Table 2
Frequency of delusions and hallucinations in FTD cases with C9ORF72 mutations

Author	Subject	Control	Delusions	Hallucinations
Sha et al., [9]	FTD ($n=15$)	FTD non-carriers ($n=48$)	21%*	–
Snowden et al., [8]	FTD ($n=19$) PPA ($n=4$) FTD-MND ($n=9$)	non-carriers ($n=366$)	50%	19%
Mahoney et al., [10]	FTD ($n=12$) PPA ($n=1$) FTD-MND ($n=3$)	–	<12%	<12%
Hsiung et al., [75]	FTD ($n=15$) FTD-MND ($n=7$) ALS ($n=8$)	–	3%	0%
Boeve et al., [11]	FTD ($n=16$) FTD-MND ($n=3$) ALS ($n=1$)	–	45%	50%
Simon-Sánchez et al., 2012 [74]	FTD ($n=28$) PPA ($n=8$) FTD-MND ($n=6$)	–	0%	5%
Galimberti et al., [121]	FTD ($n=29$) PPA ($n=2$) FTD-MND ($n=8$)	non-carriers ($n=37$)	12%	15%
Le Ber et al., [122]	FTD, PPA, PSP/CBDS, FTD-ALS ($n=202$)	–	–	7%

*at the first observation. ALS, amyotrophic lateral sclerosis; C9ORF72, chromosome 9 open reading frame 72; FTD, frontotemporal degeneration; FTD-ALS, FTD with ALS; FTD-MND, FTD with motor neuron disease; PPA, primary progressive aphasia; PSP/CBDS, progressive supranuclear pulsy/corticobasal degeneration syndrome.

linked to chromosome 17q (FTDP-17), accounting for 10–15% of familial FTD subjects [58]. Some studies reported cases or families with the MAPT gene mutation at S356T presenting psychosis from a very early age and being subsequently diagnosed as FTD [48, 59]. This S356T mutation leads to atypical FTD-P pathology with more 3R tau and classical Pick bodies. Given that a few case studies addressed this gene mutation, it remains uncertain whether the type of MAPT mutation or the age at which this mutation is expressed is a determining factor in the presentation of psychosis.

GRN mutation

More than 60 mutations in the GRN gene on chromosome 17 have been identified, responsible for a relatively large proportion of patients with familial FTD. Patients with FTD with the GRN mutation account for approximately 5–10% of all patients with FTD, and approximately 20% of patients with familial FTD [60]. Their neuropathology is characterized by the tau-negative and TDP-43-positive linear nuclear inclusions. Several case and family reports suggested a relationship between GRN gene mutation and psychosis in patients with FTD [61, 62]. Le Ber et al. found GRN mutations in 10 out of 210 patients with FTD. They also identified that 30% of GRN mutations carriers had visual hallucinations, and 20% had delusions during the course of the disease [63]. Later, they analyzed 502 probands with FTD and related disorders, and found that 32 had a GRN mutation. Among them, visual hallucinations were found in 8 patients (25%) and delusions were found in 2 patients (6%). They suggested that hallucinations may help differentiate GRN mutation carriers from other FTD patients [64].

C9ORF72 mutation

C9ORF72 is considered to be one of the most frequent genetic causes of FTD, FTD with motor neuron disease (FTD-MND), and amyotrophic lateral sclerosis (ALS) [65, 66]. C9ORF72 mutations are pathologically associated with the deposition of the FTLD-TDP type B, although some patients have a pattern that looks more like FTLD-TDP type A [67]. Additionally, in these patients there are Tau, FUS, and TDP-43 negative but P62-positive aggregates in hippocampal, thalamic, and cerebellar regions. There are many clinico-pathological-genetic studies reporting that patients with FTD with C9ORF72 mutation have a high prevalence of psychotic features (hallucinations or delusions) up to 50%, as well as other neuropsychiatric features, such as depression or anxiety, suggesting that these symptoms could be markers of this mutation [8, 9, 11].

Table 2 summarizes reports on the frequency of delusions and hallucinations in patients with C9ORF72 mutations, including FTD. This table includes studies on FTD, primary progressive aphasia (PPA), FTD-MND, and ALS. Studies only investigating FTD-MND and ALS were excluded. Among the included studies, delusions and hallucinations were reported in 0% to 50% of the patients with C9ORF72 mutations.

Prominent psychotic symptoms were observed in carriers with C9ORF72 expansion as early manifestations. Snowden et al. found that psychotic symptoms were found more frequently in carriers (38%) than in non-carriers (<4%), which led to initial diagnoses of delusional psychosis, somatoform psychosis, or paranoid schizophrenia of mutation groups [8]. The delusions were somatic and alterations in temperature perception, preoccupation with bowel movements, and leg pain contributed to the delusional disorder, although there is still discussion whether we can define these changes in perception as delusions. Sha et al. compared clinical symptoms between C9ORF72 mutation carriers and non-carriers and reported delusions were more frequently reported as the initial neuropsychiatric symptoms in the carriers (21%) than the non-carriers (0%) [9]. Contrary to the findings of

Snowden et al., delusions were of the paranoid type and included delusions of jealousy; somatic delusions were not observed. Interestingly, significant differences in delusions between carriers and non-carriers disappeared when using the NPI at evaluation, suggesting that delusions could be attributed to C9ORF72 mutations when they were reported as the first symptom. Hallucinations were not reported as initial neuropsychiatric symptoms in C9ORF72-associated disease, and were also uncommon at evaluation.

Moreover, there are several case reports describing the relationship between C9ORF72 mutation and psychosis, including clinico-pathological studies [67], imaging studies [68], and kindred reports [69]. Furthermore, some case reports suggested that psychosis may precede the development of dementia, indicating that psychosis may potentially be prodromal or an early symptom of FTD with C9ORF72 mutation [70]. Within these case reports, subjects in whom psychosis preceded dementia included three atypical psychiatric patients [71], one patient with delusions of pregnancy [72], and one patient with bipolar affective disorder [73].

By contrast, some other studies suggested a lower prevalence rate of psychosis in carriers with the C9ORF72 mutation. For example, Simón-Sanchez et al. found that only two out of 42 mutation carriers presented with hallucinations and none had delusions [74]. Mahoney et al. reported that the prevalence of psychotic symptoms was approximately 10% in patients with C9ORF72 mutation [10]. In this study, delusions were late manifestations in mutation carriers. Delusions were not observed in the initial assessment, whereas hallucinations were reported in about one-half of patients at the initial assessment. Hsiung et al. reported one FTD mutation carrier out of 30 that presented with delusions, who was initially diagnosed with psychosis/schizophrenia [75]. The wide-variety in the results coming from these studies may suggest different ways to detect and code the delusions and hallucinations, different timing of appearance of the symptoms during the illness, and variety of the persistence of symptoms.

