dementia. The most common disturbances among patients with mild cognitive impairment (MCI) are depression, apathy and irritability (Lyketsos et al. 2002). A study by Zahinoor I et al. shows that the overall pooled prevalence of depression in patients with MCI is 32% (Zahinoor et al. 2017).

Psychiatric symptoms in dementia can be due to neurodegenerative disease itself, but they can also arise from former psychiatric disorders. Family history of psychiatric illness, uncontrolled pain and systemic illnesses increase the risk of development of psychiatric symptoms in dementia (Chiadi 2016).

On the other hand, depression, anxiety, bipolar disorder, schizophrenia and alcohol abuse are risk factors for dementia (Zilkens et al. 2014, Da Silva et al. 2013).

These disorders are connected to earlier onset of late-life dementia (Zilkens et al. 2014). Some studies show a two-fold higher risk for dementia in patients with depression. The risk for patients with depression and bipolar disorder is associated with the severity and frequency of symptoms and seems to be higher in men (Da Silva et al. 2013).

Adequate management of psychiatric symptoms is important because psychiatric symptoms contribute to caregiver stress and they are connected to faster progression of dementia and functional disabilities. Thus, they lead to earlier nursing home placement of the patients and higher morbidity (Chiadi 2016, O'Donnell et al. 1992, Beeri et al. 2002).

It is recommended to use low-dose selective serotonin reuptake inhibitors for treating patients with depression and dementia (Phan et al. 2019). Studies have shown that citalopram has few mid-side effects among patients with dementia and that it may approve agitation as well (Nyth et al. 1990, Pollock et al. 2002). Tricyclic antidepressants and other agents with significant anticholinergic effects should be avoided (Phan et al. 2019).

Benzodiazepines are often used in patients with dementia, especially among the institutionalized ones, even though there is little evidence of their efficacy in treating psychiatric symptoms in dementia (Phan et al. 2019). Furthermore, benzodiazepines are connected with worse cognitive decline and a higher risk of falls in patients with dementia (Defrancesco et al. 2015).

The aim of this study is to investigate the prevalence of depression in dementia and MCI, the use of benzodiazepines and antidepressants among patients with dementia and MCI, and the impact of former education on their cognitive decline.

## SUBJECTS AND METHODS

In this study, we have enrolled 100 patients with clinical diagnoses of either MCI or dementia, as was established by a single cognitive neurology subspecialist. All patients were assessed during their regular outpatient follow-ups in the University Clinical Center Zagreb, Croatia, in the period between November 2019 and March 2020.

Using the patients' medical history data within the hospital informatics system, we have obtained the demographic data, namely patient's age, sex and education duration in years. The disease characteristics such as duration, type of dementia (divided into Alzheimer's, vascular and mixed dementia), and the current Mini-Mental State Examination (MMSE) score were noted as well. The data on radiological brain examinations pertaining to evidence of multilobar vascular lesions or brain atrophy was obtained where available. The following data regarding the use of psychotropic medications was assessed: current use of benzodiazepine based medications, as well as the type(s) of benzodiazepines used, use of antidepressant medications and their type, and the use of neuroleptic drugs and their type and number. The current

usage of antedementia drugs was noted as well. The diagnosis of depression in medical history was included, divided into depression that occurred earlier in life and such symptomatology when it followed after the diagnosis of MCI or dementia. Prior medical history regarding arterial hypertension, diabetes mellitus and hyperlipidemia was noted as well.

