

Case Report

Citalopram Improves Obsessive-Compulsive Crossword Puzzling in Frontotemporal Dementia

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Keywords

Behavioral variant frontotemporal dementia · Citalopram · Obsessive-compulsive behavior · Selective serotonin reuptake inhibitors · Serotonin

Abstract

Behavioral variant frontotemporal dementia (bvFTD) is characterized by severe changes in personality/behavior. Recent studies have provided evidence that a decrease in serotonin receptors and neuronal loss in the raphe nuclei play a role in the bvFTD pathology. Serotonergic antidepressants have been reported to diminish behavioral disturbances in bvFTD, particularly repetitive behaviors, disinhibition, apathy, sexually inappropriate behaviors, and hyperorality. Here, we present the case of an 80-year-old Caucasian male patient with clinically and biomarker supported bvFTD ("probable" bvFTD; disease-specific alterations in ¹⁸F-fluorodesoxyglucose positron emission tomography and magnetic resonance imaging). The patient

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exhibited behavioral disinhibition, apathy, a loss of empathy, perseverative behavior during testing, hyperorality, changes in diet, and executive deficits in neuropsychological testing. Remarkably, he failed in solving crosswords by systematically filling in the blanks by letters in alphabetical order (A, B, C, D, etc.), indicating obsessive-compulsive behavior. One year later, the patient visited the clinic again for a follow-up investigation. He had taken 20 mg of citalopram per day for 1 consecutive year. Remarkably, he had regained the ability to fill in crossword puzzles correctly, although the neuropsychiatric inventory showed overall only small improvement in behavioral impairment. A regimen of 20 mg citalopram per day over the course of 1 year led to a specific improvement in one of the bvFTD core symptoms, obsessive-compulsive behavior, most pronounced in solving crossword puzzles. This case contributes to the understanding of the neuropharmacological correlates of bvFTD and supports the treatment of bvFTD's behavioral symptoms with selective serotonin reuptake inhibitors.

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Introduction

Frontotemporal lobar degeneration is a common type of dementia below the age of 65 years. Behavioral variant frontotemporal dementia (bvFTD) is its most common subtype. Recently, revised criteria have been suggested to diagnose bvFTD more accurately [1]. These criteria are structured as a diagnostic hierarchy. The diagnosis of “possible” bvFTD is solely based on clinical symptoms and aims to detect the disease in its early stages. Three of the following six clinical features must be present: disinhibition, apathy/inertia, loss of sympathy/empathy, perseverative/stereotyped or compulsive/ritualistic behavior, hyperorality/dietary changes, and a dysexecutive neuropsychological profile. Furthermore, if the patient who must meet the clinical criteria for “possible” bvFTD also exhibits a significant functional decline and shows brain imaging results consistent with bvFTD, in particular frontal and/or anterior temporal atrophy, hypoperfusion or hypometabolism, she/he can be classified as having “probable” bvFTD. In the presence of histopathological evidence and/or known pathogenic mutations and symptoms that meet the criteria for “possible” or “probable” bvFTD, the patient would be diagnosed with “definite” bvFTD. These criteria have been shown to be more sensitive than the older consensus criteria, which is critical to diagnose bvFTD in its earlier stages [1].

Recent studies have provided evidence that a decrease in serotonin receptors for 5-hydroxytryptamine 1A and 5-hydroxytryptamine 2A and neuronal loss in the raphe nuclei play a role in the bvFTD pathology [2]. In line with these findings, serotonergic antidepressants are reported to diminish behavioral disturbances in bvFTD [3–6], particularly repetitive behaviors, disinhibition, apathy, sexually inappropriate behaviors, and hyperorality [7], while they have apparently no effect on cognitive and functional abilities. A recent study demonstrated effects of citalopram on behavioral symptoms of frontotemporal lobar degeneration (12 bvFTD, 2 primary progressive aphasia, and 1 semantic dementia patients), in particular disinhibition, irritability, and depression [3], which suggests that citalopram treatment might be effective in targeting behavioral disturbances in bvFTD. Here, we present a patient with

bvFTD in whom citalopram treatment specifically improved one of the bvFTD core symptoms, namely obsessive-compulsive behavior.