Other mutations related to psychosis in FTD

Several other genetic mutations were also reported. Mosca et al. described a proband of the transactive response DNA-binding protein (TARDBP) mutation carriers that developed hallucinations [76]. Tang-Wai et al. identified a presenilin 1 (PSEN1) gene mutation in one allele in a kindred consisting of three FTD cases presenting with delusions and illusions [77]. Gourzis et al. found a genetic defect on chromosome 1 (46, XX, 1qh-) in a patient with early-onset FTD who had been misdiagnosed with schizophrenia [78].

As a whole, C9ORF92 mutation, which is related to the TDP-43 type B pathology, may be the most common genetic factor in patients with FTD presenting psychosis. GRN mutation, which is related to the TDP-43 type A pathology, may be the second most common. However, some additional factors, such as anatomical distinctions, within these specific genetic groups may have contributed to the development of psychosis.

Neuroimaging studies on psychosis in FTD

Several neuroimaging studies have investigated patients with C9ORF72; this mutation is reported to be associated with a high frequency of psychosis in FTD. These studies emphasized thalamic and cerebellar atrophy in mutation carriers [9, 10, 79]. Thalamic and cerebellar projections could be related to the psychosis associated with the C9ORF72 mutation although further research is warranted [10, 45].

Chan et al. examined relationships between predominant right temporal lobe atrophy (RTLA) and clinical profiles in patients with FTD. They found that predominant RTLA (i.e., mean volume reduction of 41% and 51% in the right hippocampus and amygdala, respectively) is associated with a higher rate of visual hallucinations (10%) in patients with FTD compared to those with semantic dementia (left dominant atrophy patients) (0%) [80]. These results suggest a relationship between right temporal damage and the presence of psychotic symptoms.

Some of the recent studies addressed the condition FTD phenocopy syndrome [81], which has similar behavioral disturbances to "real FTD" but shows normal structural and functional neuroimaging findings, and a slow progression over many years [82, 83]. However, the relationship between these phenocopy groups and psychosis are still uncertain.

Altogether, there is still a lack of clear evidence regarding anatomical correlation of psychosis using neuroimaging methods.

Treatment for psychosis in FTD

To date, there is no specific disease modifying treatment or preventative treatment for FTD. Medications for AD and psychiatric disorders are frequently used as off-label treatments for FTD [84]. Current pharmacological studies on FTD mainly focus on treating behavioral symptoms, such as compulsions, repetitive

behaviors, stereotypical movements, eating abnormalities, and apathy, using various kinds of psychotropics, including acetylcholinesterase inhibitors, antidepressants, atypical antipsychotics, and NMDA glutamate receptor antagonists [85, 86]. No systematic studies confirmed that they are effective for psychosis in patients with FTD, only several case studies exist to date. There are two case reports of patients with FTD with Cotard's syndrome, which had not responded to pharmacotherapy but were subsequently improved by electroconvulsive therapy [87, 88]. While several open label studies examined the effects of alternative medicines on delusions and hallucinations in FTD [89, 90], the sample size is too small and further research is warranted.

Atypical antipsychotics are still widely used for behavioral symptoms of patients with FTD, however, there are no large scale systematic studies about the effectiveness of these drugs. Adverse effects often limit the use of these drugs for FTD, and the decision to use them should be made with caution. An important concern is the increased susceptibility to extrapyramidal symptoms induced by antipsychotics in patients with FTD [91]. Age and long-term antipsychotic exposure are risk factors for development of treatment-resistant tardive dyskinesia [92–94]. Additionally, a meta-analysis of randomized, placebo-controlled trials suggested that antipsychotic treatment of elderly patients with dementia is associated with a 1.6- to 1.7-fold increase in mortality secondary to cardiac events or infection, which in turn prompted the Food and Drug Administration to place a 'black-box warning' on their use. Thus, given the absence of treatment for psychosis in FTD, further research is needed to elucidate the mechanisms underlying psychosis in FTD in order to develop new therapeutic options for this symptom.

DISCUSSION

Relationships between FTD and schizophrenia

In summary, we have described the following: 1) psychosis is a clinically relevant symptom accompanying FTD, with a prevalence rate of approximately 10–15%; 2) psychosis in FTD may be related to genetic mutations of C9ORF72 and GRN; 3) neuroimaging studies did not achieve conclusive results; and 4) no treatment is currently available for psychosis in FTD.

Psychotic symptoms are seen in multiple different neurodegenerative and neuropsychiatric disorders, including AD, DLB, epilepsy, schizophrenia, and bipolar disorder. A similar pathophysiology for susceptibility to psychosis may exist in these various illnesses. Taking into consideration that psychosis is among the most frequent symptoms in schizophrenia, the potential link between FTD and schizophrenia should be further investigated in order to elucidate the mechanisms underlying psychosis in FTD. Current reports regarding the relationship between FTD and schizophrenia identify potential overlaps in clinical presentation, neuroimaging, neuropsychology, and genetics, while significant differences are found with regard to pathology [12, 95].

First, typical behavioral symptoms in FTD, such as inappropriate social behaviors and repetitive compulsion-like behaviors, symptomatically resemble to confusion and disorganization seen in patients with schizophrenia. Similarly, apathy and deficits in emotional expression in FTD resemble affective flattening and lack of motivation in schizophrenia. Also, it is reported that nearly half of FTD patients with mutations in C9ORF72 experience delusions or hallucinations [8, 11]. Second, neuroimaging research on schizophrenia demonstrates structural and functional alterations in frontal and temporal lobes when compared to healthy controls. Previous studies employing structural MRI report volume reductions in frontal, temporal, limbic, striatal, and thalamic regions in patients with schizophrenia [96]. A meta-analysis of 18 first episode schizophrenia studies (555 patients and 621 control subjects) and 20 studies of FTD (311 patients and 431 control subjects) reveals a spatial overlap of structural brain changes. Both disorders share gray matter deficits in the bilateral caudate, left insula, and bilateral uncus regions [97], although the degree of atrophy differs between symptomatic FTD and schizophrenia. Functional brain imaging in schizophrenia shows altered function and impaired functional connections in frontal and temporal regions [98], similar to what has been found in FTD. Third, neuropsychological data shows poor frontal-executive function in patients with schizophrenia, as demonstrated through tests of set-shifting abilities or selective attention [99]; this impairment is typical of FTD. Finally, certain genetic reports suggest that relatives of probands with GRN or VCP mutations who present with FTD may have a high family history frequency of schizophrenia [62, 100]. Schoder et al. report that the morbid risk for schizophrenia is significantly higher in relatives of probands with FTD (1.35) than in relatives of probands with AD (0.32). Some questions regarding this finding arise due to the fact that the rate of schizophrenia in this genetic group is only 1.1%, which is comparable to the general population. It is also