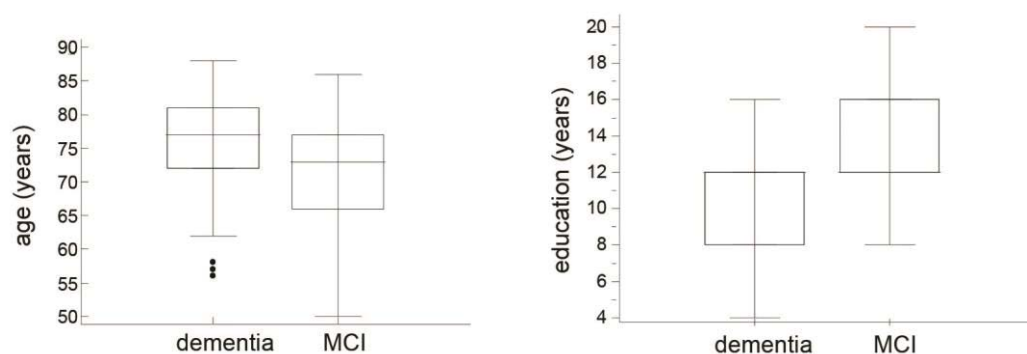
The statistical tests were used depending on the distribution of variables. For comparisons between normally distributed variables, Student's t-test was used when comparing two, and ANOVA (with Tukey-Kramer test for post-hoc analyses) when comparing three or more variables. In situations where normality criteria have not been met, we have compared variables using the Mann-Whitney U-test in case of two variables, and the Kruskal-Wallis rank-sum test (with Dunn's test for post-hoc analyses) in case of multiple variables. Correlations were assessed using either Pearson's test or Spearman's rank correlation test, depending on distribution normality. In the case of dichotomous variables, we have used either chi-squared or Fisher's exact test. Normally distributed values are shown in mean  $\pm$  SD form, and those not fulfilling the criteria for the normal distribution are shown in median  $\pm$  IQR form. The level of statistical significance was set at  $<0.05$ . All statistics were carried out using Statistica software (TIBCO software, Palo Alto, CA, USA), version 13.4.0.14.

The design of this study was approved by the University hospital center Zagreb ethics committee. Adequate measures were taken to protect the patient's anonymity.

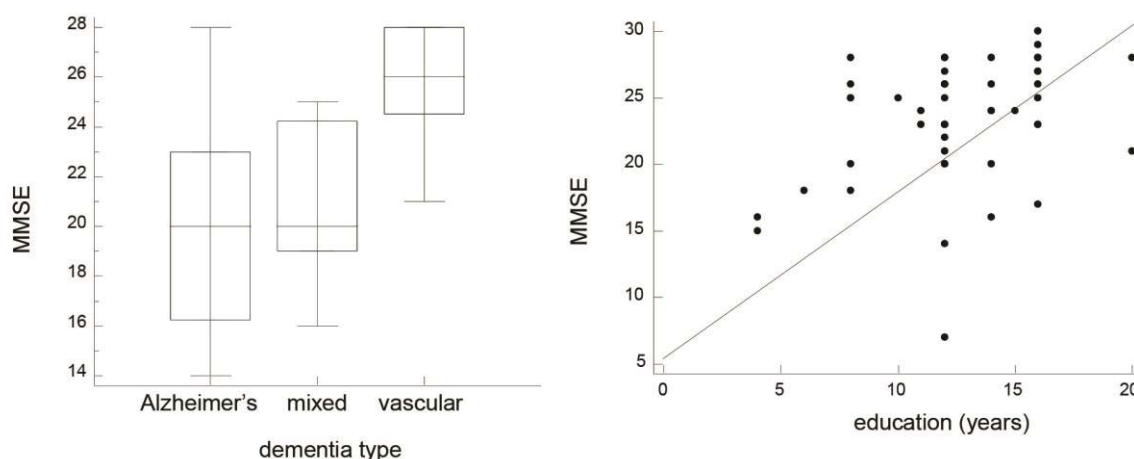
## RESULTS

In total, there were 34 patients diagnosed with dementia, and 66 diagnosed with MCI. In the group of patients with dementia, there were 13 male and 21 female patients, while in the MCI group the ratio was 28 male to 38 female patients. In total, there were 41 male and 59 female patients. The median age was  $77\pm 9$  years in the dementia group, and  $73\pm 11$  years in the MCI group ( $p=0.006$ , Mann-Whitney U-test, Figure 1A). Patients in the dementia group had a median of  $12\pm 4$  years of education. The patients in the MCI group had a median of  $12\pm 4$  years of education as well. However, because their 25<sup>th</sup> and 75<sup>th</sup> percentiles were significantly higher, the difference between those two groups was statistically significant ( $p=0.002$ , Mann-Whitney U-test), as shown in Figure 1B.

