http://www.tsukuba-psychiatry.com/wp-content/uploads/2013/06/H24Report_Part1.pdf.

[4] Cheng G, Huang C, Deng H, et al. (2012) Diabetes as a risk factor for dementia and mild cognitive impairment: a meta-analysis of longitudinal studies. *Intern Med J* **42**, 484-491.

[5] Pendlebury ST, Rothwell PM. (2009) Prevalence, incidence, and factors associated with pre-stroke and post-stroke dementia: a systematic review and meta-analysis. *Lancet Neurol* **8**, 1006-1018.

[6] Santangeli P, Di Biase L, Bai R, et al. (2012) Atrial fibrillation and the risk of incident dementia: a meta-analysis. *Heart Rhythm* **9**, 1761-1768.

[7] Coleman EA, Smith JD, Frank JC, et al. (2004) Preparing patients and caregivers to participate in care delivered across settings: the Care Transitions Intervention. *J Am Geriatr Soc* **52**, 1817-1825, 2004.

[8] Elliott J, Forbes D, Chesworth BM, et al. (2014) Information sharing with rural family caregivers during care transitions of hip fracture patients. *Int J Integr Care* **14**, e018, 2014

[9] Ko H, Turner T, Jones C, et al. (2010) -held medical records for patients with chronic disease: a systematic review. *Qual Saf Health Care* **19**, 1-7.

[10] Gysels M, Richardson A, Higginson IJ. (2007) Does the patient-held record improve continuity and related outcomes in cancer care: a systematic review. *Health Expect* **10**, 75-91.

[11] Ito H, Frank RG, Nakatani Y, Fukuda Y. (2013) Regional healthcare strategic plan: growing impact of mental disorder in Japan. *Psychiatric Services* **64**, 617-619.

[12] Farrelly S, Brown GE, Flach C, Barley E, Laugharne R, Henderson C. (2013) User-held personalised information for routine care of people with severe mental illness. Cochrane Database of Systematic Reviews 2013, Issue 10. Art. No.: CD001711. DOI: 10.1002/14651858.CD001711.pub2.

[13] Brunero S, Lamont S, Myrtle L, et al. (2008) The Blue Card: a hand-held health record card for mental health consumers with comorbid physical health risk. *Australasian Psychiatry* **16**, 238-243.

[14] Lester H, Allan T, Wilson S, et al. (2003) A cluster randomized controlled trial of patient-held medical records for people with schizophrenia receiving shared care. *Br J Gene Practice* **53**, 197-203.

[15] Stafford A, Hannigan B. (1997) Client-held records in community health. *Nursing Times* **93**, 50-51.

[16] Warner JP King M, Blizard R, et al. (2000) Patient-held shared care records for individuals with mental illness. *Br J Psychiatry* **177**, 319-324.

[17] Ouwens M, Wollersheim H, Hermens R, et al. (2005) Integrated care programmes for chronically ill patients: a review of systematic reviews. *Int J Qual Health Care* **17**, 141-146, 2005.

[18] Peisah C, Sorinmad OA, Mitchell L, et al. (2013) Decisional capacity: toward an inclusionary approach. International *Psychogeriatrics* **25**, 1571-1579.

[19] Campbell LA, Kisely SR. (2009) Advance treatment directives for people with severe mental illness. *Cochrane Database Syst Rev* 2009.

[20] Folstein MF, Folstein SE, McHugh PR (1975). ""Mini-mental state". A practical method for grading the cognitive state of patients for the clinician". *Journal of Psychiatric Research* **12**,: 189-198.

[21] Lawton MP, Brody EM. (1969) Assessment of older people: self-maintaining and instrumental activities of daily living. *Gerontologist* **9**, 179-186.

[22] Cummings, J., Mega, M., Gray, K., Rosenberg-Thompson, S., Carusi, D. A., & Gornbein, J. (1994).The Neuropsychiatric Inventory: Comprehensive assessment of psychopathology in dementia. *Neurology* **44**, 2308-2314.

[23] Ito H, Sugiura S, Noda H, Higuchi T. (2013) Creating an online patient follow-up system. *Shakai Hoken Jyunpo* **2531**, 10-14 (in Japanese). Available at http://mhcnp.jp/pdf/130513_syakaiHokenJunpo.pdf. Accessed on September 30, 2014.

[24] Ito H, Setoya Y, Suzuki Y (2012) Lessons learned in developing community mental health care in East and South East Asia. *World Psychiatry* **11**, 186-190.

[25] OECD 2010, "Health care systems: Getting more value for money", OECD Economics Department Policy

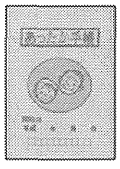
Notes, No. 2. Available at http://www.oecd.org/eco/growth/46508904.pdf. Accessed on September 30, 2014.

[26] Nakamura Y. (2010) Maternal and Child Health Handbook in Japan. *JMAJ* **53**, 259-265. Available at https://www.med.or.jp/english/journal/pdf/2010_04/259_265.pdf. Accessed on September 30, 2014.

Fig. 1. Coversheets of family-held/patient-held records of patients

Orange handbook
Ogaki city, ***Gifu prefecture***
Population: 163,000

Support handbook
Sagamihara city,
Kanagawa prefecture
Population: 722,000

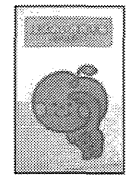


Warm handbook
Toshin area, ***Nagano prefecture***
Population: 256,000

Worry Free Notebook
for people with dementia
Arao city, ***Kumamoto prefecture***
Population: 55,000

Connected notebook
Kawanishi city, ***Hyogo prefecture***
Population: 156,000

Smile notebook
Jyoetsu area, ***Niigata prefecture***
Population: 279,000



Support and joint notebook
Nakasorachi area, ***Hokkaido prefecture***
Population: 118,000

Next to you notebook
Tokushima prefecture
Population: 764,000

Table 1. Contents of family-held/patient-held records

		1	2	3	4	5	6	7	8
Prefecture		Gifu	Nagano	Kumamoto	Hyōgo	Niigata	Kanagawa	Hokkaido	Tokushima
Year (first version)		2011	2012	2012	2013	2013	2013	2013	2014
Style	Size	A5	A5	A5	A5	A5	A5	A5	A5
	Binder			×	×	×	×		
Patient profile		×	×	×	×	×		×	×
Hope/preference			×		×	××	×	×	×
Daily planner (appointment)			×	××	××	××	××		
Resources		×	×	×	×	×	×	×	×
Diagnosis and treatment (dementia)		×	×	×	×	×	×	×	×
Diagnosis and treatment (other diseases)		×		××	×	×	×	×	×
Monitoring		××	×	××	×	×	××	×	
Exchange notebook with multiple services			×	××	××	××	×	×	
Referral				××				××	××
Use of information technology		××		×					

×: The element is included. ××: The included element is evaluated as rich and innovative.

Clinical Features of Delusional Jealousy in Elderly Patients With Dementia

Mamoru Hashimoto, MD, PhD; Shinichi Sakamoto, MD; and Manabu Ikeda, MD, PhD

ABSTRACT

Objective: Delusional jealousy is a psychotic syndrome characterized by a belief in the infidelity of one's spouse that reaches delusional intensity. Although delusional jealousy has been described in relation to organic psychosis, little is known concerning the actual role of delusional jealousy in dementia. The aim of the present study was to investigate the clinical features of delusional jealousy and possible mechanisms whereby delusional jealousy arises in patients with dementia.

Method: We studied 208 consecutive outpatients with dementia (diagnosis based on *DSM-III-R* criteria; mean [SD] age of 77.0 [8.0] years; study period: September 2011–August 2012). *Delusional jealousy* was defined as a false belief derived from a pathological jealousy that makes the patient believe that his or her spouse is unfaithful. The prevalence of delusional jealousy was compared between Alzheimer's disease, dementia with Lewy bodies, and vascular dementia. Patients with and without delusional jealousy were compared in terms of general characteristics. In addition, each patient with delusional jealousy and their primary caregivers were interviewed about the clinical features of the syndrome.

