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Case Report / Olgu Sunumu

Donepezil Treatment of Hypersomnia After COVID-19

COVID-19 Sonrası Hipersomnide Donezepil Tedavisi

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Abstract

The long-term effects of coronavirus disease-2019 (COVID-19) are not yet fully understood and some are due to central nervous system involvement. COVID-19 was reported to cause fatigue in some people after a long-term viral illness, characterized by daytime wakefulness and disturbed sleep cycles. Herein, a 90-year-old patient is presented, who developed hypersomnia after COVID-19 and showed signs of cortical atrophy in the left chronic thalamic infarction area and bilateral temporal lobe anteromedial parts in cranial magnetic resonance imaging, as well as increased wakefulness with donepezil treatment. Donepezil is an acetylcholinesterase inhibitor that increases the level of acetylcholinesterase that inhibits gamma-aminobutyric acid release in the forebrain via the serotonin system, which increases dopamine levels in the nucleus accumbens. The serotonin system has been noted for its positive effect on excessive sleepiness and Epworth sleepiness scale score improvement.

Keywords: COVID-19, ultradian rhythm, hypersomnia, donepezil

Öz

Koronavirüs hastalığı-2019'un (COVID-19) uzun vadeli etkileri henüz tam olarak anlaşılmamıştır ve bunlardan bazıları doğrudan merkezi sinir sistemi tutulumundan kaynaklanıyor olabilir. COVID-19'un bazı kişilerde gündüz uyanıklık ve rahatsız uyku döngüleri ile karakterize, uzun süreli viral hastalık sonrası yorgunluk durumlarına neden olabileceği bildirilmiştir. Burada COVID-19 sonrası gelişen hipersomni ve kraniyal manyetik rezonans incelemesinde sol kronik talamik enfarkt alanı ve bilateral temporal lob anteromedial bölümlerinde kortikal atrofi bulguları izlenen, tedavide donezepil ile uyanıklık artışı gözlenen 90 yaşındaki bir hastadan bahsedilmektedir. Nükleus akkumbensteki dopamin düzeylerini artıran serotonin sistemi üzerinden ön beyinde gama-aminobütirik asit salınımını inhibe eden asetilkolinin düzeyini yükselten asetilkolinesteraz inhibitörü olan donezepilin, aşırı uyku hali üzerindeki olumlu etkisine Epworth uykululuk ölçeği puanında iyileşme ile dikkat çekilmiştir.

Anahtar Kelimeler: COVID-19, ultradyan ritm, hipersomni, donezepil

Introduction

The long-term effects of coronavirus disease-2019 (COVID-19) are not yet fully understood and some are directly due to the involvement of central nervous system. COVID-19 was reported to cause fatigue after a prolonged viral illness, characterized by daytime wakefulness and disturbed sleep cycles, which affect ultradian rhythm in some individuals (1). This case report aimed to draw attention to the positive effect of donepezil, an acetylcholinesterase inhibitor that increased acetylcholine levels, which inhibited gamma-aminobutyric acid (GABA) release in the forebrain through the serotonin system, and increased dopamine levels in the nucleus accumbens, on excessive sleepiness, as well as the Epworth sleepiness scale score improvement.

Case Report

A 90-year-old female patient was examined in a center approximately 1.5 months ago due to respiratory distress, fever, and dry cough. The reverse transcription-polymerase chain reaction (RT-PCR) test in the swab samples from the nasopharynx and oropharynx was positive. Additionally, thoracic computed tomography revealed an increased widespread ground-glass density in all segments of both lungs and pneumonia. She was diagnosed with COVID-19 based on her findings. The laboratory examinations revealed white blood cell count of 6.1 (4.60-10.20) K/ul, hemoglobin of 12.6 (12.20-18.10) g/dl, lymphocyte count of 0.64 (0.60-3.40) K/ul, platelet count of 313.000 K/ul, lactate dehydrogenase of 263(0-247) U/l, sodium of 128 (136-146) mmol/l, potassium of 4.41 (3.5-5.1) mmol/l, calcium of 8.35 (8.8-