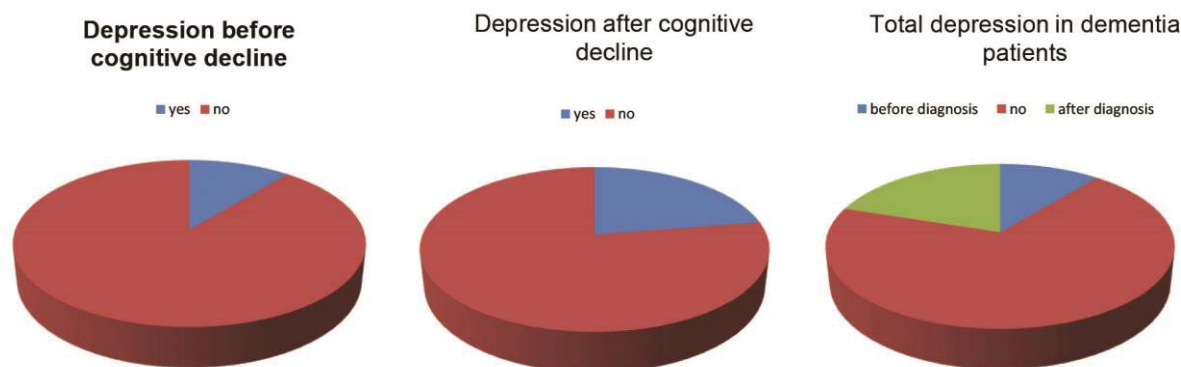
The etiology of dementia or MCI was deemed as Alzheimer's disease in 29 cases, vascular dementia in 18 cases, and mixed dementia in 8 cases. The definite cause of dementia was not yet established in remaining 45 cases. The patients with either type of dementia did not differ in sex or age, but the MMSE scores were significantly lower in patients with incipient or advanced Alzheimer's disease ( $20\pm 6.75$ ) than in patients with vascular MCI or dementia ( $26\pm 3.5$ ,  $p=0.008$ , Kruskal-Wallis rank-sum test with post-hoc Dunn's test, Figure 2A).



**Figure 1.** A. Age distribution of patients with dementia and MCI; B. Education duration (years) in dementia and MCI patients



**Figure 2.** A. MMSE values according to dementia type; B. The correlation between MMSE values and the duration of patients' education



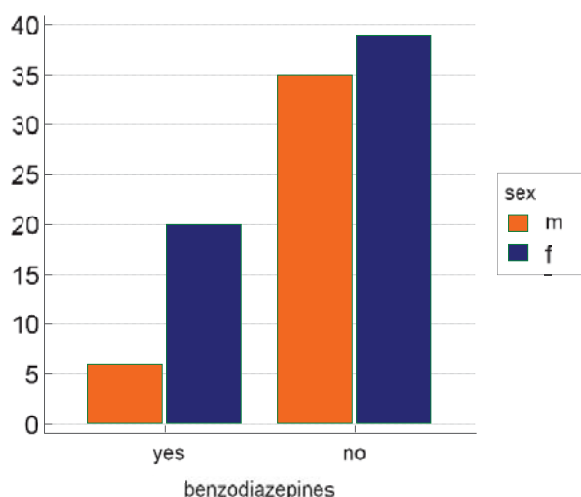
**Figure 3.** Proportion of patients with depression before (A) and after the cognitive decline (B); the total proportion of patients with depression (C)

Generally, MMSE values correlated significantly with the duration of education ( $p=0.341$ ,  $p=0.017$ , Spearman's rank correlation test, Figure 2B). They were higher in patients with a diagnosis of hyperlipidemia ( $26.5 \pm 4.5$ ) than in patients without such diagnosis ( $24 \pm 6$ ) ( $p=0.048$ ; Mann-Whitney U-test), while no differences were observed regarding the medical history of arterial hypertension or diabetes. MMSE values were higher in patients whose brain scans revealed the existence of vascular lesions ( $26 \pm 7$  vs.  $23 \pm 8.5$ ,  $p=0.012$ , Mann-Whitney U-test), but not in patients with signs of brain atrophy.

Brain atrophy was more common in the patients with dementia than in MCI patients ( $p=0.032$ , Fischer's

exact test), but did not differ between certain types of dementia. The presence of vascular lesions is predictably more common in patients with vascular dementia. In patients with Alzheimer's disease, arterial hypertension was considerably less common ( $p=0.042$ , chi-squared test).

The diagnosis of depression before the onset of dementia or MCI was established in 11/100 patients (11%), and it has developed in further 20 patients (20%) after cognitive deterioration, which represents an increase of 81.81%. The total prevalence of depression in the study group is thus 31% (Figures 3A, B, C).