Results: Of the 208 patients with dementia, 18 (8.7%) showed delusional jealousy. The prevalence of delusional jealousy in patients who had dementia with Lewy bodies (26.3%) was significantly higher than that in patients with Alzheimer's disease (5.5%) ($P < .01$). There were no significant differences between patients with and without delusional jealousy in regard to gender ($P = 1.00$), age ($P = .81$), educational attainment ($P = .29$), presence of other persons living with the couple ($P = .22$), and Mini-Mental State Examination score ($P = .47$). On the other hand, delusional jealousy was preceded by the onset of serious physical diseases in nearly half of the patients. Delusional jealousy resolved within 12 months after treatment in 15 of 18 patients (83%).

Conclusions: Although delusional jealousy is a considerable problem in dementia, the prognosis of delusional jealousy in demented patients appears to be relatively benign. In dementia, delusional jealousy may develop more easily in patients who have dementia with Lewy bodies and those with coexisting serious physical disorders.

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Delusional jealousy, also known as Othello's syndrome, is a psychotic disorder characterized by the belief in the infidelity of one's spouse or lover that reaches delusional intensity.[1,2] Delusional jealousy may be observed in many psychiatric disorders, but previous clinical reports have noted the association of this morbid condition in several organic psychoses, including stroke,[3,4] Parkinson's disease,[5,6] traumatic brain injury,[7] and dementia.[8] Soyka et al[9] found that the prevalence of delusional jealousy was highest in organic psychoses (7.0%), followed by paranoid disorders (6.7%), alcohol psychosis (5.6%), and schizophrenia (2.5%); whereas in affective disorder, delusional jealousy was found in only 0.1% of patients. These findings suggest that neurologic elements very likely combine with psychodynamic factors to produce this specific condition.[10]

In dementia, delusions constitute one of the most prominent psychiatric complications.[11] Delusional jealousy was described as the initial clinical symptom in the first clinical Alzheimer's disease case reported by Alois Alzheimer.[8] Tsai et al[12] comprehensively investigated the clinical features of delusional jealousy in patients with dementia within a psychiatric ward and identified delusional jealousy in as many as 15.6% of demented patients. Furthermore, with respect to individual delusional symptoms, delusional jealousy has been identified as a risk factor for aggression and homicide, especially against one's partner.[13] These findings suggest that evaluation and treatment of delusional jealousy are of considerable importance in practice for demented patients. However, to our knowledge, there have been few systematic studies about the clinical features of delusional jealousy in persons suffering from dementia,[12] and little is known concerning the actual role of delusional jealousy in dementia. The aim of this study was to investigate the clinical features of delusional jealousy and possible mechanisms whereby delusional jealousy arises in patients with dementia.

METHOD

All procedures followed the Clinical Study Guidelines of the Ethics Committee of Kumamoto University Hospital, Kumamoto, Japan, and were approved by the internal review board. Informed written consent was obtained from patients and their caregivers in compliance with the research standards for human research for all participating institutions and in accordance with the Helsinki Declaration.

Subjects

A total of 208 patients (mean [SD] age of 77.0 [8.0] years) were selected according to the following inclusion/exclusion criteria from a consecutive series of 327 demented patients who attended 1 of 2 dementia clinics from September 2011 to August 2012 at Kumamoto University Hospital or Heisei Hospital, which is a mental hospital. All patients were examined comprehensively by senior

Clinical Points

- Among diagnostic categories of dementia, delusional jealousy develops more easily in patients with dementia with Lewy bodies.
- In addition to cognitive decline, coexisting serious physical illness is a significant risk factor of delusional jealousy in demented patients.
- Although delusional jealousy is often accompanied by violent behavior and can add to the stress experienced by the patient's spouse, the prognosis of delusional jealousy in demented patients is relatively benign.

Table 1. Demographics of Demented Patients With and Without Delusional Jealousy

Characteristics	Delusional Jealousy Group (n = 18)	Non–Delusional Jealousy Group (n = 190)	*P* Value
Age, mean (SD), y	77.4 (5.6)	76.9 (8.2)	.81
Male/female, n/n	9/9	95/95	1.00
Education, mean (SD), y	10.1 (2.7)	10.9 (2.9)	.29
Presence of other people living with the couple, n (%)	6 (33)	92 (48)	.22
MMSE score, mean (SD)	18.7 (5.9)	17.5 (6.8)	.47

Abbreviation: MMSE = Mini-Mental State Examination.

neuropsychiatrists with sufficient experience in examining patients with dementia, and all patients underwent routine laboratory tests and standard neuropsychological examinations including the Mini-Mental State Examination (MMSE).[14] Brain magnetic resonance imaging (MRI) or computed tomography (CT) was also performed. Exclusion criteria consisted of the following: (1) patients with serious psychiatric diseases such as schizophrenia or major depression before the onset of dementia and (2) patients without a spouse.

The diagnosis of dementia was based on *DSM-III-R* criteria.[15] The diagnosis of each dementia was established according to the international consensus criteria. Diagnostic categories consisted of probable Alzheimer's disease (n = 127),[16] probable dementia with Lewy bodies (n = 38),[17] vascular dementia (n = 21),[18] frontotemporal lobar degeneration (n = 7),[19] possible idiopathic normal pressure hydrocephalus (iNPH) (n = 6),[20] probable progressive supranuclear palsy (n = 4),[21] probable corticobasal degeneration (n = 3),[22] and unspecified etiology (n = 2).

Assessments of Delusional Jealousy

In the present study, *delusional jealousy* was defined as a false belief derived from a pathological jealousy that makes the patient believe that his or her spouse is unfaithful.[12] Specifically, the delusion had to be clearly and repeatedly stated some time during the follow-up period and had to require therapeutic intervention. Patients with these characteristics were assigned to the delusional jealousy group. Thus, the delusional jealousy group did not include patients with mild or episodic delusional jealousy without therapeutic intervention. The remaining patients were assigned to the non–delusional jealousy group. In each case in the delusional jealousy group, the patient and primary caregiver were interviewed by the authors, senior neuropsychiatrists, about the presence of the following features: (1) coexisting psychiatric symptoms such as hallucinations, other types of delusions, or depression; (2) coexisting severe physical disorder of the patient (*severe physical disorder* was defined as present if the disorder was severe enough to require hospitalization or to interfere with the patient's activities of daily living); (3) violent behavior by the patient; (4) past history of infidelity by the spouse; (5) health condition of the spouse; and (6) spouse's frequent absence in the home (*frequent absence* was defined as present if the spouse went out alone a few times a week or more).

Statistics

The prevalence of delusional jealousy was compared against each diagnostic category that comprised 10 or more patients. Fisher exact probability test was utilized. In addition, to examine risk factors for delusional jealousy, gender, age, educational attainment, presence of other people living with the couple, and MMSE scores were compared between the delusional jealousy and non–delusional jealousy groups. Student *t* test and χ^2 test were used when appropriate. The significance level was set at $P < .05$ for all analyses.

RESULTS

Of the 208 demented patients with a spouse, 18 (8.7%) met the inclusion criteria for having delusional jealousy. Patients with delusional jealousy were found to have various types of dementia; 7 patients had Alzheimer's disease, 10 patients had dementia with Lewy bodies, and 1 patient had vascular dementia. The prevalence of delusional jealousy in patients with dementia with Lewy bodies (26.3%) was significantly higher than that in patients with Alzheimer's disease (5.5%) ($P < .01$), and patients with dementia with Lewy bodies tended to have a higher prevalence of delusional jealousy than patients with vascular dementia (4.8%) ($P = .08$). Nine patients already had delusional jealousy at the initial visit; in the other 9 patients, delusional jealousy developed during the follow-up period. Table 1 shows the clinical characteristics of the delusional jealousy and non–delusional jealousy groups. We found no significant differences between the 2 groups in regard to gender, age, educational attainment, presence of other people living with the couple, and MMSE scores. However, 10 of the 18 patients with delusional jealousy had mild dementia; these patients' MMSE scores were 20 or greater.