unclear whether the individuals with these mutations will continue to have typical FTD-like presentations. Huey et al. studied samples of 192 unrelated subjects with schizophrenia to assess the presence of C9ORF72 mutation. None of the subjects with schizophrenia had the pathogenic expansion [101]. It remains elusive whether schizophrenia should be viewed as related to these mutations. The available literature suggests that a link between FTD and schizophrenia may exist although more studies are needed [102].

This link between FTD and schizophrenia is indicative of potential vulnerability to psychosis in brain systems and pathways shared by both disorders. For example, dysfunction in frontal-subcortical circuits has been implicated in the loss of executive behavioral control in both groups of patients. This dysfunction may lead to alterations in affective state, disinhibition, and specific manners of thinking, such as a tendency to jump to conclusions, which may increase the risk of formation of psychosis in both diseases [103, 104]. Further, thalamic dysfunction may also result in a reduced ability to adjust one's sensory responsiveness to ongoing behaviors in patients with schizophrenia [105]. Psychosis is associated with source-monitoring deficits whereby self-initiated behaviors become attributed to outside sources. A function of the thalamus is to adjust sensory responsiveness in accordance with behavioral contextual cues. Thus, the vulnerability potentially shared by FTD and schizophrenia, including the dysfunction in the frontal cortex and thalamus, may clinically represent psychosis in both types of patients.

Further research

Based on the limitations of previous studies, further research on psychosis in patients with FTD needs to be conducted in larger cohorts with biologically confirmed disease pathologies using clear and standardized definitions of psychosis. Focusing on a specific target potentially related to psychosis, structural and functional neuroimaging studies should compare patients with or without psychosis. Longitudinal follow-up studies from the early stage before the onset of dementia are also required as psychosis often precedes cognitive decline in patients with FTD.

Also, based on the potential linkage between FTD and schizophrenia, future research that references current findings on psychosis in schizophrenia should help to elucidate the mechanisms underlying psychosis in FTD. For example, on the neurotransmitter level, positron emission tomography studies have shown that dopamine synthesis capacity, dopamine release, and baseline dopamine levels are elevated in the striatum in patients with schizophrenia [106]. Similar studies have not been performed in FTD. In addition, increased glutamate signaling in the striatum has been reported in subjects at ultra-high risk for psychosis and in those with first-episode psychosis using magnetic resonance spectroscopy [107]. These increases in dopamine and glutamate in the striatum have been linked to positive symptoms, such as hallucinations and delusions in schizophrenia. Patients with FTD generally show presynaptic deficiencies in striatal dopamine neurotransmitter systems [108, 109], while no consistent finding is reported on the relationship between glutamate and psychosis in FTD. However, only a few studies have examined the relationship between dopaminergic or glutamatergic systems and psychosis in FTD. For example, Engelborghs et al. examined the relationship between cerebrospinal fluid (CSF) levels of dopamine metabolites (DOPAC and HVA) and neuropsychiatric symptoms in patients with FTD ($n = 25$) [110]. They found that CSF DOPAC levels correlated with neuropsychiatric symptoms. Vermeiren et al. examined the relationship between CSF levels of glutamate and neuropsychiatric symptoms in patients with FTD ($n = 32$) [111]. They demonstrated that CSF levels of glutamate negatively correlated with verbally agitated behavior in patients with FTD. These findings suggest that abnormal dopaminergic or glutamatergic neurotransmission may be associated with neuropsychiatric symptoms in FTD. However, no study has specifically focused on the relationship between psychosis in FTD and these neurotransmitter systems.

Thus, further research is required to elucidate the mechanisms underlying psychosis in FTD, with a focus on the systems to which psychosis in schizophrenia is attributed.

Limitations

This review has to be considered in light of the limitations within the literature in addition to the aforementioned limitations in each section. First, research techniques such as neuroimaging, immunostaining, and genetics, were recently developed. Thus, the clinical and pathological concept of FTD continues to change, altering the diagnosis and classification of FTD. Ultimately, this has resulted in various groups employing differing methods to diagnose and classify FTD. Further, few studies specifically addressed psychosis in patients with FTD and the definition of psychosis differed across them. Symptoms comprising

psychosis in FTD may be different among individuals as well as genetic groups. Second, with regard to the genetic roles, East-Asian patients with FTD are known to have fewer family histories [112, 113], and no C9ORF72 mutations cases were found in 75 Japanese subjects with FTD, PSP, and CBD and 75 Korean subjects with FTD [114, 115]. Thus, genetic background may have different roles in the presentation of psychosis between Western and East-Asian patients with FTD. This may be one explanation why symptomatic studies in Asia failed to find psychosis among patients with FTD [27]. Further studies are needed on psychosis in patients with FTD between different ethnic groups.

Third, the sample sizes of most of the references are relatively small. Also, many studies relied on retrospective review of clinical records, and thus, information bias issues should be considered. Fourth, despite the presence of a potential overlap in FTD and schizophrenia in terms of neuropsychology and neuroimaging, significant differences are found between them with regard to pathology [12, 95]. FTD is a neurodegenerative disorder and the degree of neuronal loss is clearly different in FTD from that in schizophrenia, as there is little evidence of large scale neuronal loss in the latter [116]. In addition, this overlap should be explored with caution given that schizophrenia is a syndrome presenting psychosis and FTD presents psychosis as a symptom with a relatively low prevalence.