Case Presentation

An 80-year-old Caucasian male presented with changes in behavior and personality, consistent for over 1 year. As illustrated in Figure 1, he failed in solving crosswords by systematically filling in the blanks by letters in alphabetical order (A, B, C, D etc.). He set his alarm repetitively over the course of the day, urinated publicly during a family celebration, lost interest in his grandchildren and wife. Furthermore, he watched TV all day long, had a reduced sense of distance towards other people (started using things of their everyday life without asking for permission, lay down in their beds, etc.), started eating more than he used to, and his table manners deteriorated. When asked if he noticed any changes in his behavior or personality, he declined and was not aware of any change at all.

Noteworthy, his medical history comprised recurrent depressive episodes (at 45, 47, and 62 years of age), while an euthymic mood state was noted at the present investigation. The patient's former depressive episodes were severe and psychotic, and they were treated with amitriptyline, fluoxetine, mirtazapine, escitalopram, reboxetin, olanzapine, and electroconvulsive therapy. Taking the case history revealed arterial hypertension for approximately 50 years and obesity as vascular risk factors. Accordingly, the patient had presented with cerebral small vessel disease, indicated by white matter hyperintensities in magnetic resonance imaging (MRI) and a lacunar infarction in the right paramedian pons 3 years ago, leading to a left-sided hemiparesis. At baseline admission, the patient did not show any significant deficits related to the hemiparesis limiting activities of daily living. A heart attack related to coronary heart disease was adequately treated approximately 15 years ago.

Results

Clinical Assessment at Baseline Investigation

Neurological tests showed a positive palm-chin reflex on both hands. Results for the comprehensive multimodal neuropsychological testing are presented in Table 1. Detailed neuropsychological testing revealed heavy executive dysfunctions, namely in the subtests Zoo Map and Key Search of the Behavioral Assessment of the Dysexecutive Syndrome Test Battery, with perseverations in the Hamasch 5-point test and, slightly, in the Digit Span backward test. In tests for other neuropsychological functions, the patient showed age-appropriate and normal performance.

The patient's performance in dementia-related and behavioral assessments is displayed in Table 2. Behavioral impairment was assessed with the neuropsychiatric inventory (NPI), a validated, caregiver-based, behavioral rating system for dementia syndromes [8]. The patient showed symptoms in the domains apathy, disinhibition, aberrant motor behavior, the latter mainly due to obsessive-compulsive symptoms, and changes in appetite and eating behavior. Note that the latter was not related to obsessive-compulsive but rather disinhibited symptoms and hyperorality. These deficits were reinforced by the frontal systems behavioral scale

revised, where the relative reported more deficits than the patient himself, presumably reflecting well-known anosognosia in bvFTD in this patient.

Biomarkers at Baseline Investigation

Cerebrospinal fluid showed an elevated total protein (530 mg/L) and increased phospho-tau level (69 pg/mL) besides normal values for tau (124 pg/mL) and amyloid-beta (510 pg/mL). Figure 2 illustrates the findings of the brain imaging investigations. Structural MRI showed a subtle bifrontotemporal and mesencephalic atrophy. A diagnosis of progressive supranuclear palsy was improbable due to normal oculomotor function. Additionally, MRI displayed a former lacunar paramedian pons infarction on the left side and a small extent of white matter lesions. ¹⁸F-fluorodesoxyglucose positron emission tomography (FDG-PET) revealed regional hypometabolism in the bilateral mesial frontal and the anterior part of the temporal lobe, in the right temporal lobe already spreading posteriorly. Those visual findings were confirmed using quantitative approaches as shown in Figure 2. Electroencephalography revealed a frontotemporal continuous theta-delta focus on the right side.