Table 2 shows a comparison of coexisting psychiatric symptoms among dementia with Lewy bodies, Alzheimer's disease, and vascular dementia. All but 1 patient with dementia with Lewy bodies had at least 1 other psychotic symptom. Eight patients with dementia with Lewy bodies exhibited visual hallucinations. The contents of the visual hallucinations included images of the patient's spouse in a

Table 2. Number of Patients With Coexisting Psychiatric Symptoms and Violence

	Dementia With Lewy Bodies (n = 10)	Alzheimer's Disease (n = 7)	Vascular Dementia (n = 1)	Total (N = 18)
Hallucinations				
Visual	8	0	0	8
Auditory	1	1	0	2
Delusions				
Misidentification	8	0	0	8
Theft	2	0	0	2
Persecution	2	2	0	4
Depression	2	1	0	3
Violence	6	5	0	11

Table 3. Period Between Initiation of Therapy and Disappearance of Delusional Jealousy[a]

	Dementia With Lewy Bodies (n = 10)	Alzheimer's Disease (n = 7)	Vascular Dementia (n = 1)	Total (N = 18)
1–3 months	3	3	1	7
4–12 months	4	4	0	8
Intractable	3	0	0	3

[a]Values represent the number of patients (n).

sexual situation (2 patients), the spouse having an affair in the house (3 patients), and the spouse having a child with his or her lover (2 patients). Six patients with dementia with Lewy bodies misidentified his or her spouse as another person in a delusional manner. In 1 patient with dementia with Lewy bodies, delusional jealousy persisted after the death of the spouse. Two patients with dementia with Lewy bodies were noted to have increased sexual desire after the onset of dementia. Two patients with Alzheimer's disease had other psychotic symptoms. One patient with Alzheimer's disease suffered from auditory hallucinations, including hearing knocking at the door that the patient attributed to the spouse's lover. In this series, 7 of 9 males and 4 of 9 females committed actual physical assault on their spouse. We found no significant gender differences in regard to the prevalence of violent behavior ($P = .15$).

Several precipitating or predisposing factors for delusional jealousy were identified. Delusional jealousy was preceded by the onset of serious physical diseases, such as cancer, aortic aneurysm, or femoral neck fracture in 8 patients (44%). In contrast, all the spouses, except for 1, who suffered from iNPH, were active and in good health. Eight of 18 spouses (44%) frequently spent time away from home without the patient. In the present study, only 1 spouse (5.6%) was confirmed to have a previous history of infidelity. Although delusional jealousy has been described in Parkinson's disease patients on dopaminergic therapy,[23,24] only 1 patient who had dementia with Lewy bodies was treated with antiparkinson medication in this series; this patient had undergone dopaminergic therapy 3 years prior to the development of delusional jealousy.

All 10 patients who had dementia with Lewy bodies were treated with donepezil medication. In addition to donepezil, treatment for 6 of the patients with dementia with Lewy bodies also included atypical neuroleptics such as quetiapine, olanzapine, and aripiprazole. All 7 patients with Alzheimer's disease were treated with neuroleptic medications: 6 were treated with risperidone, and 1 was treated with sulpiride. In 3 of the 7 patients with Alzheimer's disease, donepezil was discontinued or decreased. One patient who suffered from vascular dementia improved with risperidone medication for a couple of months. Delusional jealousy resolved after treatment in 15 of 18 patients (83%) (Table 3), and all of the 7 patients with Alzheimer's disease experienced complete resolution of delusional jealousy within 12 months, although antipsychotic therapy continued for over 12 months after delusional jealousy disappearance in all patients. In 3 patients with dementia with Lewy bodies, delusional jealousy showed no response to treatment. In 1 female patient with dementia with Lewy bodies, delusional jealousy improved with donepezil administration for 8 months; however, she had a relapse in delusional jealousy after an improvement in her husband's health following an operation for iNPH. Two of the 3 recalcitrant patients exhibited visual hallucinations of their spouses in sexual acts, and the remaining patient recurrently mistook her husband for her father-in-law. Only 1 patient with dementia with Lewy bodies was placed in a nursing home due to active delusional jealousy.

DISCUSSION

Although delusional jealousy is a known risk factor for violence and homicide,[13] it has been considered a rare syndrome. Soyka et al[9] studied the prevalence of delusional jealousy in over 8,000 psychiatric inpatients and found an overall low prevalence of 1.1%. However, the authors also found that delusional jealousy was most frequently seen in patients with organic psychoses, in whom its prevalence reached 7.0%. In the present study, we reported that 8.7% of demented patients exhibited delusional jealousy, which was well within the 2.3%[25] to 15.6%[12] range reported in previous studies. These findings suggest that delusional jealousy is a frequent symptom in dementia and that neurologic elements including cognitive decline quite likely produce delusional jealousy in combination with psychosocial factors.

The most remarkable finding of the present study was the fact that as many as 26.3% of patients with dementia with Lewy bodies exhibited delusional jealousy, and the prevalence of delusional jealousy in patients with dementia with Lewy bodies was significantly higher than that in patients with Alzheimer's disease. Although delusional jealousy has been observed in neurologic patients, particularly in those with Parkinson's disease,[5] little is known about the association between delusional jealousy and dementia with Lewy bodies. In a recent case series of 105 patients with delusional jealousy, Graff-Radford et al[26] reported that 29 of 56 patients with a neurodegenerative disorder had Lewy body disease, which was seen with a higher frequency than Alzheimer's disease (n = 22). Both the findings of Graff-Radford et al and the present study indicate the possibility that patients with dementia with

Lewy bodies exhibit a higher frequency of delusional jealousy as compared to other demented patients, including those with Alzheimer's disease.

Most of the patients with dementia with Lewy bodies in the present study presented with visual hallucinations with concrete contents suggesting spousal infidelity. This phenomenon had been reported elsewhere. Graff-Radford et al[26] reported that 4 of 20 patients with dementia with Lewy bodies had visual hallucinations specific to spousal infidelity resulting in delusional jealousy. Although visual hallucinations and delusions are common symptoms in patients with dementia with Lewy bodies,[27,28] the underlying mechanisms of these symptoms have not been fully clarified. Nagahama et al[29] investigated the association between psychotic symptoms in dementia with Lewy bodies and brain perfusion using single-photon emission computed tomography and revealed that delusions and visual hallucinations were served by distinguishable cerebral networks. On phenomenological grounds, it is not clear whether visual hallucinations pertaining to a sexual theme induced the thought of the spouse's infidelity or whether suspicion about the spouse's infidelity induced hallucinations involving the spouse committing sexual indiscretions. Nevertheless, the common theme of visual hallucinations with delusional jealousy may suggest a potential link between these symptoms in dementia with Lewy bodies.

Low self-esteem and feelings of insecurity and inferiority have been considered central to many psychological theories of delusional jealousy in the literature.[1,2,30] According to Sibisi,[31] the accusation of infidelity develops in parallel with deteriorating cognitive function. However, we found no significant differences between the delusional jealousy and non–delusional jealousy groups in regard to MMSE score. Rather, in 10 of the 18 patients with delusional jealousy, MMSE score was greater than 20, suggesting that the occurrence of delusional jealousy may require a certain level of cognitive function. In dementia, especially in mild cases, cognitive decline can give the patient a feeling of inferiority compared to his or her spouse. Numerous studies have reported that awareness of deficits decreased with disease progression in patients with dementia,[32] meaning that impaired intellect in the later stages of dementia could weaken the patient's feelings of inferiority. Thus, delusional jealousy in patients in earlier stages of dementia may be strengthened by the fact that the patient has considerable remaining intellectual ability, and is thus more likely to have feelings of inferiority.

Disparities in health between the patient and spouse have also been proposed as specific and distinct risk factors for delusional jealousy in the elderly.[33] In the present study, 8 patients (44%) had serious physical diseases before the onset of delusional jealousy; as a result, these patients became more dependent upon their spouses for daily living and activities. In contrast, all but 1 of the spouses were active and in good health. In addition, nearly half of the spouses in our study often spent time away from the home alone. Physical disorders of the patient and good health of the spouse could therefore contribute to the patient's feelings of inferiority with regard to the spouse. In addition to cognitive decline, coexisting serious physical disorders may be a significant risk factor of delusional jealousy in demented patients.