Moreover, evidence of cognitive decline and the development of dementia in patients with schizophrenia is still unclear, although cognitive impairment is shared by both disorders. The majority of studies on cognition and schizophrenia are uncontrolled. Patients with schizophrenia have many confounding dementia risk factors, including lifestyle, diet, smoking, antipsychotic use, and alcohol and substance abuse [117]. While controversial, it is suggested that patients with schizophrenia do not experience acceleration in cognitive aging [118], rather schizophrenia appears to be a disorder marked by generalized cognitive dysfunction. Finally, frontal areas are influenced in other neuropsychiatric and neurodegenerative diseases. This suggests that the frontal involvement in aforementioned findings, implicated in psychosis, may not be specific to FTD and schizophrenia.

CONCLUSION

Important advances in research exploring the genetics and molecular mechanisms of FTD over the last decades have led to changes in the concept of FTD. As such, the recognition and diagnosis of this disease has increased. Also, recent advances in understanding the genetic mechanisms of FTD reveal that FTD patients with specific genetic background, such as C9ORF72 mutation, have a higher frequency of psychosis than do patients with other mutations. In addition to the frontal dysfunction common in patients with FTD, additional factors in this genetic group may contribute to the development of psychosis.

Psychosis is a common symptom in several neurodegenerative and neuropsychiatric diseases, including FTD and schizophrenia, which may have common vulnerability and endophenotypic mechanisms. These genetic cases that are linked to FTD can be instrumental in clarifying the mechanism of psychosis beyond FTD and may offer principles for understanding the biological correlates of psychosis.

Additionally, psychosis in patients with FTD contributes to worse clinical outcomes, social dysfunction, poorer quality of life, and greater caregivers' burden. Given that no treatment is currently available for psychosis in FTD, there is an urgent need to identify new therapeutic strategies that target these symptoms. Interventions aimed at specific targets shared by FTD and schizophrenia may be effective for the treatment of psychosis in both disorders. Still, no decisive conclusions have been made regarding the biological mechanism of psychosis in FTD. Further research is warranted to elucidate this mechanism, with reference to findings pertaining to psychosis in schizophrenia.

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Psychosomatics 2015:■:■■■–■■■

Original Research Reports

Cognitive Dysfunction in Patients With Late-Life Somatic Symptom Disorder: A Comparison According to Disease Severity

Keisuke Inamura, M.D., Shunichiro Shinagawa, M.D., Ph.D., Tomoyuki Nagata, M.D., Ph.D., Kenji Tagai, M.D., Kazutaka Nukariya, M.D., Ph.D., Kazuhiko Nakayama, M.D., Ph.D.

Background: *Late-life somatic symptom disorder (SSD) is characterized by various aging-associated factors, such as a functional decline, psychosocial problems, and cognitive dysfunction. However, the details of the cognitive dysfunction that occur in late-life SSD are still unknown.* **Objective:** *The aims of this study were to reveal the cognitive profile of patients with late-life SSD and to evaluate how cognitive dysfunction affects disease severity.* **Methods:** *We compared the cognitive profiles of patients with late-life SSD (n = 40) with those of normal control subjects (n = 21). In addition, we divided the patients with late-life SSD into mild-to-moderate (n = 24) and severe (n = 16) groups and compared the cognitive profiles of the 3 groups.* **Results:** *Patients with late-life SSD exhibited a lower Mini-Mental State Examination total score and attention decline. In the 3-group comparison, the severe group had a lower Mini-Mental State Examination score and Frontal Assessment Battery score than the normal control group, whereas no significant difference was seen between the mild-to-moderate and the normal control groups.* **Conclusions:** *Our data suggest that different cognitive patterns may exist depending on disease severity, possibly indicating differences in pathogenesis.*

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INTRODUCTION

Somatic symptom disorder (SSD) is a psychiatric disorder that is commonly observed in primary health care, as these patients tend to visit medical facilities to elucidate their pathogenesis and to receive treatment.[1] According to current diagnostic criteria of the Diagnostic and Statistical Manual of Mental Disorders (fifth edition) (DSM-5), SSD is characterized by somatic symptoms that either are very distressing or result in a significant disruption of functioning, as well as excessive and disproportionate thoughts, feelings, and behaviors regarding those symptoms.[2] The diagnosis of SSD requires both criterion A, the somatic symptoms, and criterion B, which covers excessive thoughts, feelings, and behaviors related to these somatic symptoms or associated health concerns. At least one of the following must be present: (1) disproportionate and persistent thoughts about the seriousness of one's symptoms, (2) a persistently high

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level of anxiety about health or symptoms, and (3) excessive time and energy devoted to these symptoms or health concerns.

Among elderly people, somatic complaints now appear to be as common as they are among young people.[3] Furthermore, the prevalence of somatoform disorders (as diagnosed according to the former DSM-IV text revision diagnostic criteria) is relatively high among the elderly.[4]

SSD exhibits high levels of comorbidity with other anxiety-related disorders or major depressive disorders or both.[6] Therefore, few studies have focused on SSD, especially in the elderly population, and the disease mechanism of late-life SSD remains unclear. In view of this situation, we focused on elderly patients with SSD without any psychiatric comorbidity.

Somatic complaints in the elderly tend to be related to various factors characterized by the aging process[5] and cognitive dysfunction.[6] Moreover, the severity of somatic complaints in late-life influences the patients' quality of life and their disabilities.[3]

From cognitive viewpoints, several studies showed that the presence or severity of anxiety is associated with a lower cognitive performance in the elderly.[7] In a previous study, we observed correlations between disease severity and cognitive dysfunction in patients with late-life somatoform disorders (as diagnosed according to the former DSM-IV text revision diagnostic criteria).[6] We suspected that the cognitive profiles influencing the appearance of symptoms and the symptomatic severity might differ.

No other previous studies comparing the cognitive profiles of normal control (NC) subjects and patients with late-life SSD have been reported. We hypothesized that the representation of distinct characteristics in patients with intractable somatic symptoms occurred as a result of cognitive dysfunction. Thus, it may be necessary to compare cognitive function in patients with late-life SSD according to disease severity.

Based on previous findings regarding the effect of cognitive dysfunction on late-life SSD, the aim of the present study was to examine how cognitive deficits influence the presence of late-life SSD using age-matched NCs.

Furthermore, we confirmed the influence of cognitive profiles on the severity of late-life SSD. We classified the patients into a mild-to-moderate SSD group and a severe SSD group according to the DSM-5 criteria. The cognitive profiles of these groups were then compared with those of NCs. Severity was evaluated as follows:

Mild: Only one of the symptoms specified in criterion B was fulfilled.
Moderate: Two or more of the symptoms specified in criterion B criteria were fulfilled.
Severe: Two or more of the symptoms specified in criterion B were fulfilled, plus there were multiple somatic complaints.