Discussion for Baseline Investigation

The patient exhibited behavioral disinhibition, apathy, a loss of empathy towards his wife and grandchildren, perseverative behavior during testing, hyperorality, and a change in diet as described by his wife and son. Remarkably, he showed obsessive-compulsive behavior in crossword puzzling. Furthermore, comprising executive deficits could be assessed, while his memory functions seemed to be intact. Although the patient reached a normal score in the Mini-Mental State Examination, the Bayer-Activities of Daily Living Scale indicated impairments in daily living (Table 1, 2). Clinically relevant deficits were also confirmed by the Clinical Dementia Rating Scale (CDR) and its frontotemporal lobar degeneration-modified version (Table 2).

All in all, the patient showed all clinical symptoms for bvFTD according to the recently revised criteria (“possible” bvFTD, criteria A–F; [1]). Imaging with ¹⁸F-FDG-PET revealed hypometabolism in the mediofrontal lobe and the temporal pole (Fig. 2) – typical findings in bvFTD [1], which are in agreement with the neural correlates as discussed in the literature [8–13]. Accordingly, imaging supported the diagnosis of “probable” bvFTD. Because of severe changes in personality and behavior, the patient was prescribed the selective serotonin reuptake inhibitor citalopram 20 mg once a day, which has been shown to improve alterations in personality and behavior in bvFTD patients [3].

Clinical Assessment at Follow-Up Investigation

One year later, the patient visited the clinic for a follow-up investigation. He had taken 20 mg of citalopram per day for 1 consecutive year. According to his wife, his self-reliance, motivation, manners in eating, and disinhibition had improved. He had been able to eat at restaurants on two occasions and showed empathy towards his wife and grandchildren. In contrast, his son still reported pronounced apathy, lying in bed all day long, watching TV, reductions in empathy, and that the patient would empty the fridge overnight. Most remarkably, he regained the ability to fill in crossword puzzles correctly (Fig. 1). However, he still counted compulsively how often specific letters appeared in the crossword.

As illustrated in Table 2, the NPI showed overall only slightly improvement. However, some domains changed, leading to a different pattern. In comparison with the baseline situation of 1 year ago, apathy had been increased, whereas aberrant motor behavior representing mainly obsessive-compulsive symptoms had been decreased. Notably, he did not score on the disinhibition scale now. According to the relative, everyday activities had been improved as shown by the Bayer-Activities of Daily Living Scale. The Frontal Systems Behavioral Scale revised did not show remarkable changes according to the patient's assessment, whereas it was not completely available by relatives for the follow-up. The patient still scored normal in the Mini-Mental State Examination (Table 1). Clinical deficits were relatively stable in the CDR (increased in the CDR itself but reduced in its frontotemporal lobar degeneration-modified version; Table 2).

Neuropsychological testing at follow-up revealed only slight changes in comparison to the baseline findings (Table 1). The focus of his cognitive deficits continued to be a severe impairment in executive function (Zoo Map and perseverations in the Hamasch 5-point test revised; Key Search improved, presumably due to repetition effects; still slight deficits in the Digit Span backward test). Only visual memory seemed to be additionally impaired now in the Consortium to Establish a Registry for Alzheimer's Disease Test Battery (Constructional Praxis: Delayed Recall and Savings), although performance in the Wechsler Memory Scale revised was unchanged in this domain, still in the normal range.

Biomarkers at Follow-Up Investigation

Structural MRI showed a subtle bifrontotemporal and mesencephal atrophy similar to that of 1 year ago. In comparison with baseline MRI, slightly accentuated pointy and patchy signal enhancements were visible in the fast fluid-attenuated inversion recovery sequence in the supratentorial white matter, together with the capsula interna and externa. The latter alterations indicated a slight-to-moderate small vessel disease. Electroencephalography was administered but showed no pathological findings – in contrast to the baseline examination.

