CASE REPORT

Efficacy of combination treatment of fluvoxamine and tiapride for repetitive behaviors in frontotemporal lobar degeneration

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Received 22 September 2003; accepted 17 October 2003.

Key words: *fluvoxamine, frontotemporal lobar degeneration, repetitive behaviors, tiapride.*

Abstract

The present study reports a 63-year-old right-handed man with frontotemporal lobar degeneration (FTLD) who manifested severe repetitive and disinhibited behaviors. Combination treatment of fluvoxamine and tiapride decreased the frequency of these behaviors. The results indicate that these drugs are effective for the treatment of repetitive and disinhibited behaviors for patients with FTLD. The behaviors caused by FTLD are discussed in terms of obsessive–compulsive spectrum disorder.

INTRODUCTION

Frontotemporal lobar degeneration (FTLD) is the third most common cause of cortical degenerative dementia.[1] The characteristic clinical manifestation of FTLD is a profound alteration in personality and behavior.[1] Management of theses behavioral and psychological symptoms is needed to maintain quality of life for patients and their caregivers. Although some behavioral interventions to manage the symptoms have proved to be effective,[2] an effective pharmacologic strategy has not been established. Some reports have shown serotonin reuptake inhibitors (SRIs) are effective against repetitive behaviors in FTLD.[3,4] However, quantitative assessment of their effectiveness is difficult. In the present case study, we report a patient with FTLD who exhibited severe repetitive and disinhibited behaviors, which improved/diminished soon after oral administration of fluvoxamine and tiapride. We counted the frequency of the behaviors before and after administration of the drugs and quantitatively demonstrate the efficacy of the drugs on the behaviors.

CASE REPORT

A 63-year-old right-handed man was referred to our clinic because of personality changes and behavioral problems. He was an office worker with 16 years education. At the age of 57 he had insomnia and apathy. He was diagnosed as having depression and was medicated accordingly. Although he was promoted to an administrative post, he often took leave from his work and retired at 58 to take care of his wife who suffered from breast cancer. After retirement his behavior became gradually to be disinhibited and inflexible. The subject sometimes rushed to the hospital where his wife had been admitted at midnight with no apparent reason. He drove roughly and often braked suddenly or run onto the road shoulder. At home he was irritable in the evening. He adhered to a rigid routine and became agitated if his daily schedule was altered. The subject took his medicine, smoked and ate at the same time every day. He would repeatedly to go to the restroom despite having no urologic disorders. The subject was suspected of having dementia because of mild

cognitive dysfunction and slight atrophy of the brain.

There was no family history of psychiatric illness, dementia or other neurologic disorders. The subject had undergone a two-third gastrectomy for a gastric ulcer at 57 years.

On admission to our hospital, laboratory tests showed that he was undernourished and slightly anemic (total protein 5.9 mg/dL, albumin 3.7 mg/dL, red blood cell (RBC) number: $3.95 \times 10^6/\mu L$, hemoglobin 13.1 g/dL). The levels of vitamins B1, B2, B12 and thyroid function were normal. Venereal disease research laboratory (VDRL), human immunodeficiency virus (HIV) infection, and tumor markers such as carcino embryonic antigen (CEA), α-fetoproteins (AFP), and carbohydrate antigen 19–9 (CA19-9) were all negative.

Neurologic examination was unremarkable except for the grasp reflexes of both hands. In the cerebral spinal fluid (CSF) general findings were normal and the levels of Tau, $A\beta_{42}$ and Tau/$A\beta_{42}$ were 244 pg/mL, 827 pg/mL and 0.30, respectively (Tau/$A\beta_{42}$ in patients with Alzheimer's disease (AD) is 1.63 ± 1.32 and in neurodegenerative disorders without AD (ND) is 0.56 ± 0.63).[5] Electroencephalogram (EEG) was normal. A brain magnetic resonance image (MRI) showed slight atrophy of the bilateral medial frontal and anterior temporal lobes, and several small ischemic lesions in the subcortical areas (Fig. 1). ^{99m}Tc-HMPAO single photon emission computed tomography (SPECT) revealed a mild decrease in the cerebral blood flow (CBF) in the atrophic regions and the bilateral medial temporal lobes (Fig. 1).

Psychiatric evaluation revealed no psychotic symptoms or mood disorders. Although the subject was told repeatedly that he was admitted to the hospital because of insomnia and pollakiuria, he seemed not to take the situation seriously. When undergoing neuropsychologic tests, he often looked at a clock and asked the time.