METHODS

Participants

From October 2012 to June 2013, 89 consecutive outpatients aged 65 years old or older who met the criteria for SSD according to the DSM-5 and who had been referred to The Jikei University Kashiwa Hospital outpatient clinic were assessed. All the patients were referred by general physicians, and the absence of any physical disease capable of explaining the somatic symptom was confirmed. All the patients were diagnosed as having SSD according to the DSM-5 diagnostic criteria by 2 expert geriatric psychiatrists (K. I. and T. N.).

The study exclusion criteria were as follows: (1) the presence of severe physical illness, (2) the presence of neurocognitive disorders according to the DSM-5 diagnostic criteria, (3) the presence of atrophy of cortical lesion on magnetic resonance imaging findings (an expert radiologist measured the atrophy of the cerebral cortex using a technique that has been validated via histologic[8] as well as manual measurements),[9] (4) the presence of mild cognitive impairment (MCI) according to the diagnostic criteria for amnestic MCI,[10] (5) the presence of major depressive disorder or a Hamilton Depression Scale score >14 (this number is a valid cutoff score for the Hamilton Depression Scale for patients with dysphasia, compared with the standard cutoff score[11,12]), (6) a diagnosis of another significant psychiatric disorder (e.g., another anxiety-related disorder, hypochondriasis, illness anxiety disorder, pain disorder, or conversion disorder), and (7) a history of major depression or another anxiety-related disorder during the last 5 years. In total, 40 patients with SSD were eligible for inclusion in the present study.

In total, 21 age-matched NC subjects were also recruited for this study. None of these NC subjects had any psychiatric disorder, neurologic illness, history of substance abuse, or history of a psychiatric disorder.

The present study was approved by the Ethics Committee of the Jikei University School of Medicine. A written informed consent was obtained from the subjects or their designated representatives.

Psychologic Assessment

The Short Health Anxiety Inventory

The Short Health Anxiety Inventory (SHAI) was created to measure health anxiety in a manner that would be applicable in medical contexts.[13] In patients with somatic complaints, health anxiety is one of the factors that can amplify somatic perception.[14] We used the SHAI to evaluate the excessive fears or beliefs of patients that led to their misinterpretation of bodily sensations or symptoms.

The Hamilton Anxiety Scale

The Hamilton Anxiety Scale (HAMA) is a rating scale for evaluating the severity of anxiety-related disorders.[15] The HAMA consists of 2 subscores, psychic anxiety (HAMA-PSY; ranging from 0–28 points) and somatic anxiety (HAMA-SOM; ranging from 0–28 points). HAMA-SOM consists of the following items: muscular symptoms, sensory symptoms, cardiovascular symptoms, respiratory symptoms, gastrointestinal symptoms, genitourinary symptoms, and autonomic symptoms (ranging from 0–4 points). The HAMA test and its subscores are reliable and valid for anxiety-related disorders,[15] and the HAMA total and HAMA-SOM have proven to be sensitive measures for evaluating the severity of somatic symptoms.[16–19]

Cognitive Assessment

Mini-Mental State Examination

The Mini-Mental State Examination (MMSE) is a well-known and widely used test for screening cognitive impairment. Possible scores range from 0–30. A score of 28 is the median for normal octogenarians with more than 12 years of education.[20] Patients with an MMSE score <24 were regarded as possibly having dementia and were excluded from the present study.

Frontal Assessment Battery

The Frontal Assessment Battery (FAB) was recently introduced as a short screening test for exploring various functions of the frontal lobes and for evaluating executive functions.[21] The Japanese FAB version consists of 6 subtests: (1) similarities, (2) lexical fluency, (3) motor series, (4) conflicting instructions, (5) go/no go, and (6) prehension behavior. Each subtest is rated from 0–3, with the total score ranging from 0–18.

Japanese Version of the Neurobehavioral Cognitive Examination

The Japanese version of the Neurobehavioral Cognitive Examination (J-COGNISTAT) is a comprehensive cognitive test that consists of 10 subtests designed to convert raw scores for each subtest into age-matched standardized scores, which are distributed with a mean of 10 and a standard deviation of 1. The cutoff point for each standardized score is set between 8 and 9. If a subject's score is not more than 8, the score is considered to indicate an impaired level.[22]

Assessment of Other Factors

Some previous studies have reported an increased risk of cognitive impairment among benzodiazepine and antidepressant users. Thus, we examined whether the benzodiazepine and antidepressant dosage confounded the effects of cognitive functions. Evaluations of the correlations between the benzodiazepine/antidepressant dosages and cognitive functions were based on an equivalent conversion table for anxiolytic drugs.[23]

STATISTICAL METHODS

SPSS 19.0 J (SPSS Japan Inc.) was used for all the statistical analyses. To compare differences between NC subjects and patients with late-life SSD, we used the Welch *t*-test for demographic characteristics, including age, education, duration of illness, SHAI score, HAMA-SOM score, HAMA-PSY score, and HAMA total score. The sex ratio was assessed using the chi-square test. To investigate group differences in

the neuropsychologic assessments, we also used the Welch *t*-test. To compare differences among the 3 groups, we used a one-way analysis of variance with Tukey *post hoc* testing. As an exploratory study was intended, the *p* values were not initially corrected for multiple tests so that the data trends would be apparent. However, the Bonferroni-corrected *p* value requirements (MMSE subtest scores: $p = 0.05/11$, FAB subtest scores: $p = 0.05/6$, and J-COGNISTAT subtest scores: $p = 0.05/10$) were reported, and the effects of the correlations were noted. If significant differences were found within the cognitive subtests, we evaluated the correlation of each subtest and the correlation between the benzodiazepine/antidepressant dosage and the test scores using the Spearman rho test in patients with late-life SSD.

RESULTS

Demographics of NC Subjects and Patients With Late-Life SSD

Table 1 shows the characteristics of the NC subjects and the patients with late-life SSD. The patients with late-life SSD had relatively high average SHAI scores ($p < 0.01$), HAMA-SOM scores ($p < 0.001$), HAMA-PSY scores ($p < 0.001$), and HAMA total scores ($p < 0.001$).

Comparison of Cognitive Profiles Between NC Subjects and Patients With Late-Life SSD

Comparison of cognitive profiles in 2 groups is summarized in Table 2. The patients with late-life SSD had significantly lower MMSE total score ($p = 0.03$) and J-COGNISTAT subtest score for attention ($p < 0.001$) than the NC subjects did.