Most catamnestic studies have shown that delusional jealousy in older patients usually has a poor prognosis.[2,34,35] Jørgensen and Munk-Jørgensen[34] followed up with patients over 60 years of age who were diagnosed with paranoid psychosis over 5–15 years and reported that only 2 of 24 patients with delusions comprising sexual ideas or jealousy achieved full remission. In contrast, in the present study, delusional jealousy disappeared within 1 year after treatment in as many as 83% of the patients with dementia. In addition, all but 1 patient with dementia with Lewy bodies who was placed in a nursing home due to active delusional jealousy continued outpatient treatment without institutionalization or hospitalization. These findings suggest that delusional jealousy in patients with dementia may have a much better prognosis than those with other psychiatric disorders. It is noteworthy that all of the patients with treatment-resistant delusional jealousy in the present study had dementia with Lewy bodies. In addition, 1 patient with recurrent episodes of delusional jealousy had dementia with Lewy bodies. Generally, the prognosis for delusional jealousy is considered to depend on the existence of comorbid mental disorders.[36] The existence of other psychotic symptoms, such as visual hallucinations, may result in a worse prognosis in patients with dementia with Lewy bodies.

Several methodological issues limit the interpretation of the present results. First, psychiatric symptoms were assessed by a clinical interview without using a structured assessment scale, such as Neuropsychiatric Inventory (NPI).[37] In addition, delusional jealousy can be difficult to diagnose because of the reluctance of patients and caregivers to discuss personal matters. These methodological problems can make the current prevalence of delusional jealousy seem lower than it is. In the present study, senior neuropsychiatrists investigated the contents of delusional jealousy and coexisting psychiatric symptoms using both the patient and their primary caregiver. Moreover, this research excluded subjects with mild or episodic delusional jealousy and focused on clinically relevant delusional jealousy, allowing us to obtain robust observations about delusional jealousy. Second, the statistical evaluation was limited by the small sample size of the delusional jealousy group. Third, premorbid personality of demented patients was not considered in the present study. Specific types of premorbid personality (passive personality, borderline personality, or paranoid personality) have been hypothesized to be significant factors in the development of delusional jealousy.[38] In future studies, the relationship between delusional jealousy and premorbid personality in people with dementia should be evaluated.

Drug names: aripiprazole (Abilify), donepezil (Aricept and others), olanzapine (Zyprexa and others), quetiapine (Seroquel and others), risperidone (Risperdal and others).

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Author contributions: Dr Hashimoto designed this study, worked on data analysis, and drafted the article. Dr Sakamoto helped to collect the data and analyzed and interpreted the data. Dr Ikeda supervised this study and was responsible for the statistical design of the study.
Potential conflicts of interest: None reported.
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Role of the sponsor: The Japanese government, provider of the research grants, had no role in the design and conduct of the study.
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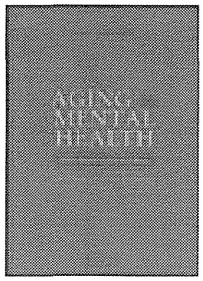
Ethical standards: The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

REFERENCES

1. Shepherd M. Morbid jealousy: some clinical and social aspects of a psychiatric symptom. *J Ment Sci*. 1961;107(449):687–704.
2. Cobb J. Morbid jealousy. *Br J Hosp Med*. 1979;21(5):511–518.
3. Richardson ED, Malloy PF, Grace J. Othello syndrome secondary to right cerebrovascular infarction. *J Geriatr Psychiatry Neurol*. 1991;4(3):160–165.
4. Luauté JP, Saladini O, Luauté J. Neuroimaging correlates of chronic delusional jealousy after right cerebral infarction. *J Neuropsychiatry Clin Neurosci*. 2008;20(2):245–247.
5. Cannas A, Solla P, Floris G, et al. Othello syndrome in Parkinson disease patients without dementia. *Neurologist*. 2009;15(1):34–36.
6. Poletti M, Perugi G, Logi C, et al. Dopamine agonists and delusional jealousy in Parkinson's disease: a cross-sectional prevalence study. *Mov Disord*. 2012;27(13):1679–1682.
7. Butler PV. Reverse Othello syndrome subsequent to traumatic brain injury. *Psychiatry*. 2000;63(1):85–92.
8. Alzheimer A. Uber eine eigenartige Erkrankung der Hirnrinde. *Allg Z Psychiat Psych Gerichtl Med*. 1907;64:146–148.
9. Soyka M, Naber G, Völcker A. Prevalence of delusional jealousy in different psychiatric disorders: an analysis of 93 cases. *Br J Psychiatry*. 1991; 158(4):549–553.
10. Malloy PF, Richardson ED. The frontal lobes and content-specific delusions. *J Neuropsychiatry Clin Neurosci*. 1994;6(4):455–466.
11. Finkel SI. Behavioral and psychological symptoms of dementia: a current focus for clinicians, researchers, and caregivers. *J Clin Psychiatry*. 2001;62(suppl 21):3–6.
12. Tsai SJ, Hwang JP, Yang CH, et al. Delusional jealousy in dementia. *J Clin Psychiatry*. 1997;58(11):492–494.
13. Silva JA, Derecho DV, Leong GB, et al. Stalking behavior in delusional jealousy. *J Forensic Sci*. 2000;45(1):77–82.
14. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;12(3):189–198.
15. American Psychiatric Association. *Diagnostic and Statistical Manual on Mental Disorders*, Third Edition-Revised. Washington, DC: American Psychiatric Association; 1987.
16. McKhann G, Drachman D, Folstein M, et al. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology*. 1984;34(7):939–944.
17. McKeith IG, Dickson DW, Lowe J, et al; Consortium on DLB. Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. *Neurology*. 2005;65(12):1863–1872.
18. Chui HC, Victoroff JI, Margolin D, et al. Criteria for the diagnosis of ischemic vascular dementia proposed by the State of California Alzheimer's Disease Diagnostic and Treatment Centers. *Neurology*. 1992;42(3, pt 1):473–480.
19. Neary D, Snowden JS, Gustafson L, et al. Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria. *Neurology*. 1998;51(6):1546–1554.
20. Ishikawa M, Hashimoto M, Kuwana N, et al. Guidelines for management of idiopathic normal pressure hydrocephalus. *Neurol Med Chir (Tokyo)*. 2008;48(suppl):S1–S23.
21. Litvan I, Mangone CA, McKee A, et al. Natural history of progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome) and clinical predictors of survival: a clinicopathological study. *J Neurol Neurosurg Psychiatry*. 1996;60(6):615–620.
22. Boeve BF, Lang AE, Litvan I. Corticobasal degeneration and its relationship to progressive supranuclear palsy and frontotemporal dementia. *Ann Neurol*. 2003;54(suppl 5):S15–S19.
23. Marsh L, Williams JR, Rocco M, et al. Psychiatric comorbidities in patients with Parkinson disease and psychosis. *Neurology*. 2004;63(2):293–300.
24. Chou KL, Messing S, Oakes D, et al. Drug-induced psychosis in Parkinson disease: phenomenology and correlations among psychosis rating instruments. *Clin Neuropharmacol*. 2005;28(5):215–219.
25. Mendez MF, Martin RJ, Smyth KA, et al. Psychiatric symptoms associated with Alzheimer's disease. *J Neuropsychiatry Clin Neurosci*. 1990;2(1):28–33.
26. Graff-Radford J, Whitwell JL, Geda YE, et al. Clinical and imaging features of Othello's syndrome. *Eur J Neurol*. 2012;19(1):38–46.
27. Ballard C, Holmes C, McKeith I, et al. Psychiatric morbidity in dementia with Lewy bodies: a prospective clinical and neuropathological comparative study with Alzheimer's disease. *Am J Psychiatry*. 1999;156(7):1039–1045.
28. Hirono N, Cummings JL. Neuropsychiatric aspects of dementia with Lewy bodies. *Curr Psychiatry Rep*. 1999;1(1):85–92.
29. Nagahama Y, Okina T, Suzuki N, et al. Neural correlates of psychotic symptoms in dementia with Lewy bodies. *Brain*. 2010;133(pt 2):557–567.
30. Seeman MV. Pathological jealousy. *Psychiatry*. 1979;42(4):351–361.
31. Sibisi CD. The phenomenology of delusional jealousy in late life. *Int J Geriatr Psychiatry*. 1999;14(5):398–399.
32. Kashiwa Y, Kitabayashi Y, Narumoto J, et al. Anosognosia in Alzheimer's disease: association with patient characteristics, psychiatric symptoms and cognitive deficits. *Psychiatry Clin Neurosci*. 2005;59(6):697–704.
33. Breitner BCC, Anderson DN. The organic and psychological antecedents of delusional jealousy in old age. *Int J Geriatr Psychiatry*. 1994;9(9):703–707.
34. Jørgensen P, Munk-Jørgensen P. Paranoid psychosis in the elderly: a follow-up study. *Acta Psychiatr Scand*. 1985;72(4):358–363.
35. Soyka M. Delusional jealousy in psychiatric disorders of later life. *Int J Geriatr Psychiatry*. 1992;7(8):539–542.
36. Kingham M, Gordon H. Aspects of morbid jealousy. *Adv Psychiatr Treat*. 2004;10(3):207–215.
37. Cummings JL, Mega M, Gray K, et al. The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. *Neurology*. 1994;44(12):2308–2314.
38. Cipriani G, Vedovello M, Nuti A, et al. Dangerous passion: Othello syndrome and dementia. *Psychiatry Clin Neurosci*. 2012;66(6):467–473.