Discussion/Conclusion

Most remarkably, at follow-up 1 year after baseline investigation and after treatment with citalopram, the patient regained the ability to fill in crossword puzzles correctly. Behavioral and neuropsychological tests showed only a slight improvement in the patient's total NPI score, but with a significant specific decrease in the aberrant motor behavior score representing mainly obsessive-compulsive symptoms. Severity of dementia and pattern of neuropsychological deficits with a focus on executive dysfunction did not change decisively. However, an increase in motivation and empathy was described by his wife, and his obsessive-compulsive behavior seemed obviously to be improved, as reflected in the now correctly filled in crossword puzzles. For the latter, one might also discuss modifications by changes in disinhibition as the NPI indicated no disinhibition any more at the follow-up visit. On the other hand, the son still reported disinhibition in eating behavior during the follow-up visit. For disinhibition, as assessed by the frontal systems behavioral scale revised, information of the relative was not available for the follow-up, whereas the patient himself reported almost no changes during the two visits.

In this case, a therapy with citalopram was indeed helpful for the patient's everyday life and that of his caregivers, as has previously been described in the literature [3]. Randomized, double-blinded, and placebo-controlled serotonergic drug trials concerning frontotemporal lobar degeneration/bvFTD are still scarce. To our knowledge, there is none concerning citalopram to this date. There have only been two randomized, double-blinded, and placebo-controlled drug trials using other selective serotonin reuptake inhibitors. One of them did not show any improvement in behavior and showed a decline of cognition [14], which stands in contrast to smaller open-label studies [3–5], and one study showing improvement in the patients' NPI scores, while no change in cognition was detected [15]. This current state of knowledge demonstrates the need for further investigation of serotonergic transmission and treatments in bvFTD.

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Statement of Ethics

The Ethics Committee of the University of Leipzig approved the study (FTLD Consortium Germany; <http://www.ftld.de>) in which the patient took part and for which data were collected (Reference No. 137-11-18042011). The patient gave informed consent to participate in the study.

The patient's wife gave written informed consent for the publication of this case report and any accompanying images as the patient died approximately 1 year after follow-up investigation from a somatic disease.

The data generated and/or analyzed during the current study are not publicly available due to doctor-patient confidentiality and to ensure the patient's anonymity, but they are available from the corresponding author on reasonable request.

The authors have no ethical conflicts to disclose.

Disclosure Statement

The authors have no conflicts of interest to declare.

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Author Contributions

S.M. and M.L.S. drafted the manuscript. M.L.S., C.G., K.G., and A.M. performed the neuropsychiatric and neuropsychological assessment. M.L.S., K.M., S.T., and H.B. were involved in imaging acquisition and analyses. K.M., C.G., K.G., A.M., S.T., H.B., and O.S. critically revised the manuscript. All authors read and approved the final manuscript.

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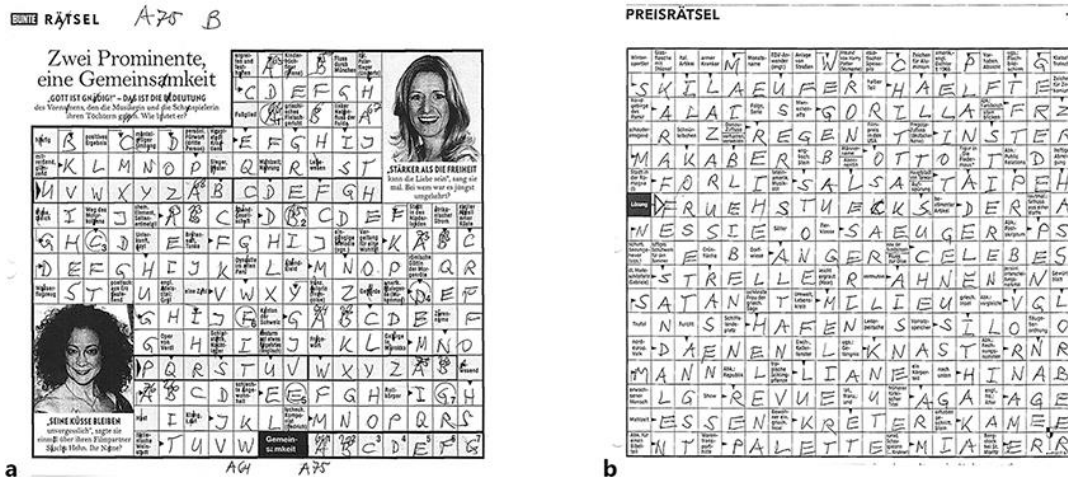