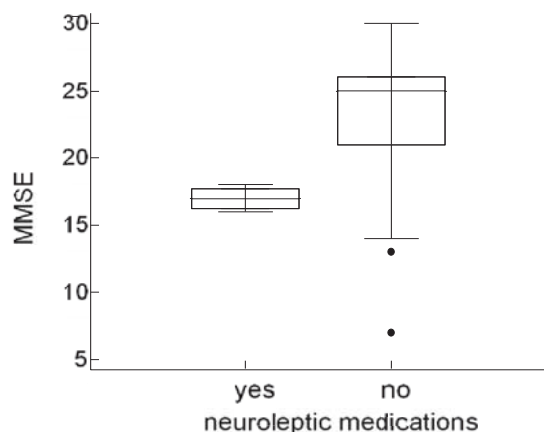


**Figure 4.** Use of benzodiazepines depending on patients' sex

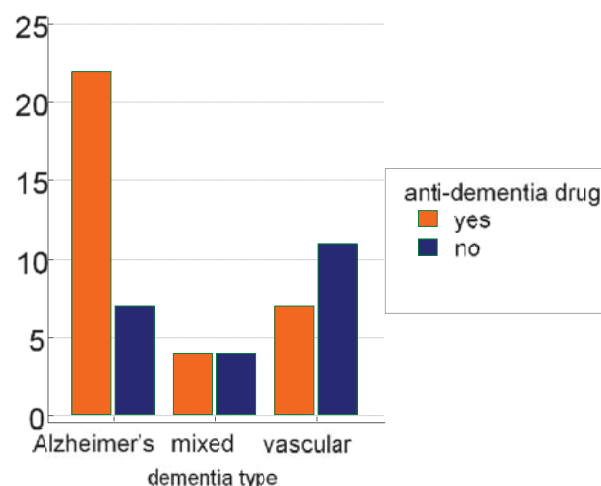
The proportion of patients currently taking benzodiazepines was 26% (26/100). Of those patients, 9 (34.61%) were taking diazepam, 8 (30.77%) were taking alprazolam, 3 (11.54%) were taking oxazepam or lorazepam, two nitrazepam and one clonazepam. Benzodiazepine use was more prevalent in female patients (Figure 4).

Of all patients, 17 (17%) were taking antidepressants, of which 9 (52.94%) were using selective serotonin reuptake inhibitors (SSRI), two were using serotonin-norepinephrine reuptake inhibitors (SNRI); two were using vortioxetine, one mirtazapine, and one tianeptine. For the remaining two patients, there was no data on the type of antidepressant.

A total of 11 patients were using neuroleptic medications, of which two were using more than one such medication. The use of such medications was more common in patients with lower MMSE scores ( $17 \pm 1.5$  vs.  $25 \pm 5$ ,  $p=0.022$ , Figure 5) in comparison to the patients with higher scores. MMSE score correlated inversely with the number of neuroleptic medications a certain patient was taking ( $\rho=-0.314$ ,  $p=0.022$ ).



**Figure 5.** MMSE score in patients depending on the use of neuroleptic medications



**Figure 6.** Use of anti-dementia drugs depending on dementia type

There were 8 patients taking benzodiazepines and antidepressants, and further 3 patients taking all three of the before mentioned types of medications.

There was no difference in the use of any kind of aforementioned medications depending on disease duration, MMSE score (apart from differences shown in Figure 5), or dementia type. The use of both benzodiazepines and antidepressants was more prevalent in patients with either premorbid depression ( $p=0.002$  and  $p \leq 0.001$  respectively, chi-squared test) or later onset of depression ( $p=0.033$ ,  $p=0.001$  respectively, chi-squared test).

Of all patients, 33 (33%) were using anti-dementia medications (memantine or donepezil), the usage was more prevalent in patients with Alzheimer's disease ( $p=0.035$ , chi-squared test, Figure 6).

## DISCUSSION

Cognitive decline presents a significant problem in societies with an aging population, which is true for a majority of developed countries. Global burden of all neurological disorders, including Alzheimer's disease and other dementias continues to increase worldwide as well as their economic burden, both in Europe and in Croatia (GBD 2016 Neurology Collaborators 2019, World Health Organization 2006, Olesen et al. 2012, Tomasovic et al. 2019). Dementia presents a burden that affects not only ones diseased with such illness, but also their families, their caregivers, and the society as a whole.

The fact that dementia and cognitive decline is an illness that is ever-increasing in importance parallel to the elongation of predicted human lifespan is demonstrated by the median age of dementia patients in our study. The patients who have dementia in our study are on average four years older than patients with MCI. That difference probably illustrates the time in which mid cognitive decline develops into full-blown dementia.