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Correlation between cognition and symptomatic severity in patients with late-life somatoform disorders

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Correlation between cognition and symptomatic severity in patients with late-life somatoform disorders

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Objectives: Various aging associated factors, such as functional decline, psychosocial problems, and cognitive dysfunction, are risk factors for somatoform disorders (SDs) in the elderly. The aim of the present study was to evaluate how cognition is correlated with the severity of late-life SDs from a neuropsychological viewpoint.
Methods: Fifty-three patients over 60 years of age who had been diagnosed as having SDs were examined in this study. The severity of the somatic symptoms was assessed using the Hamilton Anxiety Rating Scales (HAMA). Cognitive functions were assessed using the Mini-Mental State Examination (MMSE), the Frontal Assessment Battery (FAB), and the Japanese version of the Neurobehavioral Cognitive Examination (J-COGNISTAT).
Results: The J-COGNISTAT subtest score for attention was below the cutoff point (8 points) but was not correlated with the severity of the somatic symptoms in the patients with late-life SDs. The severity of anxiety as assessed using the HAMA was significantly correlated with the calculation scores ($P < 0.005$) among the J-COGNISTAT subtests, the FAB total ($P < 0.05$), and the FAB subtest scores (similarities and motor series) ($P < 0.01$). Other factors, including the benzodiazepine dosage, antidepressant dosage, the duration of illness, and the onset age, were not significantly correlated with the symptomatic severities.
Conclusion: Patients with late-life SDs showed attention deficits, but no correlation was seen between the attention deficits and symptomatic severities. Attention deficits might be associated with the appearance of symptoms. Executive dysfunction and working memory might be associated with the severity of symptoms.

Keywords: cognitive functioning; anxiety; other disorders

Introduction

According to the current concepts of the Diagnostic and Statistical Manual of Mental Disorders (4th edition, text revision) (DSM-IV-TR), somatoform disorders (SDs) are mainly characterized by chronic multiple physical symptoms that cannot be explained in terms of an underlying organic pathology (American Psychiatric Association, 2000). Thus, patients with SDs often visit medical facilities to elucidate their pathogenesis and to receive treatment. Somatization is defined as a tendency to experience medically unexplained somatic symptoms, to attribute them to physical illness, and to seek medical help for them (Lipowski, 1988). Various beliefs or perceptions may contribute to the process of somatization, including heightened bodily sensations, physical abnormalities resulting in a heightened awareness of bodily sensations, and inappropriate illness beliefs or sickness behavior. The current view of somatization has been regarded to result from complex interactive etiological factors, including psychosocial and/or neuropsychological factors (Mayou, Bass, & Sharpe, 1995). Cognitive–behavioral models of SDs emphasize the role of inadequate body-related interpretations and health-related beliefs (Salkovskis & Warwick, 2001).

From psychosocial viewpoints, late-life SDs are related to various factors characterized by the aging process, such as a decline in bodily functions, an increase in physical illness, psychosocial problems, and life events (Harwood, Prince, Mann, & Ebrahim, 1998). The occasional experience of medically unexplainable symptoms (such as dizziness, an upset stomach, or palpitations) is common under stressful circumstances, such as various social adversities, life events, or physical illnesses, especially among the elderly. A previous study has reported that the attendance of older people with somatization is as common as that of younger people (Sheehan, Bass, Briggs, & Jacoby, 2003).

Previous studies have shown age-associated differences in the prevalence of SDs. Altamura, Carta, Tacchini, Musazzi, and Pioli (1998) reported that the prevalence of undifferentiated SD tends to increase with age. Kuwabara et al. (2007) found that the age of onset is higher in patients with hypochondriasis or pain disorder than in patients with somatization disorder or body dysmorphic disorder. The reason why such anxiety or stress-related disorders are dependent on aging has remained unclear.

From a neuropsychological viewpoint, several studies have investigated the neuropsychological performance of subjects with late-life anxiety disorder and have hypothesized that the presence or severity of anxiety is associated with a lower cognitive performance in the elderly (Beaudreau & O'Hara, 2008). According to this report, we

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hypothesized that cognitive functions might be related to the etiology of SDs. Cognitive functions decline with aging (Nilsson, 2003), especially memory, attention, and executive functions (Buckner, 2004). Among several neuropsychological tests, the Mini-Mental State Examination (MMSE) and the Frontal Assessment Battery (FAB) are useful screening tests for measuring general cognition including memory, attention, and executive functions in elderly people (Dubois, Slachevsky, Litvan, & Pillon, 2000; Folstein, Folstein, & McHugh, 1975). The Japanese version of the Neurobehavioral Cognitive Examination (J-COGNISTAT) is a brief but comprehensive test that can be used to assess multiple cognitive domains. J-COGNISTAT is a sensitive diagnostic tool for dementia (Matsuda & Nakatani, 2004). These tests are easy to administer and can be completed at the patient's bedside within a comparatively short period. These three neuropsychological tests have been established as a convenient means of screening patients and may be useful for the testing of our hypothesis.

The clarification of which neuropsychological functions are associated with symptomatic severity in patients with late-life SDs may be important for understanding their relation with aging. Therefore, the aim of the present cross-sectional study was to determine which cognitive functions are associated with disease severity in patients with late-life SDs using comparatively simple neuropsychological screening tests.

Methods

Participants

Fifty-three consecutive Japanese patients with undifferentiated SD, who were over 60 years of age and had been referred to the Jikei University Kashiwa Hospital outpatient clinic for psychiatry, were enrolled in this study. All the patients were recruited from a private general medicine practice, and the absence of any physical disease capable of explaining the somatic symptoms was confirmed. All the patients were diagnosed as having undifferentiated SD according to the DSM-IV-TR by an expert geriatric psychiatrist. Undifferentiated SD was operationalized according to whether the sufferer was unable to perform mundane activities of daily living (ADL). Focusing on undifferentiated SD seemed reasonable, since SD often appears initially as undifferentiated SD (Al-Lawati et al., 2000; Altamura et al., 1998). The exclusion criteria for the study were (1) the diagnosis of another significant axis I disorder (e.g., another anxiety-related disorder, major depressive disorder, substance abuse, somatization disorder, hypochondriasis, or pain disorder), (2) a history of major depression or other anxiety-related disorder during the last five years, (3) the presence of mild cognitive impairment (MCI) according to the diagnostic criteria for amnestic MCI (Petersen et al., 2001), (4) the presence of dementia or some other brain organic syndrome according to the DSM-IV-TR, (5) the presence of severe physical illness, or (6) the presence of psychiatric comorbidity. The present retrospective study was approved by the Ethics Committee of the Jikei University School of Medicine. Written informed consent was obtained from the patients or their designated representatives.

