Frontotemporal Dementia: Treatment Response to Serotonin Selective Reuptake Inhibitors

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Background: Patients with frontotemporal dementia (FTD) present initially with primarily behavioral rather than cognitive symptoms. Decreased serotonin receptor binding has been reported in the frontal lobes, temporal lobes, and hypothalamus in autopsy-proven FTD cases. This study tests the hypothesis that many of the behavioral symptoms of FTD (including disinhibition, depressive symptoms, carbohydrate craving, and compulsions) will respond to serotonin selective reuptake inhibitors (SSRIs).

Method: Eleven subjects meeting the Lund-Manchester clinical, neuropsychological, and neuroimaging criteria for FTD were treated with SSRIs (fluoxetine, sertraline, or paroxetine). After 3 months, treatment responses for disinhibition, depressive symptoms, carbohydrate craving, and compulsions were evaluated prospectively without placebo control.

Results: After treatment, disinhibition, depressive symptoms, carbohydrate craving, and compulsions all showed improvement in at least half the subjects in which they had been present. One subject stopped sertraline treatment because of diarrhea, while another stopped paroxetine treatment due to increased anxiety. The presence of individual behavioral symptoms and also the response of each symptom to SSRIs were unrelated to cognitive impairment as measured by baseline Mini-Mental Status Examination ($.07 \leq p \leq 1.00$).

Conclusion: The behavioral symptoms of FTD may improve after treatment with SSRIs. Future neurochemical studies and controlled pharmacologic trials may improve available treatments.

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Frontotemporal dementia (FTD)[1] refers to a clinical syndrome first described over 100 years ago[2] caused by selective degeneration of the frontal and anterior temporal lobes, resulting in distinct clinical, neuroimaging, and neuropathologic features.[3–5] Various terms, such as Pick's disease,[6,7] frontal lobe dementia of the non-Alzheimer type,[8] dementia of the frontal lobe type,[9] and frontal lobe degeneration,[10] have been used to describe this syndrome. The primary early clinical features of FTD include personality changes, such as impulsive disinhibition, affective lability, and apathy.[1,11,12] Cummings and Duchen[13] reported a series of patients with Pick's disease who had symptoms consistent with the Klüver-Bucy syndrome,[14] such as hyperorality and dietary changes, as well as blunted, depressed, or irritable emotional affect. Other investigators also have reported carbohydrate craving with weight gain,[15] depressive symptoms,[10,16,17] and compulsions.[15,18]

Despite these distinctive clinical features, many FTD patients are often misdiagnosed as having Alzheimer's disease. A recent report of patients with a postmortem diagnosis of Pick's disease found that only 3 (14.3%) of 21 were correctly diagnosed before autopsy, with the remaining 18 misdiagnosed as Alzheimer's disease.[19] An improved understanding of FTD symptoms and their neurochemical associations would improve diagnostic accuracy and, perhaps, increase treatment specificity.

Recently, a set of diagnostic criteria for FTD, the Lund-Manchester Research Criteria, was published.[1] This document includes clinical, neuropsychological, and neuroimaging criteria for FTD. Clinical criteria include behavioral symptoms (such as disinhibition, loss of social awareness, overeating, perseverative behaviors, and impulsivity), affective symptoms (such as depression, emotional indifference, and apathy), and speech disorder (such as reduced speech, stereotypy of speech, echolalia, perseveration, and late mutism). Neuropsychological testing criteria include profound failure on "frontal lobe" tests of executive function in the absence of severe amnesia, aphasia, or visuospatial skills. Neuroimaging criteria include frontal and/or anterior temporal cortical abnormalities on structural and/or functional imaging. Neuropathologic criteria include gross (frontal and/or anterior temporal lobe atrophy, with sparing of the striatum,

amygdala, or hippocampus) and microscopic (microvacuolation and astrocytic gliosis) changes for either the Pick type (Pick bodies present) or non-Pick type (Pick bodies not present) of FTD. A recent publication[20] reported that the Lund-Manchester Research Criteria accurately predicted prior to autopsy the neuropathologic diagnosis of FTD in seven of seven cases.

Functional neuroimaging with single photon emission computed tomography (SPECT) has proved quite useful in diagnosing FTD. A recent study[21] of cerebral blood flow (CBF) in autopsy-proven FTD reported bilateral or unilateral cerebral blood flow reductions in the frontal or frontotemporal cortex in 27 of 27 cases. Read et al.[20] recently reported that SPECT accurately distinguished 11 of 12 autopsy-proven Alzheimer's dementia cases from seven of seven autopsy-proven FTD cases. In that study, Alzheimer's dementia subjects showed bilateral posterior temporoparietal hypoperfusion in all 11 accurately predicted cases and multifocal hypoperfusion in 1 case. All seven FTD cases showed bilateral frontotemporal hypoperfusion.