Neuropsychologic tests showed mild attentional deficits and writing disturbances, although the subject was alert and well oriented. Memory function in everyday and constructional ability were preserved. His spontaneous speech was fluent. Paraphasias and perseverations were not observed. Agraphia of "kanji" (Japanese morphogram) and agrammatism were found in writing. No

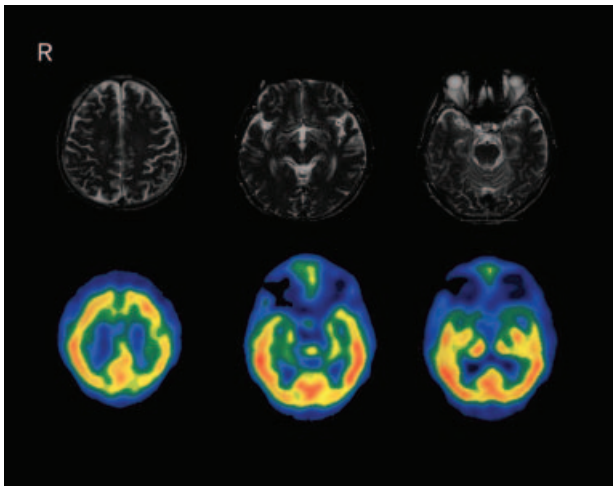

Figure 1 This T2-weighted magnetic resonance image shows slight atrophy of the bilateral medial frontal and anterior temporal lobes, and several small ischemic lesions in the subcortical areas. ^{99m}Tc-HMPAO SPECT shows a mild decrease in the cerebral blood flow in the atrophic regions and the bilateral medial temporal lobes. R indicates the right side of the brain.

signs of apraxia and agnosia were present. The MMSE score was 25. On the Wechsler adult intelligence scale-revised (WAIS-R), his full-scale IQ was 87, with a verbal IQ of 87 and a performance IQ of 88. On the Wechsler memory scale-revised (WMS-R), his verbal and visual memory index, attention-concentration index, and delayed recall index was 66, 79, 76, and 68, respectively.

He was diagnosed as having frontotemporal dementia (FTD) in FTLD because of his disinhibited, stereotyped and repetitive behaviors, the pattern of cognitive dysfunction, and neuroimaging findings. The result of CSF tau and Aβ (tau/Aβ) did not indicate that he had AD.[5]

He was treated with a combination of fluvoxamine and tiapride. The former is one of the SRIs that are sometimes reported to be effective for repetitive behaviors in FTLD. The latter is a selective D_2-antagonist that is used to treat disinhibition. The subject showed several disinhibited, stereotyped and repetitive behaviors such as going to the restroom every 10 min, frequent smoking, and repeated question about test results. His most pronounced repetitive behavior was to go to the restroom, we counted the frequency of this behavior, which was used as the main outcome measure for medication. The dose of these drugs and the