Psychological assessment

The severity of the somatic symptoms was assessed using the Hamilton Anxiety Scales (HAMA) (Hamilton, 1959). HAMA can be used as a scale for rating the severity of anxiety-related disorders. HAMA consists of two subscores: psychic anxiety (HAMA-PSY) (ranging from 0 to 28 points) and somatic anxiety (HAMA-SOM) (ranging from 0 to 28 points). HAMA-PSY consists of the following items: anxious mood, tension, fears, insomnia, intellectual retardation, and behavior at interview. 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 to 4 points). HAMA and its subscores are reliable and valid for anxiety-related disorders (Maier, Buller, Philipp, & Heuser, 1988), and HAMA and HAMA-SOM have proven to be sensitive measures for evaluating the severity of SDs (Maier et al., 1988). Many previous studies have used HAMA to measure the severity of SDs (Müller, Mannel, Murck, & Rahlfs, 2004; Volz, Möller, Reimann, & Stoll, 2000; Volz, Murck, Kasper, & Möller, 2002), and we believe that HAMA is the most appropriate tool for measuring the severity of SDs.

Neuropsychological assessment

Mini-Mental State Examination (MMSE)

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

Frontal Assessment Battery (FAB)

The FAB was recently introduced as a short screening test for exploring various functions of the frontal lobes and for evaluating executive functions (Dubois et al., 2000). The Japanese FAB version consists of six subtests: (1) similarities (conceptualization), (2) lexical fluency (mental flexibility), (3) motor series (programming), (4) conflicting instructions (sensitivity of interference), (5) go/no go (inhibition control), and (6) prehension behavior (environmental autonomy). Each subtest is rated from 0 to 3, with the total score ranging from 0 to 18.

Japanese version of the Neurobehavioral Cognitive Examination (J-COGNISTAT)

The 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 at between 8 and 9. If a subject's score is not more than 8, the score is considered to indicate an impaired level (Matsuda & Nakatani, 2004). The J-COGNISTAT can also be used as a screening tool for dementia that can be easily administered at the patient's bedside. However, the J-COGNISTAT can be used to evaluate multiple cognitive status profiles, which is useful for identifying how a certain domain has decreased in comparison with other domains. The validity of each domain of the J-COGNISTAT has been well examined (Matsuda & Saito, 2009). More intricate neuropsychological testing can impose a burden on patients with late-life SDs. Thus, we used the J-COGNISTAT to evaluate each cognitive domain relatively easily.

Assessment of other factors

Some previous studies have reported an increased risk of cognitive impairment in benzodiazepine users (Stewart, 2005). Thus, whether benzodiazepine dosage confounded the effect on cognitive functions was examined. Antidepressants also influence cognitive functions (Barch et al., 2012). The benzodiazepine and antidepressant dosage was based on the equivalent conversion table for psychometric drugs (Inagaki & Inada, 1999). In addition, we also evaluated the correlations between cognitive functions and other factors (onset age and duration of illness). As described previously, some studies have shown age-associated differences in the prevalence of SDs.

Statistical analysis

SPSS 19.0J for Windows (SPSS Japan Inc., Tokyo, Japan) was used for all the statistical analyses. To analyze the correlation between clinical parameters (HAMA score, HAMA-PSY score, and HAMA-SOM score) and cognitive parameters (MMSE total, subtest scores, FAB total, subtest scores, and J-COGNISTAT subtest scores), we performed a partial correlation analysis. The analyses were adjusted according to patient age and duration of education because some neuropsychological tests are strongly influenced by aging and education level. 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: $P = 0.05/11 \fallingdotseq 0.005$; FAB subtest scores: $P = 0.05/6 \fallingdotseq 0.008$; and J-COGNISTAT subtest scores: $P = 0.05/10 = 0.005$) were reported and the effects of the correlations were noted. We also used a partial correlation analysis adjusted according to age and education level to evaluate the correlations between cognitive functions and other factors (benzodiazepine dosage, antidepressant dosage, onset age, and duration of illness).

Results

Patient characteristics

The demographic variables of the 53 late-life SD patients aged 60 years and older are summarized in Table 1.

Table 1. Subject characteristics of patients with late-life somatoform disorders.

	$n = 53$ (mean ± SD)
Sex (male/female)	9/44
Age	71.7 ± 7.2
Education (years)	12.1 ± 2.2
Duration of illness (years)	6.7 ± 6.4
Onset age	64.7 ± 8.6
HAMA total score	14.8 ± 7.2
HAMA-SOM score	8.0 ± 4.1
HAMA-PSY score	6.8 ± 4.0
MMSE total score	27.6 ± 2.0
FAB total score	16.0 ± 1.5

Note: HAMA (The Hamilton Anxiety Scale), HAMA-SOM (The Hamilton Anxiety Scale, somatic subscore), HAMA-PSY(The Hamilton Anxiety Scale, psychic subscore), MMSE (Mini-Mental State Examination), FAB (Frontal Assessment Battery)

Cognitive profiles according to J-COGNISTAT

Table 2 shows the cognitive profiles according to J-COGNISTAT. The mean J-COGNISTAT subtest score for attention was 6.2 (SD = 3.0), which was below the cutoff value (8 points). None of the other subtest scores were below the cutoff values (Table 2).

Correlations between cognitive functions and disease severity

The MMSE total score was not significantly correlated with disease severity (HAMA score and HAMA-SOM score). The MMSE subtest scores were also not significantly correlated with disease severity. The FAB total score was significantly correlated with disease severity (HAMA score: $P = 0.002$; and HAMA-SOM score: $P = 0.02$). The FAB subtest scores for similarities (HAMA score: $P < 0.001$; and HAMA-SOM score: $P < 0.001$) and motor series (HAMA score: $P = 0.003$) were also significantly correlated with severity (Table 3). The J-COGNISTAT subtest score for calculation was

Table 2. Cognitive profiles of patients with late-life somatoform disorders.

	J-COGNISTAT subscores (mean ± SD)
Orientation	9.6 ± 0.9
Attention*	**6.2 ± 3.0**
Comprehension	8.5 ± 1.9
Repetition	9.9 ± 1.3
Naming	9.8 ± 0.6
Constructive ability	8.1 ± 1.5
Memory	9.6 ± 0.7
Calculation	8.9 ± 1.4
Similarities	10.1 ± 0.8
Judgment	10.7 ± 1.1
	(average)

Note: J-COGNISTAT (The Japanese version of the neurobehavioral cognitive examination)
*Attention score was below the cutoff value of J-COGNISTAT (8 points).

Table 3. Partial correlations between FAB scores and HAMA scores.

	HAMA-SOM	HAMA total
FAB total score	−0.33*	−0.46*
Subtest		
Similarities	−0.53**	−0.55**
Lexical fluency	−0.05	−0.01
Motor series	−0.36	−0.46**
Conflicting instructions	−0.08	−0.13
Go/no go	0.13	0.26
Prehension behavior	–	–

*$p < 0.05$, **Bonferoni-corrected $p < 0.05/6 = 0.008$

significantly correlated with disease severity (HAMA score: $P = 0.001$) (Table 4) Other FAB subtest scores, MMSE total and subtest scores, and J-COGNISTAT subtest scores were not significantly correlated with the HAMA score.

Correlations between cognitive functions and other factors

No significant correlation between cognitive function (FAB total score, FAB similarities, FAB motor series score, and J-COGNISTAT calculation score) and benzodiazepine dosage was seen among the patients with undifferentiated SD. The antidepressant dosage also showed no correlation with cognitive functions (FAB total score, FAB similarities, FAB motor series score, and J-COGNISTAT calculation score). These cognitive functions were not correlated with either onset age or the duration of illness.

Discussion

Summary of findings

In the present study, we investigated the correlations between cognitive functions and symptomatic severities in patients with SDs who were over 60 years of age. We found a decrease in the 'attention' average score among the J-COGNISTAT subscales. The HAMA scores were negatively correlated with the FAB total score, the FAB subtest score (similarities, motor series), and the calculation score among the J-COGNISTAT subscales. However, no other neuropsychological scores were significantly correlated with the HAMA scores. Therefore, in the present study, the symptomatic severities of late-life SDs were associated with executive function as assessed using the FAB and calculation skill as assessed using the J-COGNISTAT. Moreover, cognition and symptomatic severity in late-life SDs were not significantly influenced by the dosages of psychotropic agents (e.g., benzodiazepine and antidepressants) or other factors.

