

[Case Report]

**EFFECTS OF FLUVOXAMINE ON BEHAVIORAL AND PSYCHOLOGICAL
SYMPTOMS OF DEMENTIA IN ALZHEIMER'S DISEASE :
A REPORT OF THREE CASES**

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Abstract : OBJECTIVE : To report 3 cases of severe behavioral and psychological symptoms of dementia (BPSD) in Alzheimer's disease (AD) with fluvoxamine treatment and to discuss the treatment implications for use of the drug.

CASE SUMMARY : An 83-year-old woman was diagnosed with AD. Before treatment, she showed sudden irritation and excitement. Her BEHAVE-AD score was 40. She was started on fluvoxamine and quetiapine. Eight weeks later, she was friendly and thankful towards the staff. Her BEHAVE-AD score was 10. The second case was a 79-year-old woman diagnosed with AD. Before treatment, she attempted to leave our hospital and wandered and shouted throughout the day. Her BEHAVE-AD score was 42. She was started on fluvoxamine, and the dosage was gradually increased. Eight weeks later, the shouting and excitement disappeared almost completely. Her BEHAVE-AD score was 13. The third case was a 79-year-old man diagnosed with AD. Before treatment, we put him in a private, locked room because he was extremely agitated and violent because of delusions. His BEHAVE-AD score was 42. He was started on fluvoxamine and sodium valproate. Eight weeks later, the delusion became mild and did not affect his mood or behavior. His BEHAVE-AD score at this point was 4.

DISCUSSION : Fluvoxamine was effective in controlling BPSD with AD. This finding shows that the pathophysiology of BPSD due to AD may occur because of a hyposerotonergic state in the brain.

CONCLUSION : These cases show that fluvoxamine appears to be effective in

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the control of BPSD with AD.

Key words : Alzheimer's disease, AD ; behavioral and psychological symptoms of dementia, BPSD ; Behavioral Pathology in Alzheimer's Disease Rating Scale, BEHAVE-AD ; fluvoxamine

INTRODUCTION

Elderly individuals with dementia commonly show psychotic symptoms, such as delusions and hallucinations, and nonpsychotic symptoms, such as aggression, wandering and phobias¹⁾. These symptoms are defined as behavioral and psychological symptom of dementia (BPSD)²⁾. BPSD is difficult to treat in patients with Alzheimer's disease (AD).

In the past, typical neuroleptics, such as haloperidol, have been used to treat BPSD, but the response rates vary from 25% to 75%^{3,4)}. Moreover, they frequently show adverse effects, mainly extrapyramidal symptoms, such as Parkinsonism and akathisia. Recently, atypical neuroleptics, such as risperidone, olanzapine and quetiapine⁵⁾, are used for BPSD because of their effectiveness and fewer adverse effects. This class of drugs blocks various receptors for neurotransmitters, and while they do have adverse effects, these are fewer in number than typical neuroleptics.

A double-blind, placebo-controlled study was performed to compare the acute efficacy of citalopram, a selective serotonin reuptake inhibitor (SSRI), and that of perphenazine, a neuroleptic used as a placebo, in the treatment of psychosis and behavioral disturbances in nondepressed patients with dementia. Citalopram was found to be more efficacious⁶⁾. Furthermore, reports showed a decline in neurons expressing serotonin 2A, and also serotonin 6 receptor in AD⁷⁾. This report indicates hyposerotonergic function in the pathophysiology in AD. Fluvoxamine and paroxetine are SSRIs that were approved for clinical use in Japan at that time. Fluvoxamine has fewer anticholinergic effects than paroxetine⁸⁾, and therefore, we examined fluvoxamine, another SSRI, in the treatment of BPSD in AD.

SUBJECTS AND METHODS

The subjects included three patients with BPSD due to AD staying in Kotokukai Sato Hospital from 2002 to 2004. AD was diagnosed according to the International Statistical Classification of Diseases and Related Health Problems 10. BPSD was evaluated by BEHAVE-AD.