Demographics of NC Subjects, Patients With Mild-to-Moderate Late-Life SSD, and Patients With Severe Late-Life SSD

The characteristics of the 3 groups are summarized in Table 3. The dosages of the benzodiazepine agents ($p < 0.001$) and antidepressant agents ($p = 0.004$) in the 3 groups differed significantly. The SHAI ($p < 0.001$), HAMA-SOM ($p < 0.001$), HAMA-PSY ($p < 0.001$), and HAMA total scores ($p < 0.001$) of the 3 groups also differed significantly.

Comparison of Cognitive Profiles Among NC Subjects, Patients With Mild-to-Moderate Late-Life SSD, and Patients With Severe Late-Life SSD

Cognitive profiles in 3 groups are summarized in Tables 4 and 5. The patients with severe late-life SSD had significantly lower MMSE total scores than the NC subjects did ($p = 0.01$). This group also showed lower FAB total scores ($p = 0.009$), conflicting

TABLE 1. Comparison of Demographic Data for Normal Control (NC) Subjects vs Patients With Late-Life Somatic Symptom Disorders (Late-Life SSD)

	NC subjects ($n = 21$) (mean ± SD)	Patients with late-life SSD ($n = 40$) (mean ± SD)	χ^2 score	*p* Value
Sex (male/female)	9/12	8/32	3.58	0.06
Age	74.9 ± 5.9	74.6 ± 5.2		0.85
Education (y)	11.9 ± 1.9	11.8 ± 2.1		0.84
Duration of illness (y)	–	7.0 ± 6.9		NA
Onset age	–	67.4 ± 7.7		NA
Benzodiazepine dosage (mg/d)	–	4.7 ± 4.1		NA
Antidepressant dosage (mg/d)	–	16.9 ± 25.1		NA
SHAI score	10.9 ± 8.1	23.0 ± 9.1		<0.01*
HAMA-SOM score	0.2 ± 0.5	7.9 ± 4.3		<0.001†
HAMA-PSY score	1.1 ± 1.0	7.2 ± 4.2		<0.001†
HAMA total score	1.4 ± 1.2	15.2 ± 7.4		<0.001†

NA = not available; NC = normal control; HAMA = the Hamilton Anxiety Scale; HAMA-PSY = the Hamilton Anxiety Scale, psychic score; HAMA-SOM = the Hamilton Anxiety Scale, somatic subscore; SHAI = the Short Health Anxiety Inventory; SD = standard deviation; SSD = somatic symptom disorder.

*$p < 0.05$.

†$p < 0.01$.

TABLE 2. Comparison of Cognitive Profiles for Normal Control (NC) Subjects vs Patients With Late-Life Somatic Symptom Disorders (Late-Life SSD)

	NC subjects ($n = 21$) (mean ± SD)	Patients with late-life SSD ($n = 40$) (mean ± SD)	p Value
MMSE total score	28.5 ± 1.4	27.4 ± 2.0	0.03*
FAB total score	16.1 ± 1.4	15.7 ± 1.6	0.31
J-COGNISTAT subscores			
Orientation	9.5 ± 0.9	9.6 ± 0.9	0.77
Attention	9.2 ± 1.2	6.2 ± 3.1	<0.001†
Comprehension	9.2 ± 1.6	8.3 ± 2.0	0.14
Repetition	10.3 ± 0.7	9.8 ± 1.4	0.12
Naming	9.6 ± 0.8	9.8 ± 0.7	0.50
Constructive ability	8.8 ± 1.2	7.9 ± 1.4	0.02
Memory	9.2 ± 0.7	9.5 ± 0.7	0.27
Calculation	9.7 ± 0.6	8.9 ± 1.4	0.006
Similarities	9.9 ± 0.8	10.2 ± 0.8	0.17
Judgment	10.1 ± 1.0	10.6 ± 1.0	0.28

FAB = frontal assessment battery; J-COGNISTAT = the Japanese version of the Neurobehavioral Cognitive Examination; MMSE = Mini-Mental State Examination; NC = normal control; SD = standard deviation; SSD = somatic symptom disorder.

*$p < 0.05$.

†Bonferroni-corrected $p < 0.05/10 = 0.005$.

TABLE 3. Comparison of Demographic Data for 3 Groups: Normal Control (NC) Subjects, Patients With Mild-to-Moderate Late-Life Somatic Symptom Disorders (Late-Life SSD), and Patients With Severe Late-Life SSD

	NC subjects ($n = 21$) (mean ± SD)	Mild-to-moderate late-life SSD ($n = 24$) (mean ± SD)	Severe late-life SSD ($n = 16$) (mean ± SD)	χ^2 or F score	p Value	*Post hoc**
Sex (male/female)	9/12	6/18	2/14	4.32†	0.12	
Age	74.9 ± 5.9	75.5 ± 5.5	73.3 ± 4.8	0.79	0.46	
Education (y)	11.9 ± 1.9	12.3 ± 2.0	11.1 ± 2.0	1.59	0.21	
Duration of illness (y)	–	7.9 ± 6.9	5.7 ± 6.8	1.00	0.32	
Onset age	–	67.3 ± 7.3	67.5 ± 8.4	0.02	0.90	
Benzodiazepine dosage (mg/d)	0.0 ± 0.0	4.2 ± 4.2	5.6 ± 3.9	13.4	<0.001‡	Control < mild-to-moderate, Control < severe
Antidepressant dosage (mg/d)	0.0 ± 0.0	13.1 ± 19.1	23.8 ± 33.3	6.00	0.004‡	Control < severe
SHAI score	10.9 ± 8.1	19.6 ± 7.8	28.1 ± 9.0	17.62	<0.001‡	Control < mild-to-moderate < severe
HAMA-SOM score	0.2 ± 0.5	5.7 ± 2.9	11.2 ± 3.9	57.41	<0.001‡	Control < mild-to-moderate < severe
HAMA-PSY score	1.3 ± 1.2	4.7 ± 2.9	10.8 ± 3.0	54.44	<0.001‡	Control < mild-to-moderate < severe
HAMA total score	1.4 ± 1.2	10.6 ± 4.2	22.1 ± 5.7	95.66	<0.001‡	Control < mild-to-moderate < severe

NC = normal control; HAMA = the Hamilton Anxiety Scale; HAMA-PSY = the Hamilton Anxiety Scale, psychic score; HAMA-SOM = the Hamilton Anxiety Scale, somatic subscore; SHAI = the Short Health Anxiety Inventory; SD = standard deviation; SSD = somatic symptom disorder.