Table 4. Partial correlations between J-COGNISTAT and HAMA scores.

	HAMA-SOM	HAMA total
Orientation	0.05	0.05
Attention	0.23	0.16
Comprehension	−0.11	−0.03
Repetition	−0.20	−0.22
Naming	−0.24	−0.16
Constructive ability	0.17	0.10
Memory	−0.16	−0.15
Calculation	−0.39	−0.46*
Similarities	−0.22	−0.22
Judgment	0.04	0.05

*Bonferoni-corrected $p < 0.05/10 = 0.005$

Comparison with previous studies

In previous studies investigating cognitive declines in patients with late-life anxiety disorders, significant reductions in episodic memory and attention function were reported (Beaudreau & O'Hara, 2008). In the present study, we also found a decrease in the attention score using the J-COGNISTAT subscales, but no reduction in episodic memory was observed. The reason for this difference between the two studies is thought to be that patients with dysfunctional episodic memory were excluded from our study, based on the presence of MCI or dementia. An attention decrement was confirmed in our patients, but the decrease was not correlated with disease severity. Several possibilities may explain this result. One possibility is that a deficit in attention may have existed in our patients prior to the somatic symptoms and may have triggered the somatic symptoms, rather than being a result of the somatic symptoms. Another possibility is that attention deficits in patients with late-life SDs may be a vicarious or compensative reaction of the awareness of bodily sensations as a defense mechanism (Lipowski, 1988).

Interpretation of results

Regarding the FAB subtest score, 'similarities' reflect executive functions that enable the establishment of an abstract link between items or adherence to concrete aspects of objects. Furthermore, 'the motor series' measures the capacity to execute a sequence of actions successively in separate tasks, resembling the 'first-palm-edge' task in Luria's motor series. Therefore, we hypothesized that such disabilities of conceptualizing or executing performances in patients with late-life SDs might reflect a distortion of self-monitoring or self-correcting for physical symptoms, which might be linked to the aggravation of convinced ideations related to anxiety or dysphoria in SD patients (Nagata et al., 2009). In patients with late-life SDs, the loss of self-correction in executive functions might influence their ability to access corrective information necessary for the modification of their irrational beliefs (Kashyap, Kumar, Kandavel, & Reddy, 2012). The J-COGNISTAT score for calculation was negatively correlated with the severity of late-life SDs patients. A poorer calculation performance is caused by a dysfunction of working memory, since the calculation skill in the J-COGNISTAT requires the patient to perform single-step calculations where instructions can be repeated at the patient's

request (Gupta & Kumar, 2009). The present study showed that the severity of late-life SDs was significantly correlated with executive functions and working memory. On the other hand, attention decline was not correlated with severity. This finding suggests that attention deficits in SD patients may be a trait marker of late-life SDs; thus, impairments in executive functions and working memory may be state markers of late-life SDs.

Implications for research

From the viewpoint of coping strategies, patients with SDs may adopt somatic complaints as a mode of coping with life's vicissitudes, psychological needs and conflicts, feelings of guilt and anger, and low self-esteem (Lipowski, 1988). In other words, poor coping strategies can lead to somatization. Hall, Kuzminskyte, Pedersen, Ørnbøl, and Fink (2011) reported that coping strategies are associated with attention, working memory, and executive functions. However, the present results partially differ from this previous report. These results suggest that working memory and executive functions may contribute to coping strategies, rather than attention, in patients with late-life SDs. Further study involving a large number of patients and detailed neuropsychological test batteries is needed to clarify this hypothesis.

Implications for practice

The reason why the other FAB subtest scores were not correlated with disease severity was thought to be due to the ceiling effect of the FAB. Patients with MCI or dementia were excluded from our sample in the present study, and the FAB is somewhat limited at examining the details of cognition. This reasoning is also thought to be applicable to the J-COGNISTAT subtests.

As described previously, the HAMA score consists of the HAMA-SOM score and the HAMA-PSY score. The HAMA total score is often used to measure the severity of SDs (Volz et al., 2000; Volz et al., 2002). Therefore, we mainly used the HAMA total score to examine the severity of the SDs. Additionally, we evaluated the HAMA-SOM score to ascertain whether it can be used as an indicator of the severity of SDs. As a result, the HAMA-SOM score almost resembled the HAMA total score. However, the HAMA total score and the HAMA-SOM score were somewhat different. The HAMA total score was correlated with the 'motor series' score among the FAB subtests and with the 'calculation' score among the J-COGNISTAT subtests. On the other hand, the correlation between the HAMA-SOM score and these subtests was not statistically significant, but an associative trend was seen (former, $P = 0.01$; latter, $P = 0.005$). Some possible reasons for this difference can be considered. First, the distribution of type-I errors should be examined. To clarify this problem, further study involving a large number of patients with late-life SDs is needed. However, the HAMA total score is generally used to measure the severity of SDs (Volz et al., 2000; Volz et al., 2002), and we believe that our results are valid.

Limitations

The present study had some limitations. First, the sample size was comparatively small. Thus, we defined a valid statistical value using the Bonferroni correction to examine the association between symptomatic severity and cognitive functions. Second, we did not use normal sample data and instead investigated the cognitive profiles of late-life SD patients according to the only standardized cognitive scale available, the J-COGNISTAT subscales. Third, many other neuropsychological test batteries for evaluating executive functions exist, and these test batteries might have provided useful information. However, the FAB is one of the easiest tests to administer and can be completed at bedside without requiring any tools or instruments. J-COGNISTAT is also easy and can be used with less burden to the patients. We believe that the simplicity of these tests makes them valuable tools. Finally, the HAMA is not a specific scale for SDs. The use of more specific scale for SDs would be preferable, although a standardized specific scale is not available. Furthermore, in some previous studies, the HAMA was used to measure the severity of SDs. Thus, we believe that the use of HAMA is valid.

Conclusion

In conclusion, to elucidate the pathogenesis or to investigate risk factors for late-life SDs, we focused on the correlation between symptomatic severity and cognitive function. We found that the cognitive profiles that influenced the appearance of symptoms and symptomatic severity differed. Therefore, a subgroup of patients with a poor prognosis may exist among patients with late-life SDs based on differences in pathogenesis and the appearance of symptoms. The further development of treatment strategies targeting prognostic subgroups, rather than SD itself, is needed in the future.

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Description of authors' roles

Keisuke Inamura designed this study, examined the subjects, and wrote the manuscript. Norifumi Tsuno, Kenji Tagai, Tomoyuki Nagata and Shunichiro Shinagawa gave advice, including suggestions regarding the analysis method, and reviewed this manuscript. Kazuhiko Nakayama reviewed and commented on the final manuscript.

References

Al-Lawati, J., Al-Lawati, N., Al-Siddiqui, M., Antony, S.X., Al-Naamani, A., Martin, R.G., ... Al-Adawi, S. (2000). Psychological morbidity in primary healthcare in Oman: A

preliminary study. *Journal for Scientific Research: Medical Sciences, 2*, 105–110.

Altamura, A.C., Carta, M.G., Tacchini, G., Musazzi, A., & Pioli, M.R. (1998). Prevalence of somatoform disorders in a psychiatric population: An Italian nationwide survey. Italian Collaborative Group on Somatoform Disorders. *European Archives of Psychiatry and Clinical Neuroscience, 248*, 267–271.

American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders: DSM-IV-TR* (4th edition, text revision). Washington, DC: American Psychiatric Association.

Barch, D.M., D'Angelo, G., Pieper, C., Wilkins, C.H., Welsh-Bohmer, K., Taylor, W., ... Sheline, Y.I. (2012). Cognitive improvement following treatment in late-life depression: Relationship to vascular risk and age of onset. *American Journal of Geriatric Psychiatry, 20*, 682–690.

Beaudreau, S.A., & O'Hara, R. (2008). Late-life anxiety and cognitive impairment: A review. *American Journal of Geriatric Psychiatry, 16*, 790–803.

Buckner, R.L. (2004). Memory and executive function in aging and AD: Multiple factors that cause decline and reserve factors that compensate. *Neuron, 44*, 195–208.