RESULTS

CASE 1

An 83-year-old woman was diagnosed with AD at a hospital in 2001. She had shown signs of dementia for 5 years, and was treated for a lumbar spine compression fracture and osteoporosis, receiving both active vitamin D₃ 1 g/d and calcium carbonate 400 mg/d. She was referred to Kotokukai Sato Hospital for psychiatric consultation because she kept saying that her son and his wife stole her money and was greatly irritated, especially from the evening to midnight. She also claimed repeatedly that her family was attempting to kill her, and attempting to leave home at night. Eventually, she was admitted to the same hospital. On admission, she showed sudden irritation and excitement. She attempted to leave the hospital and she was disoriented to place, time, and person. Her affect was blunted and she refused to be cared for. Results of medical, neurologic, and metabolic workups were negative. Brain CT scan showed cerebral atrophy, especially in the temporal and parietal areas. Her BEHAVE-AD score was 40. AD was diagnosed, and she was started on fluvoxamine 50 mg/d and quetiapine 50 mg/d. Two days later, however, dysbasia developed and the dose of quetiapine was decreased gradually and then discontinued. On the other hand, the dose of fluvoxamine was gradually increased to 100 mg/d. Four weeks later, there was an almost complete abolition of the irritation and excitement. She occasionally showed a delusion of persecution, but hardly bothered the staff or other patients. The BEHAVE-AD score at this time was 14. Eight weeks later, the delusion of persecution disappeared completely and she was friendly and thankful to the staff. The BEHAVE-AD score was 10. She verbalized no subjective adverse effects, and the staff noted no adverse effects. Treatment continued for another 4 weeks and was then discontinued without evidence of relapse at a 4-month follow-up examination.

CASE 2

A 79-year-old woman was diagnosed with AD at a hospital. She had shown signs of dementia for 5 years, and had mild anemia. She had been diagnosed as having gastric cancer 1 year before. The cancer had spread to the large intestine, and was inoperable, but she had not been informed of the fact. She received histamine H₂ blocker famotidine 20 mg/d and sodium ferrous citrate 100 mg/d. She was referred to the above hospital for psychiatric consultation for disorientation and amnesia, because she shouted and used violence in the home. Then she was moved to a nursing home. From her first day there, she attempted to leave the nursing home and wandered and shouted throughout the day. Thus, she was difficult to care for and bothered the other patients. The staff recommended that she be sent to our hospital, although she refused. In our hospital, too, she repeatedly attempted to leave. Brain CT scan showed cerebral atrophy, mainly in the temporal area, and

ventricular dilatation without a tumor shadow. Her BEHAVE-AD score was 42, and AD was diagnosed. She was started on fluvoxamine 50 mg/d, which was gradually increased to 150 mg/d. Four weeks later, her shouting and excitement diminished but she quite frequently forced the door open and wandered out. Her BEHAVE-AD score at this time was 29. Fluvoxamine 200 mg/d was given for another 4 weeks; then, the shouting and excitement disappeared almost completely, and she did not attempt to leave, although she still wandered. The BEHAVE-AD score at this time was 13. Quetiapine 25 mg/d was added, hoping it would stop her from wandering. However, it was discontinued because moderate gait disturbance developed. She went to another nursing home without evidence of relapse at a 3-month follow-up examination.

CASE 3

A 79-year-old man was diagnosed with AD. He had shown signs of dementia for 4 years. He frequently muttered to himself starting 1 year previously. He tried to open his safe with a gas burner because he had forgotten its code number. Moreover, delusions and hallucinations appeared and he frequently visited a familiar hotel, saying that he had lent money to the hotel. Finally, because he attempted to enter the hotel by force, he was reported to the police, and was brought to our hospital by police officers. On admission, we put him in a private room and locked it because he was remarkably agitated and violent. He hit the door with his bed and cried. The next day, he refused to take his medication or eat his meals. Intravenous feeding, including haloperidol 5 mg, was given, and the strong negativism moderately improved, and he began to take his medication and eat his meals. Brain CT scan showed cerebral atrophy, mainly in the temporal and parietal areas. His BEHAVE-AD score was 42. AD was diagnosed and he was started on fluvoxamine 50 mg/d and sodium valproate 100 mg/d, which were gradually increased to 100 and