*Significant *post hoc* comparisons ($\alpha < 0.05$) using Tukey-HSD test. Sex ratio was analyzed using the chi-square test.

†The chi-square score.

‡$p < 0.01$.

TABLE 4. Comparison of Cognitive Profiles for Normal Control (NC) Subjects, Patients With Mild-to-Moderate Late-Life Somatic Symptom Disorders (Late-Life SSD), and Patients With Severe Late-Life SSD

	NC subjects ($n = 21$) (mean ± SD)	Mild-to-moderate late-life SSD ($n = 24$) (mean ± SD)	Severe late-life SSD ($n = 16$) (mean ± SD)	*F* score	*p* Value	*Post hoc*[*]
MMSE total score	28.5 ± 1.4	28.0 ± 2.0	26.8 ± 1.8	4.73	0.01[§]	Control > severe
FAB total score	16.1 ± 1.4	16.3 ± 1.2	14.8 ± 1.7	5.16	0.009[†]	Control > severe, mild-to-moderate > severe
FAB subtest scores						
Similarities	2.8 ± 0.7	3.0 ± 0.0	2.6 ± 0.7	3.09	0.05	
Lexical fluency	2.1 ± 0.8	2.3 ± 0.7	2.1 ± 0.6	0.19	0.82	
Motor series	2.9 ± 0.3	2.9 ± 0.4	2.6 ± 0.8	2.24	0.12	
Conflicting instructions	2.9 ± 0.2	2.9 ± 0.2	2.5 ± 0.6	7.36	0.001[‡]	Control > severe, mild-to-moderate > severe
Go/no go	2.3 ± 0.7	2.2 ± 0.7	2.0 ± 0.8	0.58	0.56	
Prehension behavior	3.0 ± 0.0	3.0 ± 0.0	3.0 ± 0.0	NA	NA	

FAB = frontal assessment battery; MMSE = Mini-Mental State Examination; NA = not available; NC = normal control; SD = standard deviation; SSD = somatic symptom disorder.

[*]Significant *post hoc* comparisons ($\alpha < 0.05$) using Tukey-HSD test.

[†]$p < 0.01$.

[‡]Bonferroni-corrected $p < 0.05/6 = 0.008$.

[§]$p < 0.05$.

instructions among the FAB subtests ($p = 0.001$), and J-COGNISTAT subtest scores for calculation ($p < 0.001$) than the NC subjects and the patients with mild-to-moderate late-life SSD did. J-COGNISTAT subtest scores for attention were significantly lower in both the patients with mild and the patients with severe late-life SSD than in the NC subjects ($p < 0.001$).

Correlations Between Benzodiazepine/ Antidepressant Dosages and Cognitive Subscores in Patients With Late-Life SSD

Only the J-COGNISTAT subtest for calculation was correlated with the benzodiazepine dosage in patients with late-life SSD ($\rho = -0.33$, $p = 0.04$). No other subtests were correlated with either the benzodiazepine or the antidepressant dosages.

DISCUSSION

In this study, we found that the patients with late-life SSD had a lower MMSE total score and a lower attention score for the J-COGNISTAT subtest, compared with the NC subjects. In a 3-group comparison, the severe late-life SSD group had a lower MMSE total score than the NC subjects did. This group also had a lower FAB total score, a lower "conflicting instructions" FAB subtest score, and a lower calculation score for the J-COGNISTAT subtest, compared with the other groups. The attention score for the J-COGNISTAT subtest was lower in both the mild-to-moderate and severe late-life SSD groups than in the NC subjects. The benzodiazepine dosage for the mild-to-moderate and severe SSD groups was significantly higher than that for the NC subjects. The antidepressant dosage in the severe SSD group was significantly higher than that for the NC subjects.

In previous studies investigating cognitive decline in patients with late-life anxiety disorders, reductions in general cognitive functioning and attention function were reported.[7] In the present study of patients with late-life SSD, we also found an attention defect and a decline in general cognitive functioning.

In a comparison of the 3 groups, the severe late-life SSD group had a lower executive function score. However, the mild-to-moderate late-life SSD group showed no decline in executive functions. Thus, these cognitive test results appeared to differ according to disease severity among patients with late-life SSD. The FAB score assessing executive function may be an indicator of disease severity.[6]

TABLE 5. Comparison of J-COGNISTAT Subtests for Normal Control (NC) Subjects, Patients With Mild-to-Moderate Late-Life Somatic Symptom Disorders (Late-Life SSD), and Patients With Severe Late-Life SSD

	NC subjects ($n = 21$) (mean ± SD)	Mild-to-moderate late-life SSD ($n = 24$) (mean ± SD)	Severe late-life SSD ($n = 16$) (mean ± SD)	*F* score	*p* Value	*Post hoc*[*]
J-COGNISTAT subscores						
Orientation	9.5 ± 0.9	9.6 ± 0.9	9.6 ± 1.1	0.06	0.94	
Attention	9.2 ± 1.2	5.8 ± 3.2	6.9 ± 2.8	10.21	<0.001[†]	Control > mild-to-moderate, control > severe
Comprehension	9.2 ± 1.6	8.7 ± 2.2	7.9 ± 1.8	2.00	0.14	
Repetition	10.3 ± 0.7	10.0 ± 0.4	9.5 ± 1.4	2.26	0.11	
Naming	9.6 ± 0.8	9.7 ± 0.8	9.8 ± 0.5	0.33	0.72	
Constructive ability	8.8 ± 1.2	7.9 ± 1.5	7.9 ± 1.3	3.02	0.06	
Memory	9.2 ± 0.7	9.6 ± 0.6	9.4 ± 0.9	1.02	0.36	
Calculation	9.7 ± 0.6	9.3 ± 1.2	8.2 ± 1.4	8.80	<0.001[†]	Control > severe, mild-to-moderate > severe
Similarities	9.9 ± 0.8	10.3 ± 0.3	10.0 ± 0.9	1.77	0.18	
Judgment	10.1 ± 1.0	10.7 ± 1.0	10.7 ± 1.0	0.58	0.56	

J-COGNISTAT = the Japanese version of the Neurobehavioral Cognitive Examination; NC = normal control; SD = standard deviation; SSD = somatic symptom disorder.