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10.6) mg/dl, urea of 28 (17-43) mg/dl, creatinine of 0.30 (0.67-1.17) mg/dl, D-dimer of 1116 (0-500) ug FEU/l, ferritin of 740 ug/l, and international standardized ratio of 1.55 (0.80-1.30). Therefore, the following treatments were started and maintained since the first-day hospitalization in the intensive care unit of another center: 2×400 mg oral hydroxychloroquine followed by 2×200 mg oral hydroxychloroquine for 4 days, 500 mg oral azithromycin followed by 1×250 mg azithromycin for days, and subcutaneous enoxaparin sodium at 4000 anti-Xa IU/0.4 ml 2×1 for 5 days. The patient was transferred to the internal medicine service when the RT-PCR result of the swab was negative after a 3-week stay in the intensive care unit for respiratory support, and her saturation was 92-93% in the room air. The patient was consulted with the neurology unit due to the tendency to sleep during the day. She did not have any chronic disease other than heart failure in her history. Her neurological examination revealed that she opened her eyes with a loud stimulus but could not follow orders, had no active word output, no neck stiffness, and experienced bilateral light reflex. She was fed with a nasogastric tube. The painful stimulus was localized in the motor examination, but the active muscle strength and sensory examination were not done due to lack of cooperation, deep tendon reflexes were normoactive, and with plantar reflex responses. The cranial magnetic resonance imaging (MRI) revealed ischemic-gliotic areas compatible with small vessel disease in the bilateral cerebral deep white matter at the level of corona radiata, bilateral basal ganglia, and right thalamus, and prominent cerebral cortical sulci in the anteromedial parts of the bilateral temporal lobes due to diffuse atrophy (Figure 1). The anamnesis taken from the relatives of the patient revealed no obvious previous dementia complaints but revealed insomnia from time to time, introversion in social environments due to hearing problems, and inability to walk due to orthopedic knee complaints. The patient had donepezil at 5 mg/day added to her treatment that showed Epworth sleepiness scale score decreasec from 24 to 16, as her alertness and responses to loud stimuli increased a few days after the treatment.

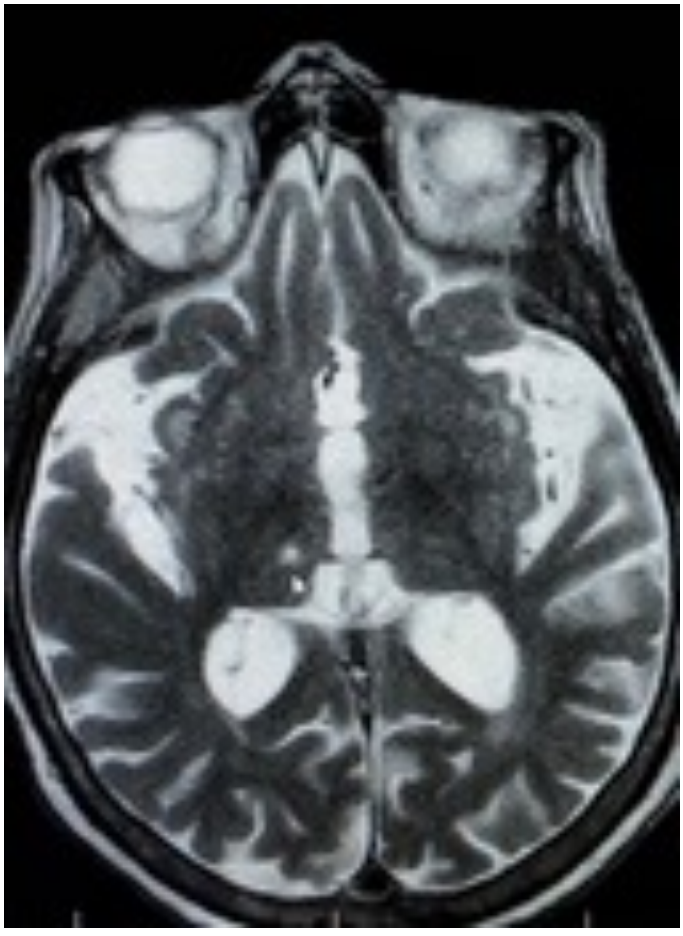

Figure 1. Ischemic-gliotic areas compatible with small vessel disease in the bilateral cerebral deep white matter at the level of corona radiata, bilateral basal ganglia, and right thalamus, and prominent cerebral cortical sulci in the anteromedial parts of the bilateral temporal lobes due to diffuse atrophy

Written consent was obtained from the relatives of the patient for her medical data to be used.