Many behavioral symptoms found in FTD (including impulsive disinhibition, depressive symptoms, carbohydrate craving with weight gain, and compulsions) have been described in nondementia populations.[22–24] Among nondemented patients, these symptoms often improve when treated with medications that increase serotonin activity.[22,23] Given the existing literature[21–24] supporting an association between serotonin abnormalities and behavioral symptoms that are observed in FTD, it is not surprising that low serotonin receptor binding has been reported in FTD.[25]

These findings suggest that FTD symptoms might respond to medications that increase central serotonin functioning. In fact, one recent report[17] describes two cases of FTD with depression that responded to treatment with paroxetine and lithium, possibly by increasing postsynaptic serotonin activity. We report here our preliminary data using serotonin selective reuptake inhibitors (SSRIs) to treat a series of FTD subjects.

METHOD

Subjects and Diagnosis

Eleven subjects (7 men and 4 women) between the ages of 53 and 69 years (mean ± SD age = 60.4 ± 4.9 years) with a mean ± SD education level of 13.8 ± 3.3 years (range, 7–18), who had been referred to the outpatient dementia clinic at Harbor-UCLA Medical Center and subsequently diagnosed with frontotemporal dementia, agreed to a trial of an SSRI. This treatment was indicated based on clinical evidence that behavioral symptoms similar to those found in FTD respond to SSRIs in nondementia populations. The possible risks and benefits were explained to all subjects and caregivers, and informed consent was obtained before any medications were administered.

All subjects were diagnosed prospectively based on clinical neurobehavioral examination, neuropsychological testing, and neuroimaging results consistent with previously described criteria for FTD.[1–10,13] The Lund-Manchester Research Criteria[1] for FTD, which organized those criteria into one cohesive document, were published after several of our subjects already had been diagnosed. However, at the time of their diagnosis, all 11 of our subjects met the clinical, neuropsychological, and neuroimaging criteria for FTD that were used to create the Lund-Manchester Research Criteria.

All subjects underwent a neurobehavioral evaluation, including clinical interview and physical examination. Laboratory blood tests showed no evidence of reversible dementias. All subjects had at least a 2-year history of gradually progressive decline in behavior and cognition. Common behavioral symptoms were social disinhibition, apathy, irritable lability, depressive symptoms, compulsions, and carbohydrate craving. Subjects' primary caregivers were questioned as previously described[15] to help determine the prevalence of disinhibition (e.g., poor impulse control, sexually inappropriate behavior, verbal or physical outbursts), carbohydrate craving (e.g., candy, cakes, chocolate, beer), compulsions (e.g., cleaning or checking rituals, preoccupation with symmetry), and depressive symptoms. Common depressive symptoms included depressed mood, anhedonia, irritability, increased appetite, emotional withdrawal, and amotivation. Although several FTD subjects presented with depressive symptoms, none met DSM-III-R criteria for major depression. No FTD subjects presented with hopelessness, guilt, suicidality, or early morning awakenings.

Neuropsychological testing was performed on all subjects and included a complete battery of executive function tests and the Mini-Mental Status Examination (MMSE).[26] As has been previously reported,[10] all subjects showed profound impairment on tests of frontal lobe function (i.e., executive functions, including ability to change set), which was significantly more severe (> 1.5 standard deviations) than that seen with either normal aging or major depression.[27–29] The severe verbal and behavioral perseverations displayed by these FTD subjects were not consistent with major depression. No subjects displayed impaired visuospatial ability (which is commonly seen in Alzheimer's disease). The baseline mean ± SD MMSE score was 22.9 ± 5.1 (range, 11–28).

All subjects underwent magnetic resonance imaging (MRI) and SPECT head scans. MRI used T_1- and T_2-weighted images with either a Picker (Cleveland, Ohio) or General Electric (Milwaukee, Wis.) superconducting 1.5 tesla magnet. We excluded subjects with structural brain lesions or stroke. All subjects showed frontal and/or anterior temporal cortical atrophy.