[*]Significant *post hoc* comparisons ($\alpha < 0.05$) using Tukey-HSD test.

[†]Bonferroni-corrected $p < 0.05/10 = 0.005$.

Several possibilities may explain this result. Firstly, this difference might have contributed to the difference in the FAB score between the mild-to-moderate and the severe late-life SSD groups. "Conflicting instructions" resembles the Stroop test task and requires the ability to perform a contrary reaction to each of the 2 pattern directions effectively.[21] In patients with mild-to-moderate late-life SSD, the acquirement of such self-correction in executive functions might influence their ability to access corrective information necessary to modify their irrational beliefs.[24]

A second possibility may be explained by coping strategies. Poor coping strategies can lead to such somatic symptoms. Coping strategies are associated with attention, working memory, and executive functions.[6] Patients with mild-to-moderate late-life SSD may have a greater ability to cope through such reciprocal balancing of cognitive functions, compared with patients with severe late-life SSD. The collapse of such balance may lead to the poorer prognosis for patients with late-life SSD.

There is still a possibility that severe late-life SSDs are a prodromal stage of neurodegenerative diseases, such as dementia with Lewy bodies or Parkinson disease with dementia. A previous report has mentioned that somatic complaints were observed more frequently among patients with dementia with Lewy bodies or Parkinson disease with dementia than among patients with other types of dementia.[25] Although we excluded patients with amnestic MCI or dementia using cognitive assessments and a brain magnetic resonance imaging examination in the present study, patients with a prodromal stage of dementia with Lewy bodies or Parkinson disease with dementia are difficult to identify. The severe group may overlap with the nonamnesic type of MCI presentation.

A possible correlation between medication effects and disease severity must be considered because the severe SSD group received a relatively high dose of anxiolytic drugs. The dosages of anxiolytic drugs differed significantly among the 3 groups. Two possibilities may explain this result. First, the medication might influence the disease severity. Second, the severe group might have exhibited resistance to the treatment. In the present study, all the patients were medicated after confirmation of a diagnosis of SSD. Furthermore, the disease severity was classified according to the DSM-5 at the same time. Thus, we believe that the latter possibility is more likely. The disease severity of patients with SSD, as diagnosed according to the DSM-5 criteria, is probably not influenced by the effects of medication.

The HAMA-PSY score differed significantly among the 3 groups. We evaluated whether psychic anxiety in patients with late-life SSD may affect cognitive function. This problem can be explained from a psychopathologic viewpoint. Rief and Barsky suggested the applicability of a signal-filtering model in patients with somatic complaints.[14] This model mentions that somatic symptoms can be amplified by a reduction in filtering activity. Under this pathogenesis model, filtering activity is decreased by several factors (e.g., anxiety for health, depressive mood, and lack of distraction), and somatic symptoms occur because of a reduction in the filter system. Therefore, the HAMA-PSY score may reflect filtering activity. The HAMA-PSY score is just one factor in the appearance of somatic complaints, whereas the HAMA-SOM score reflects the severity of SSD precisely. Therefore, we believe that cognitive dysfunction in patients with late-life SSD is not influenced by the HAMA-PSY score directly. Additionally, we excluded patients with other anxiety-related disorders. For these reasons, cognitive dysfunction in patients with severe SSD does not appear as an anxiety effect, but results from the severity of SSD.

An attention decrement was found in both the mild and the severe late-life SSD groups. This result may indicate that an attention decrement may be a surrogate marker for disease specificity, rather than disease severity. A lower calculation skill in patients with severe late-life SSD reflects a defect in working memory. However, the effect of the benzodiazepine must be considered, as the calculation score was correlated with the benzodiazepine dosage.

This study had some limitations. First, the sample size was comparatively small. The reason for this is that we sampled the participants strictly and excluded patients with any possibility of a different diagnosis. Second, we evaluated executive functions using the FAB test, which has a ceiling effect. Patients with MCI or dementia were excluded from our sample in the present study, and there is a limitation to examining the details of executive functions using the FAB test. Third, our investigation used a cross-sectional research approach. To confirm our hypothesis, further longitudinal study is needed.

CONCLUSION

We elucidated the cognitive profiles of patients with late-life SSD and concluded that the cognitive profiles influenced the severity of late-life SSD. We found differences in the cognitive profiles among NC subjects, patients with mild-to-moderate late-life SSD, and patients with severe late-life SSD. Therefore, differences in pathogenesis might result in a subgroup of patients with severe late-life SSD among patients with late-life SSD. The further development of treatment strategies targeting prognostic subgroups, rather than late-life SSD itself, is required.

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Non-Pharmacological Management for Patients with Frontotemporal Dementia: A Systematic Review

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Abstract. Frontotemporal dementia (FTD) is a neurodegenerative disorder characterized by changes in behavior and language caused by focal degeneration of the frontal and anterior temporal lobes. The behavioral symptoms are distressing to patients and their caregivers. Non-pharmacological management is important as no disease-specific pharmacological treatment for FTD is currently available. The primary objective is to review the literature on non-pharmacological management for FTD and to propose directions for future research, with reference to findings. A search was performed using PubMed, MEDLINE, and EMBASE. Search terms included "frontotemporal dementia", and words related to non-pharmacological management, and it identified a total of 858 articles. Results revealed that very few randomized controlled trials exist on non-pharmacological management interventions for FTD. These interventions have been proposed by literature based on clinical experience. A small number of studies have supported behavioral management techniques that exploit disease-specific behaviors and preserved functions in patients with FTD, along with the management of caregivers' distress. These limitations warrant well-designed large-scale research to examine effects of non-pharmacological interventions on behavioral symptoms of FTD.

Keywords: Behavioral management, caregiver support, environmental strategies, non-pharmacological interventions in frontotemporal dementia

INTRODUCTION

Frontotemporal dementia (FTD) is a neurodegenerative disorder, caused by focal degeneration of the frontal and anterior temporal lobes, and characterized by progressive changes in behavior, emotion, and personality [1]. The disease begins insidiously and progresses gradually; core clinical criteria include early behavioral disinhibition, early apathy, early loss of sympathy or empathy, impulsive stereotypic behavior, and dietary changes [2]. FTD is a common cause of early-onset dementia, and has a similar incidence and prevalence to Alzheimer's disease (AD) among early-onset dementia cohorts [3]. FTD can be classified into three clinical syndromes based on the early and predominant symptoms, behavior variant FTD (bvFTD)

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