Table 1. The effect of fluvoxamine on behavioral and psychological symptoms

	Case 1	Case 2	Case 3
Behavioral and psychological symptoms	Delusions, shouting, negativism	Wandering, shouting	Delusions, hallucinations, agitation
Dose of fluvoxamine	100 mg/day	150 mg/day	75 mg/day
BEHAVE-AD score before fluvoxamine treatment	40	42	42
BEHAVE-AD score after fluvoxamine treatment	10	13	4

400 mg/d, respectively, for 2 weeks. However, he fell from his bed and had rib fractures. Therefore, fluvoxamine was reduced to 75 mg/day, and sodium valproate was decreased gradually and discontinued. Four weeks later, delusion developed intermittently, but his behavior became calm. His BEHAVE-AD score was 16. We continued to administer fluvoxamine 75 mg/d for another 4 weeks. Eight weeks later, the delusions became mild and did not affect his mood or behavior. The violence disappeared completely. The BEHAVE-AD score at this point was 4. He verbalized no subjective adverse effects, nor did our staff note any adverse effects due to fluvoxamine administration. He moved to a nursing home without evidence of relapse at a 6-month follow-up examination.

DISCUSSION

Fluvoxamine reduced the BEHAVE-AD scores of patients with AD, indicating that it is effective in controlling BPSD. This finding shows that the pathophysiology of BPSD due to AD may be a hyposerotonergic state in the brain. Agitated aggressive patients with AD had an increased response to the serotonin-releasing agent fenfluramine compared with non-agitated aggressive patients⁹⁾. This may reflect damage to the serotonergic system with subsequent upregulation of the remaining postsynaptic receptors. Fluoxetine, another SSRI, improved obsessive-compulsive symptoms of AD. Six-month treatment with fluoxetine significantly increased the density of serotonin transporter sites when compared with the beginning of treatment using 123I-beta-CT SPECT¹⁰⁾. Therefore, this report suggests that fluoxetine is a treatment option for patients with AD and severe obsessive-compulsive symptoms and highlights the importance of the serotonergic system. Treatment with fluvoxamine was effective against sweater chewing, finger sucking, and eye wiping in two patients with AD¹¹⁾. These previous reports and the present study may indicate that the mechanism explaining the effect of fluvoxamine on BPSD is not only activation of the serotonergic system but also indirect attenuation of the levels of catecholamines, such as noradrenaline and dopamine, via the activated serotonergic system. However, serotonin, noradrenaline and dopamine in the brain were not measured in the present study. The relationship between the monoamine in the brain and BPSD needs to be studied in the future.

Fluvoxamine therapy had no adverse effects in cases 1 and 2. In case 3, however, the patient fell from the bed and suffered rib fractures. He received fluvoxamine 100 mg/d and sodium valproate 400 mg/d. Valproate was added because he was very violent. It is considered that valproate showed oversedation due to overdose, or treatment with fluvoxamine and valproate caused a multiplier effect. We administered fluvoxamine combined with quetiapine in Case 1 and valproate in Case 3 for severe BPSD. The administration of quetiapine and valproate gradually decreased and stopped. After monotherapy of fluvoxamine, the BEHAVE-AD score showed a decrease over time. Therefore, we considered that

fluvoxamine was effective on BPSD. Because of the oversedation that occurred in case 3, probably owing either to overdose of valproate, or a synergistic effect of fluvoxamine and valproate, monotherapy is recommended for the treatment of BPSD. Paroxetine has greater anticholinergic effects than fluvoxamine and therefore paroxetine may have unadvisable effects on cognition of AD and BPSD compared with fluvoxamine.

We hope that this report will contribute to the determination of the value of fluvoxamine for the treatment of BPSD.

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