SPECT was performed with ^{133}Xe and ^{99m}Tc-hexamethylpropyleneamine oxime (HMPAO). Subjects were studied while they were in the supine position and awake with their eyes open in a room with low ambient light and noise. After inhalation of 30 mCi (1100 MBq) of ^{133}Xe gas, CBF was measured using high-sensitivity collimation with a brain-dedicated unit (Headtome II, Shimadzu, Kyoto, Japan). Next, each patient received 20 mCi (740 MBq) of HMPAO (Ceretec; Amersham, Arlington Heights, Ill.) injected intravenously. Scanning started 2 hours after injection, to allow soft tissue background activity to clear. Transaxial scans were parallel and started at the orbitomeatal line. All SPECT scans were read visually by a nuclear medicine physician with considerable experience reading SPECT brain scans who was blinded to clinical symptoms or neuropsychological test results.

All ^{133}Xe SPECT scans were consistent with FTD, showing decreased unilateral or bilateral frontotemporal CBF, with frontal CBF < 30 mL/100 mg tissue/minute in all subjects at the time of diagnosis. HMPAO images were displayed with a color scale that defined the normal to abnormal interphase at 66% of maximal counts on each slice. All HMPAO SPECT scans also were consistent with FTD, showing unilateral or bilateral frontotemporal hypoperfusion in all subjects at diagnosis.

Autopsy results are available for 5 of our 11 subjects, including the 2 subjects with the highest MMSE scores (both scored 28 at baseline, followed by precipitous declines over the course of 2 years). Gross and microscopic neuropathology for all 5 of these subjects met the Lund-Manchester Research Criteria for FTD.[1] None of these 5 FTD subjects showed pathologic evidence of Alzheimer's disease or vascular dementia.

Design and Statistics

Clinical response to treatment with an SSRI (fluoxetine, sertraline, or paroxetine) given orally was evaluated prospectively without placebo control. Five subjects received fluoxetine 20 mg/day. Five subjects received sertraline, with doses ranging from 50 to 125 mg/day (mean ± SD dose = 75.0 ± 35.4 mg/day). One subject received paroxetine 20 mg/day. Minimal duration of treatment was 3 months, at which time treatment response was evaluated. A 7-point rating scale modeled after the Clinical Global Impressions (CGI)[30] change scale was used to prospectively rate separately the treatment response of four individual behavioral symptoms (disinhibition, depressive symptoms, carbohydrate craving, and compulsions). The following 7-point rating scale was utilized: 1 = very much improved, 2 = much improved, 3 = mildly improved, 4 = no change, 5 = mildly worse, 6 = much worse, 7 = very much worse. Improvement was defined as "much" or "very much" improved (score of 2 or 1). Percentages of subjects with individual target symptoms before treatment and percentages of these subjects showing improvement in these individual target symptoms after treatment were calculated. Pretreatment and posttreatment ratings were done by the same investigator (J.R.S.). Differences in baseline mean ± SE MMSE scores between subjects in whom the target behavioral symptoms were either present or not present, as well as between subjects who either improved or did not improve with SSRIs, were compared in unpaired, two-tailed t tests.

RESULTS

All 11 subjects exhibited at least one of the four behavioral symptoms, and 10 of 11 subjects exhibited at least two. Disinhibition was present in 9 (82%) of 11 subjects and improved in 6 (67%). Depressive symptoms were present in 6 (55%) of 11 subjects and improved in 4 (67%). Carbohydrate craving was present in 9 (82%) of 11 subjects and improved in 5 (56%). Compulsions were present in 7 (64%) of 11 subjects and improved in 4 (57%). No subject exhibited a worsening of any of the four target symptoms. Two of the 11 subjects showed no improvement in any of the behavioral symptoms.

The SSRIs were well tolerated by most subjects. Adverse reactions were relatively mild, causing 2 subjects to discontinue treatment. One subject stopped sertraline due to diarrhea, and another stopped paroxetine due to anxiety with mild psychomotor agitation.

Four comparisons of mean ± SE baseline MMSE scores were done between subgroups of subjects who either exhibited or did not exhibit each of the individual target symptoms using two-tailed, unpaired t tests. None of the four comparisons were statistically significant. These t tests yielded the following results: disinhibition, $p = .07$; depressive symptoms, $p = .47$; carbohydrate craving, $p = .46$; compulsions, $p = .18$.

Four comparisons of mean ± SE baseline MMSE scores were done using two-tailed, unpaired t tests between subgroups of subjects who either improved or did not improve in each of the individual target symptoms with SSRI treatment. None of the four comparisons were statistically significant. These t tests yielded the following results: disinhibition, $p = .91$; depressive symptoms, $p = 1.00$; carbohydrate craving, $p = .68$; compulsions, $p = .72$.

