FTD with catatonia-like signs that temporarily resolved with zolpidem

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A 69-year-old woman with no family history of mental or neurologic diseases or hypoxic episodes began to show gradual progressive apathy and difficulties in household work at about 50 years of age, followed by emotional blunting. At 68 years of age, she developed catatonia-like signs with little or no spontaneous movement, mutism, and refusal to eat or drink. Frontotemporal dementia (FTD) was suspected because of the bilateral frontal and temporal atrophy shown by an MRI study. At that time, her family found that her symptoms were temporarily resolved with zolpidem without sleepiness. Medical examinations, including a complete blood cell count, and liver, renal, and thyroid function tests, showed no abnormalities. EEG showed dominant α rhythm with occasional slow waves, without any evidence of disturbance of consciousness. Psychotropic agents including zopiclone, lorazepam, brotizolam, alprazolam, diazepam, quazepam, quetiapine, fluvoxamine, lamotrigine, mirtazapine, and amantadine did not resolve her catatonia-like signs. No psychological tests could be performed because of her catatonic state. About 30 minutes after the oral administration of zolpidem (5 mg), her catatonia-like signs gradually ameliorated, and the effect lasted for a few hours. Psychological tests following zolpidem administration demonstrated that her Mini-Mental State Examination score was 21/30, showing disturbances in orientation, attention, and calculation, while the Frontal Assessment Battery score was 11/18 with signs of perseveration that indicated the hypofunction of the frontal lobe. The Bush-Francis Catatonia Rating Scale score changed from 26 to 3 (table). Brain perfusion scans were performed before and after the administration of zolpidem (figure). In both scans, a severe

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Table Comparison of Bush-Francis Catatonia Rating Scale before and after zolpidem administration

	Before	After administration
Excitement	0	0
Immobility/stupor	1	0
Mutism	2	0
Staring	2	0
Posturing/catalepsy	3	0
Grimacing	2	0
Echopraxia/echolalia	1	0
Stereotypy	0	0
Mannerisms	0	0
Verbigeration	0	0
Rigidity	1	0
Negativism	1	0
Waxy flexibility	3	0
Withdrawal	NA	0
Impulsivity	1	0
Automatic obedience	0	0
Passive obedience/Mitgehen	3	0
Negativism/Gegenhalten	3	0
Ambitendency	0	0
Grasp reflex	0	0
Perseveration	3	3
Combateness	0	0
Autonomic abnormality	0	0
Total	26	3

Abbreviation: NA = not applicable due to the effect of repeated zolpidem treatment.

perfusion decrease was observed in bilateral high-frontal lobes, and a mild decrease was observed in bilateral temporal lobes, which was compatible with FTD. After the oral administration of zolpidem, the perfusion was decreased in the brainstem and improved in the thalamus and some cortical areas, including the left parieto-temporal lobe and left cerebellar cortex. The anticatatonic effect of zolpidem has been observed for these 2 years without any side effect.

The last stage of dementia often shows catatonia-like signs. Lesions in the frontal lobe, parietal lobe, limbic system, diencephalon, and basal ganglia may cause catatonia. There is thus an anatomical basis for the catatonia associated with all types of dementia. There have been only a few reports that described catatonia-like signs in FTD.¹ With conventional catatonia, over 70% of patients usually respond to lorazepam, and refractory cases often improve with electroconvulsive therapy.² Additionally, some reports have also described the effectiveness of zolpidem for catatonia.³ Zolpidem is an agent that shares γ -aminobutyric acid A (GABA_A) agonism with benzodiazepines, such as lorazepam, but with a more specific pharmacologic profile. We reported catatonia-like signs in a case of FTD that were not responsive to benzodiazepines but temporarily resolved with zolpidem treatment.

Previous brain perfusion study revealed that poststroke aphasia was temporarily improved with zolpidem accompanied by increased regional cerebral blood flow in Broca area.⁴ In our case, it was

Figure Brain perfusion scan using ^{123}I -IMP SPECT

The results obtained from a statistical analysis on the brain surface (3D-SSP) before (A) and after (B) the administration of zolpidem (left). A decrease in regional blood flow is visualized as an increased signal area. SPECT scans of axial sections at the level of the thalamus are shown on the right. After the oral administration of zolpidem, perfusion is seen to decrease in the brainstem (arrowhead), while it improved in the thalamus and some cortical areas, including the left parietotemporal lobe and the left cerebellar cortex (arrows).

noteworthy that the perfusion change after zolpidem administration was observed not only in the cerebral cortex but in the brainstem and subcortical areas, which may result in anticatatonia effects by modifying the ascending reticular activating system (ARAS). The effectiveness of zolpidem for a persistent vegetative state (PVS) or minimally conscious patients has been increasingly discussed.⁵ The present case was different from a vegetative state; however, observed phenotypes of arousal and awareness were similar. Wakefulness and a loss of awareness are associated with an impaired functional interaction between the ARAS and cortical network.⁶ Patients in PVS essentially show a higher blood flow in the midbrain tegmentum (ARAS) compared with healthy subjects, whereas less blood flow in the posterior medial associative cortices (precuneus) is oppositely observed.⁶ There may be an impaired balance between functions of ARAS and cerebral cortices in our case, and the decrease of perfusion in the brainstem after zolpidem administration could be associated with an improvement of the functional connectivity between them. It is also theorized that zolpidem activates GABA_A receptors on spiny neurons in the striatum to unlock severe brain injury patients.⁷ The mesocircuit hypothesis indicates that striatopallidal or thalamic structures are also important for arousal.^{5,7}

It is difficult to exclude all of the influences of confounding medications or environmental factors; however, the influences on brain perfusion studies must be minimal because concomitant medications or therapeutic approaches were not clinically effective other than zolpidem treatment in this patient. Zolpidem may also be a useful agent for the treatment of catatonia-like signs, which are often seen in patients with end-stage dementia.

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