Discussion

Hypersomnia is a state of excessive sleepiness during the day and a state of sleepiness in which wakefulness is suppressed due to the effects on the hypothalamus, thalamus, and many other different central nervous system regions. COVID-19 is increasingly recognized to cause, in some individuals, states of prolonged post-viral illness fatigue, characterized by cycles of daytime wakefulness and disturbed sleep, due to its direct effect on the hypothalamic paraventricular nucleus (PVN). The effect of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) may occur at any stage of infection with neuronal angiotensin-converting enzyme-2 (ACE2) receptor involvement in the hypothalamic PVN circuit by SARS-CoV-2 through the cribriform plate of the ethmoid bone or the subfornical region of the brain monosynaptically (1,2). Neuronal ACE2 receptors, which are supposed to be the target of SARS-CoV-2 via monosynaptic subfornical connections, have been reported to be in a different subpopulation of GABAergic-interneurons, especially in the PVN circuit (1). GABA-interneurons integrate the excitability of the main autonomic outputs of all PVN (3).

Having more than one daily cycle, the central nervous system areas that control ultradian rhythms, such as pulse, respiratory rate, stomach movements, eating, drinking, urination, defecation, and rapid eye movement (REM)/non-REM sleep periods, are indirectly damaged by disruption of the blood-brain barrier, hypoxia or cerebral edema, and intracranial hypertension, or directly damaged by SARS-CoV-2 (1,2,3,4). Affected patients can have hypersomnia or insomnia symptoms with disturbed nocturnal sleep cycles during for weeks, sometimes months (5). Non-hospitalized patients with mild to moderate COVID-19 showed a marked deterioration in the 1-2 h ultradian rhythm similarly in the basic rest-activity cycle (5). Ultradian rhythms have long been demonstrated at various electroencephalographic frequencies, a propensity to fall asleep in the day, and indices of autonomic arousal, including respiratory and heart rates (6).

Hypoxia directly affects cognitive functions, especially on memory by causing temporary or permanent synaptic transmission dysfunction. A study revealed that cognitive changes that are induced by experimental hypoxia in rodents were improved with acetylcholinesterase inhibitors (7). Another study stated that donepezil had a protective effect against damage caused by

oxygen-glucose deprivation in primary cerebral cortical neuron culture from rats, which could not be achieved with scopolamine or mecamylamine. This effect of donepezil is independent of the muscarinic cholinergic system and the nicotinic cholinergic system, therefore donepezil is expected to have a protective effect against the progressive degeneration of brain neuronal cells in ischemic cerebrovascular disease and Alzheimer' disease (8). Right thalamic infarction finding was observed in the cranial MRI of our patient. The thalamus and basal ganglia are strategic structures that are involved in the regulation of motor, sensory, autonomic, endocrine, and limbic functions. Basal ganglia pathologies may cause extrapyramidal system and cognitive dysfunctions, such as impaired memory and emotion, whereas thalamic lesions may cause sensory loss, amnesia, chronic pain, dystonia, and other disorders (9). The pathogenesis of thalamic hypersomnia revealed insufficient noradrenergic and dopaminergic activating stimuli that extend from the brain stem reticular formation to the thalamus (10,11).

Acetylcholinesterase inhibitors that increase acetylcholine levels may have a protective function against excessive sleepiness and can significantly increase daytime sleep latency and reduce excessive daytime sleepiness compared to placebo in patients with narcolepsy. A case report revealed that the Epworth Sleepiness Scale score improved from 20 to 14 in a patient who received 10 mg of donepezil treatment for 3 months for narcolepsy (12). Our patient had an average of 16 h of sleep per day, which developed after COVID-19, and this drowsiness was thought of as a worsening in her clinical condition by her relatives. Therefore, the electroencephalogram was compatible with Non-REM stage N3 sleep. Polysomnography and multiple sleep latency tests could not be performed. The anamnesis taken from the patient's relatives revealed that she did not have any obvious previous dementia complaints but had insomnia from time to time. withdrawal from social environments due to hearing problems, and inability to walk due to orthopedic knee complaints. The patient had donepezil at 5 mg/day to her treatment and showed Epworth sleepiness scale score improvement from 24 to 16, as her alertness and responses to loud stimuli increased a few days after the treatment.

Therefore, we believe that cranial MRI in cases of hypersomnia after COVID-19 in the advanced age group and donepezil treatment in cases of concurrent chronic thalamic infarction and atrophy will be beneficial. Further studies and case reports are also necessary for this subject.

Ethics

Informed Consent: Consent was obtained from the relatives of the patients.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: D.A.Ü., P.İ., Concept: D.A.Ü., Design: D.A.Ü., Data Collection or Processing: D.A.Ü., M.C.İ., Analysis or Interpretation: D.A.Ü., Literature Search: D.A.Ü., Writing: D.A.Ü.

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