DISCUSSION

These preliminary results suggest that, after treatment with SSRIs, at least half of FTD patients will show improvement in behavioral symptoms such as disinhibition, depressive symptoms, carbohydrate craving, and compulsions. SSRIs were well tolerated by our elderly subjects. The presence of individual behavioral symptoms and their response to SSRI treatment were unrelated to the degree of cognitive impairment as measured by baseline MMSE

scores. The trend toward a lower baseline MMSE score among subjects showing no disinhibition compared to those showing disinhibition was primarily due to 1 subject (MMSE 11/30) with pathologically proven FTD.

Some methodological concerns need to be addressed when considering the clinical significance of these results. These include the uncontrolled and unblinded design, the relatively small number of subjects, and the use of three different SSRIs. The natural course for these behavioral symptoms in FTD is not well documented. In addition, baseline measurements of behavioral symptoms included presence of symptoms, but not severity of symptoms. Nonetheless, we believe these data provide sufficient reason to proceed to a more methodologically rigorous study.

Recent neurochemical studies of FTD have shown a significant decline in serotonin receptor binding.[25] Among autopsy-proven FTD cases, Sparks and Markesbery[25] found presynaptic and postsynaptic serotonin receptor binding to be reduced in the frontal lobes, temporal lobes, and hypothalamus, but unchanged in the nucleus basalis of Meynert. Serotonin dysfunction in the frontotemporal cortex and hypothalamus may underlie many of the behavioral symptoms manifesting early in FTD.

The impulsive disinhibition of FTD often appears as socially or sexually inappropriate behavior. Behavioral disinhibition and impaired impulse control (manifesting as either self-mutilation/suicide or aggression toward others) have been associated with reduced central serotonin activity or low cerebrospinal fluid 5-hydroxyindoleacetic acid (5-HIAA).[31–34] These symptoms have been treated in non-FTD populations with various medications that increase postsynaptic serotonin function, including sertraline,[35,36] eltoprazine,[37] buspirone,[38,39] and lithium.[40–42]

FTD has a high prevalence of affective lability[1,10,13] and depressive symptoms,[1,10,13,16,17] such as depressed mood, anhedonia, increased appetite, emotional withdrawal, and amotivation. Untreated syndromal major depression has been consistently associated with reduced serotonin type-2 receptor responsiveness, which returns to control values after clinically effective treatment.[23,24,43,44] SSRIs are thought to treat depression by increasing the postsynaptic activity of serotonin, leading to subsequent intraneuronal changes.[23,43,44] These changes may mediate the improvement in depressive symptoms found in our FTD subjects.

Almost every FTD subject in this study exhibited a shift in eating preferences from proteins to sweet foods, such as candy or chocolate. Such a change in diet has been associated with decreased serotonin activity in the hypothalamus,[45] where serotonin normally acts as an appetite suppressant.[46] SSRIs increase postsynaptic serotonin binding and have been reported to decrease appetite in various patient populations.[23,47–50] Conversely, cyproheptadine, a postsynaptic serotonin antagonist, is used to improve appetite in anorexia nervosa.[51] The reduced serotonin binding found in the hypothalamus of FTD subjects[25] may explain the high frequency of carbohydrate craving and weight gain found in these subjects.

Compulsions in FTD include, among others, cleaning/hygiene rituals, checking, and preoccupation with symmetry. Obsessive-compulsive disorder responds to treatment with medications that increase central serotonin activity, including both clomipramine[52] (which is five times more selective for serotonin than norepinephrine reuptake blockade) and SSRIs.[53] The high prevalence of compulsions in FTD[15,18] and the postmortem neurochemical finding of reduced serotonin receptor binding[25] among these patients are consistent with the hypothesis that low central serotonin activity may be related to compulsions.

In conclusion, a significant number of FTD patients initially show impulsive disinhibition, depressive symptoms, carbohydrate craving, and compulsions. These clinical features may be related to the reduced serotonergic receptor binding in the frontal lobe, temporal lobe, and hypothalamus that is characteristic of FTD at autopsy. Medications that increase central serotonin transmission, such as SSRIs, may be effective treatments for some of the behavioral symptoms of FTD. Other medications that increase serotonin function, such as trazodone, buspirone, lithium, or eltoprazine, also may prove effective. The exact mechanism by which SSRIs improve behavioral pathology remains unknown. Alternatively, treatment response of FTD to SSRIs may be due to mechanisms unrelated to serotonin function. Future neurochemical studies and controlled pharmacologic trials of FTD should enhance our understanding of this dementia.

Drug names: buspirone (BuSpar), clomipramine (Anafranil), cyproheptadine (Periactin and others), fluoxetine (Prozac), paroxetine (Paxil), sertraline (Zoloft), trazodone (Desyrel and others).

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