The reasons are less clear for why patients with dementia seem to have shorter education duration. It is possible to speculate that in individuals predisposed to cognitive problems, the educational base helps to mitigate the mnemonic deterioration, limiting the disease to confines of MCI. In addition to this observation, we have demonstrated a good correlation between education duration and MMSE score, which fortifies the aforementioned assumptions.

MMSE results differed in our study across different dementia causes, with Alzheimer's disease patients scoring considerably worse in this type of common cognitive test. This would imply in average more swift cognitive deterioration in patients with Alzheimer's disease, as none of our study participants diagnosed with vascular dementia had a MMSE score worse than 21. Additional reason for this difference could be earlier recognition of cognitive problems in patients with vascular dementia.

Risk factors such as arterial hypertension and diabetes seemed to have little influence on the severity of cognitive symptoms, although hypertension diagnosis was present considerably less often in patients with Alzheimer's disease. Interestingly, hyperlipidaemia was associated with better results on MMSE testing, which could be explained by much better MMSE results in vascular dementia group of patients, which are probably more prone to having hyperlipidemia as comorbidity, as it is a common risk factor for vascular cerebral disease. Better MMSE scores in the group of patients with cerebral vascular lesions could be explained thusly as well. Brain atrophy being more common in dementia compared to MCI is self-explanatory.

One of the more common psychiatric illnesses associated with dementia is depression, occurrence of which has potential to significantly aggravate overall functioning of dementia patients. It is interesting to see that the proportion of patients with such diagnosis nearly triples after onset of cognitive problems.

Additional problem that arises from such comorbidities is potential for increased use of psychotropic drugs, namely anxiolytics, antidepressants and neurotropic drugs. In our study group, the most commonly used medications in those categories were benzodiazepines, which is not surprising because of their availability and swift action. Depression contributes to common usage of antidepressants, but they seem to vary greatly in type, which could point to a lack of conformity or insufficient guidelines in prescribing those medications in a subset of depressive patients who suffer from dementia.

The only demonstrated difference in psychotropic drug usage were lower MMSE scores in patients using neuroleptic drugs, which probably indicates a need for such medications in symptom control later in the course of dementia. Cognitive status did not seem to

be associated with use of benzodiazepines or antidepressants, which possibly means that symptoms of depression or anxiety do not progress with cognitive decline. Understandably, use of those two medication groups was higher in patients with depression, be it an earlier condition or a later development.

The use of anti-dementia medication seems to be more prevalent in patients diagnosed with Alzheimer's disease, which is probably due to their lower MMSE scores. On the other hand, there was more patients with presumed vascular MCI or dementia who were not taking those drugs than there was those who were.

The limits of extrapolating the results of this study to the general population arise from the fact that these are patients from a tertiary neurological facility, where protocols do not necessarily reflect the management of such patients in general practice or by other specialists, namely psychiatrists. These were also mostly patients in earlier stages of the disease, probably because of considerable drop-out of patients from neurological follow-up once they lose the ability to fend for themselves and are possibly institutionalized in psychiatric wards or retirement homes.

## CONCLUSIONS

The challenges of managing patients with dementia are probably going to increase in the following years as the population advances in average age. Depression adds another layer of complexity to difficulties in improving the social functioning of such patients. Regular monitoring of patients and their medication habits, as well as their changes over a patient's cognitive decline are warranted in the future, in order to give medical professionals a better chance to alleviate the complex issues that arise during the management of this specter of diseases.

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**Conflict of interest:** None to declare.

### **Contribution of individual authors:**

Sanja Tomasović: study concept and design, acquisition of data, analysis and interpretation of data, drafting/revising the manuscript, critical revision of the manuscript for important intellectual content, study supervision.

Josip Sremec: analysis and interpretation of data, drafting the manuscript, design of the figures.

Jelena Koščak Lukač: drafting the manuscript, interpretation of data.

Marija Sedlić: drafting the manuscript, interpretation of data.

Nataša Klepac: analysis and interpretation of data, critical revision of the manuscript for important intellectual content.

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### Correspondence:

Sanja Tomasović, MD, PhD  
Department of Neurology, University Hospital "Sveti Duh"  
Sveti Duh 64, 10 000 Zagreb, Croatia  
E-mail: stomasovic98@gmail.com