Fig. 1. Two crossword puzzles filled in by the patient. **a** At baseline. **b** After consecutive treatment with 20 mg citalopram per day.

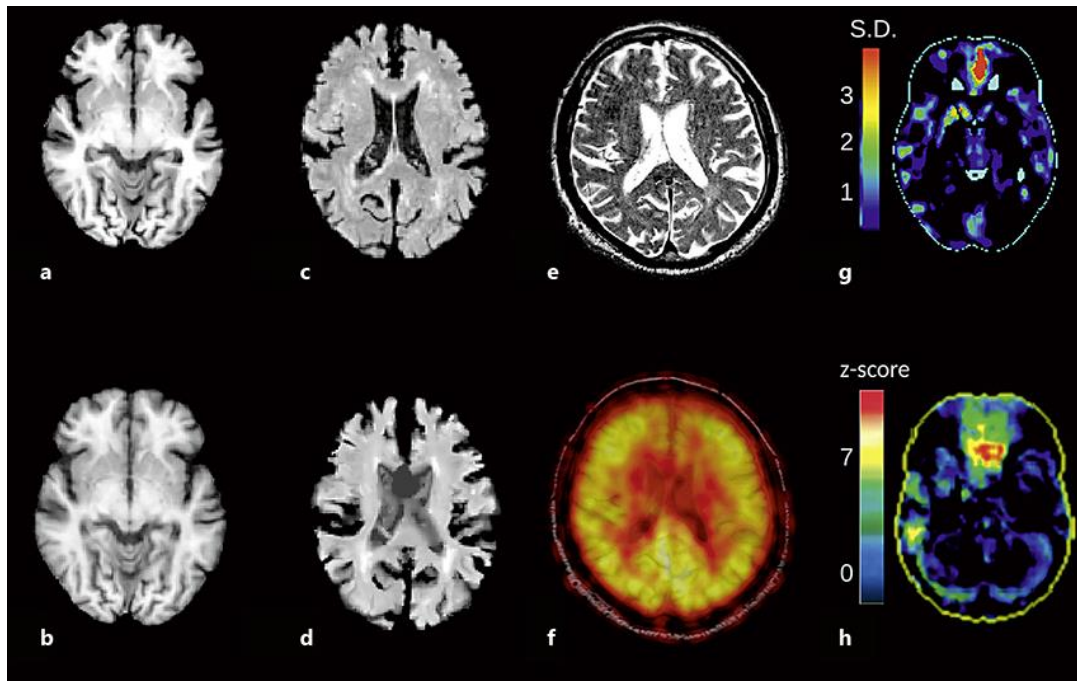


Fig. 2. The patient's T1-MRI scans at baseline (**a**) and 1 year later at follow-up (**b**), showing subtle bifrontoparietal atrophy. Fast fluid-attenuated inversion recovery images at baseline (**c**) and at follow-up (**d**), showing punctual hyperintensities in white matter. T2*-MRI scan at baseline (**e**) showing no evidence of (micro-)bleeding. Fusion image of the patient's T1-MRI scan and ^{18}F -FDG-PET scan at baseline (**f**), showing impaired glucose metabolism with a focus in the bilateral mediofrontal lobe. The relative quantitative analysis of FDG tracer uptake confirmed reduced tracer uptake in the bilateral mediofrontal lobe compared to a normal control group (25 normal subjects). **g** Representative transversal slice of the region-based evaluation using Hermes Brass software, and **h** using three-dimensional stereotactic surface projection analysis, bottom view. S.D., standard deviation.