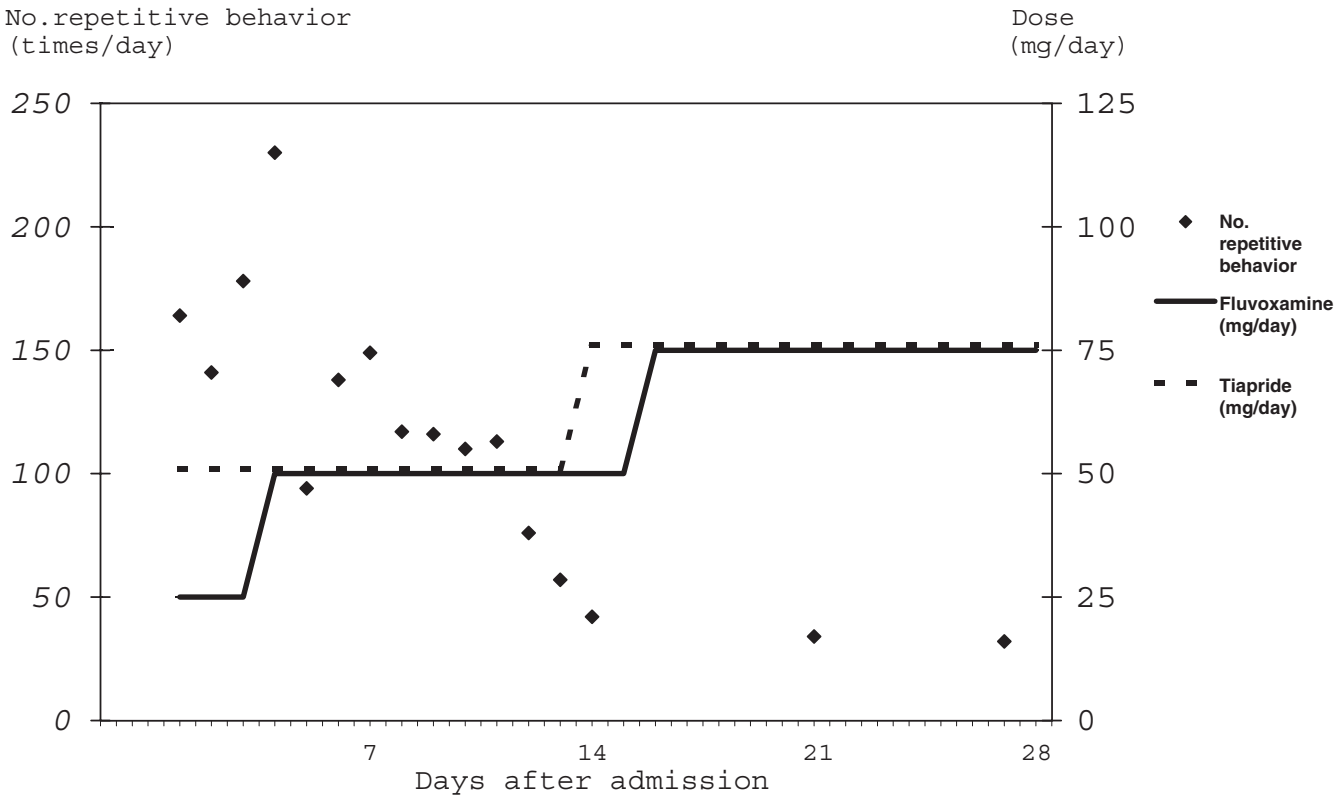

Figure 2 Frequency of the repetitive behavior and dosage of fluvoxamine and tiapride.

frequency of the behavior are shown in Fig. 2. The frequency of the subject's visits to the restroom gradually decreased soon after medication and were reduced to about one fifth after 2 weeks of medication. Disinhibition behaviors were also improved.

DISCUSSION

In the present case study, combination treatment using fluvoxamine and tiapride improved the repetitive behaviors in a patient with FTLD. Counting most pronounced repetitive behaviors made it possible to quantitatively assess the subject's behavior.

Recently the inventory for the wide range of stereotypic behaviors[6] in FTLD, which follows the rules and the organization of the neuropsychiatric inventory[7] has been developed. Although the inventory helps to assess both the frequency and the severity of each behavior, it has a limitation on its accuracy in terms of its caregiver-based evaluation. Therefore, we counted repetitive behaviors to evaluate the frequency more directly and accurately in the present study.

It was pointed out that the repetitive behaviors exhibited by patients FTLD are mainly associated with the serotonergic system of the brain. Hollander and Wong proposed a concept of obsessive-compulsive spectrum disorder (OCSD).[8] This model placed risk avoidance on the compulsivity end and risk seeking on the impulsivity end and lined up various disorders in this spectrum (Fig. 3). They considered compulsivity with serotonine hypersensitivity and frontal lobe hyperfunction, and impulsivity with serotonine hyposensitivity and frontal lobe hypofunction from biological aspects. Nishikawa *et al.* interpreted that the repetitive behaviors in FTLD might be placed at the impulsivity end of the spectrum.[9] Selective loss of the pyramidal cells in the frontal and temporal lobes in FTLD might cause a decrease in serotonergic activity and result in an impulsive state. The decrease of serotonergic activity might increase the sensitivity of the postsynaptic serotonergic receptor. Therefore, administration of

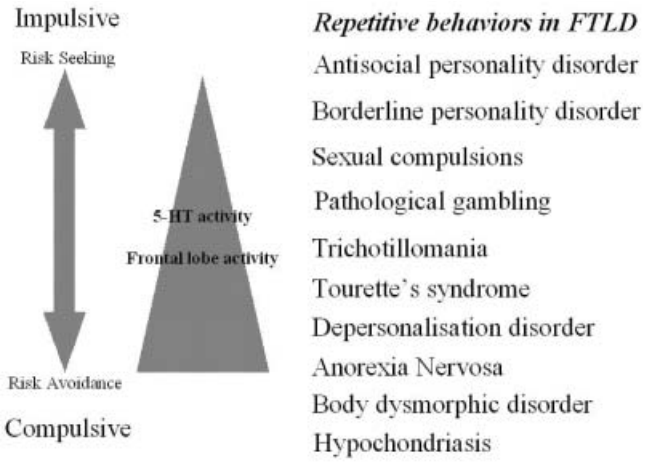

Figure 3 Compulsivity/impulsivity dimension.[8] Nishikawa *et al.*[9] interpreted that the repetitive behaviors exhibited by patients with FTLD might be placed at the impulsivity end of the spectrum.

SRIs might increase serotonergic discharge between synaptic clefts and immediately decrease impulsive behaviors as in the present case.

The repetitive behavior in the present study also have aspects of disinhibition and agitation. It is reported that tiapride is effective in the treatment of agitation and aggressiveness in dementing illnesses[10] and has fewer extrapyramidal side effects than typical antipsychotics. Therefore, we used the drug to augment SRIs treatment for the behaviors in the present case. Treatment with SRIs for repetitive behaviors in FTLD is not always effective. Although there are no reports on the efficacy of combination treatment using SRIs and tiapride, the present study indicates that additional administration of tiapride might be recommended in similar cases.

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