Table 1. The patient's performance in neuropsychological tests

Neuropsychological tests (maximum raw score)	Raw score		Percentile ^a	
	baseline	follow-up	baseline	follow-up
<i>CERAD Neuropsychological Battery</i>				
Verbal Fluency, animal naming	22	22	61	68
Verbal Fluency, s-words	15	11	78	54
Boston Naming Test (15)	15	15	85	89
Mini-Mental State Examination (30)	30	30	94	96
Word-List Learning (30)	19	19	56	63
Word-List Delayed Recall (10)	6	7	46	73
Word-List Delayed Recall Savings, % (100)	86	100	54	87
Word-List Recognition, % (100)	100	100	83	86
Constructional Praxis (11)	10	11	16	81
Constructional Praxis: Delayed Recall (11)	10	5	64	4
Constructional Praxis: Savings, % (100)	100	45	81	4
Trail Making Test A, ms	43	54	64	61
Trail Making Test B, ms	80	77	87	94
Trail Making Test A/B	1.9	1.4	78	97
<i>Test of Attentional Performance</i>				
Alertness, ms	306	277	18	42
<i>Wechsler Memory Scale Revised (standardization sample age group 65–74 years)</i>				
Digit Span forward (12)	6	7	28	53
Digit Span backward (12)	4	4	13	13
Visual Memory Span (14)	7	7	28	28
Visual Memory Span (12)	6	8	27	67
Logical Memory Immediate Recall (50/53 ^b)	28	40 ^b	74	91 ^b
Logical Memory Delayed Recall (50/39 ^b)	27	26 ^b	87	84 ^b
Visual Reproduction Immediate Recall (41)	31	29 ^b	25–42	63 ^b
Visual Reproduction Delayed Recall (41)	25	26 ^b	38–42	50 ^b
<i>Behavioral Assessment of the Dysexecutive Syndrome</i>				
Action Program Test (5)	5	5	4 of 4 ^c	4 of 4 ^c
Key Search (16)	16	16	3 of 4 ^c	4 of 4 ^c
Zoo Map (16)	3	9	1 of 4 ^c	2 of 4 ^c
<i>Hamasch 5-Point Test Revised</i>				
Designs total	63	36		
Correct designs	20	22	24	24
Perseverations	25	14	<2	2–5

The follow-up investigation was 12 months after baseline testing. CERAD, Consortium to Establish a Registry for Alzheimer's Disease. ^a Percentile indicates with a value of 16 one standard deviation below the norm, and with a value of 2 two standard deviations below the norm. ^b Wechsler Memory Scale – IV (standardization sample age group 80–85 years). ^c Profile score.

Table 2. The patient's performance in dementia-related and behavioral assessments

Dementia-related assessments	Baseline		Follow-up	
	frequency	impairment	frequency	impairment
<i>Frontal Systems Behavioral Scale revised – self-assessment (patient)</i>				
Total score	44	35	39	35
Executive dysfunction	16	15	14	14
Disinhibition	11	9	12	8
Apathy	17	11	13	13
<i>Frontal Systems Behavioral Scale revised – external assessment (relative)</i>				
Total score	66	36	n.a.	n.a.
Executive dysfunction	25	12	19	n.a.
Disinhibition	10	9	n.a.	n.a.
Apathy	31	15	24	n.a.
<i>Bayer-Activities of Daily Living Scale</i>				
External assessment (caregiver)		7.08		3.24
Self-assessment (patient)		2.84		2.68
CDR		3.5		6.5
Frontotemporal Lobar Degeneration-Modified CDR		5.5		4.5
<i>NPI</i>				
Total score		17		16
Apathy		4		8
Disinhibition		1		0
Aberrant motor behavior		8		4
Changes in appetite and eating behavior		4		4

Follow-up investigation was 12 months after baseline testing. For the NPI, only relevant behavioral symptoms are displayed. For the Mini-Mental State Examination, see Table 1. n.a., not available.