Dubois, B., Slachevsky, A., Litvan, I., & Pillon, B. (2000) The FAB: A Frontal Assessment Battery at bedside. *Neurology, 55*, 1621–1626.

Folstein, M.F., Folstein, S.E., & McHugh, P.R. (1975) 'Mini-mental state examination'. A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research, 12*, 189–198.

Gupta, A., & Kumar, N.K. (2009). Indian adaptation of the Cognistat: Psychometric properties of a cognitive screening tool for patients of traumatic brain injury. *The Indian Journal of Neurotrauma, 6*, 123–132.

Hall, N.M., Kuzminskyte, R., Pedersen, A.D., Ørnbøl, E., & Fink, P. (2011). The relationship between cognitive functions, somatization and behavioural coping in patients with multiple functional somatic symptoms. *Nordic Journal of Psychiatry, 65*, 216–224.

Hamilton, M. (1959). The assessment of anxiety states by rating. *British Journal of Medical Psychology, 32*, 50–55.

Harwood, R.H., Prince, M.J., Mann, A.H., & Ebrahim, S. (1998). The prevalence of diagnoses, impairments, disabilities and handicaps in a population of elderly people living in a defined geographical area: The Gospel Oak project. *Age and ageing, 27*, 707–714.

Inagaki, A., & Inada, T. (1999). *Dose equivalence of psychometric drugs*. Tokyo: Seiwa Shoten. [In Japanese].

Kashyap, H., Kumar, J.K., Kandavel, T., & Reddy, Y.C. (2012). Neuropsychological correlates of insight in obsessive-compulsive disorder. *Acta Psychiatrica Scandinavica, 126*, 106–114.

Kuwabara, H., Otsuka, M., Shindo, M., Ono. S., Shioiri. T., & Someya T. (2007). Diagnostic classification and demographic features in 283 patients with somatoform disorder. *Psychiatry and Clinical Neurosciences, 61*, 283–289.

Lipowski, Z.J. (1988). Somatization: The concept and its clinical application. *American Journal of Psychiatry, 145*, 1358–1368.

Maier, W., Buller, R., Philipp, M., & Heuser, I. (1988). The Hamilton Anxiety Scale: Reliability, validity and sensitivity to change in anxiety and depressive disorders. *Journal of Affective Disorders, 14*, 61–68.

Matsuda, O., & Nakatani, N. (2004). *Manual for Japanese version of the Neurobehavioral Cognitive Status Examination (COGNISTAT)*. Tokyo: World Planning. [In Japanese].

Matsuda, O., & Saito, M. (2009). Multiple cognitive deficits in patients during the mild cognitive impairment stage of Alzheimer's disease: How are cognitive domains other than episodic memory impaired? *International Psychogeriatrics, 21*, 970–976.

Mayou, R., Bass, C., & Sharpe, M. (1995). Overview of epidemiology classification and aetiology. In R. Mayou, C. Bass, & M. Sharpe (Eds.), *Treatment of functional somatic symptoms* (pp. 42–65). Oxford: Oxford University Press.

Müller, T., Mannel, M., Murck, H., & Rahlfs, V.W. (2004). Treatment of somatoform disorders with St. John's wort: A randomized, double-blind and placebo-controlled trial. *Psychosomatic medicine, 66*, 538–554.

Nagata, T., Ishii, K., Ito, T., Aoki, K., Ehara, Y., Kada, H., ... Nakayama, K. (2009). Correlation between a reduction in Frontal Assessment Battery scores and delusional thoughts in patients with Alzheimer's disease. *Psychiatry and Clinical Neurosciences, 63*, 449–454.

Nilsson, L.G. (2003). Memory function in normal aging. *Acta Neurologica Scandinavica, 179*, 7–13.

Petersen, R.C., Doody, R., Kurz, A., Mohs, R.C., Morris, J.C., Rabins, P.V., ... Winblad, B. (2001) Current concepts in mild cognitive impairment. *Archives of Neurology, 58*, 1985–1992.

Salkovskis, P.M., & Warwick, H.M. (2001). Meaning, misinterpretations, and medicine: A cognitive behavioral approach to understanding health anxiety and hypochondriasis. In V. Starcevic, & D.R. Lipsitt (Eds.), *Hypochondriasis: Modern perspectives on an ancient malady* (pp. 202–222). Oxford: Oxford University Press.

Sheehan, B., Bass, C., Briggs, R., & Jacoby, R. (2003). Somatization among older primary care attenders. *Psychological Medicine, 33*, 867–877.

Stewart, S.A. (2005). The effects of benzodiazepines on cognition: Review. *Journal of Clinical Psychiatry, 66* (Suppl.), 9–13.

Volz, H.P., Möller, H.J., Reimann, I., & Stoll, K.D. (2000). Opipramol for the treatment of somatoform disorders results from a placebo-controlled trial. *European Neuropsychopharmacology, 10*, 211–217.

Volz, H.P., Murck, H., Kasper, S., & Möller, H.J. (2002). St John's wort extract (LI 160) in somatoform disorders: Results of a placebo-controlled trial. *Psychopharmacology (Berl), 164*, 294–300.

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Psychosis in Frontotemporal Dementia

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Abstract. Frontotemporal dementia (FTD) is a neurodegenerative disorder, associated with a progressive decline in behavior caused by focal degeneration of the frontal lobes. Psychosis was an underestimated symptom of FTD, however, recent genetic research has revealed a high prevalence of psychosis in certain genetic groups. The primary objective of this work is to review the literature on psychosis in FTD and to propose directions for future research, with reference to findings on psychosis in schizophrenia. A search was performed using PubMed, MEDLINE, and EMBASE. Search terms included "frontotemporal dementia", "psychosis", "schizophreni*", "psychotic symptoms", "hallucinations", and "delusions", and it identified 122 articles. Results revealed: 1) prevalence is approximately 10%, 2) TDP-43 type B and FUS pathologies might have relatively high frequency of psychosis, 3) psychosis in FTD is higher with genetic mutations of C9ORF72 and GRN, 4) imaging researches did not achieve conclusive results, and 5) no treatment for psychosis in FTD is currently available. A limitation of this systematic review is that it includes a small number of studies specifically examining psychosis in FTD. It is suggested that a possible overlap exists between FTD and schizophrenia. This potential overlap indicates a vulnerability to psychosis due to brain systems and pathways shared by these disorders.

Keywords: Frontotemporal dementia, gene mutation, neuropathology, psychosis, schizophrenia

INTRODUCTION

Frontotemporal dementia (FTD) is a neurodegenerative disorder, frequently associated with a progressive decline in behavior and language. The clinical syndromes are caused by focal degeneration of the frontal and anterior temporal lobes [1]. FTD is a common cause of early-onset dementia and has an incidence and prevalence similar to Alzheimer's disease (AD) [2]. FTD is likely an underestimated cause of dementia in both early and late-onset patients with dementia, due to a lack of general knowledge and a high rate of misdiagnosis [3].

Psychotic symptoms, such as delusions and hallucinations, are observed in dementing neurodegenerative diseases, especially in AD and dementia with Lewy bodies (DLB) [4]. Psychotic symptoms vary in type and intensity during the course of dementia and are associated with additional disability and a poorer quality of life, which, in turn, may lead to a greater burden on caregivers [5]. Physicians treating these disorders frequently encounter therapeutic difficulties in their management of these symptoms because

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antipsychotics or antidepressants may have limited efficacy or intolerance in patients with dementia [6]. Psychotic symptoms were originally thought to be a relatively rare symptom of FTD, in comparison to behavioral manifestations, such as disinhibition, stereotypic behavior, and inappropriate social behaviors. Mendez et al. reported that only 2.3% of subjects experienced delusions among 86 FTD subjects [7]. However, recent developments in genetic research have revealed a high prevalence of psychiatric symptoms in certain genetic groups, including patients with FTD who have a C9ORF72 mutation [8–11]. Moreover, considering that delusions and hallucinations are among the main symptoms of schizophrenia, recent research has considered possible associations between FTD and schizophrenia, including symptom similarity, familial co-morbidity, and genetic findings [12].

In this article, we review existing literature on psychotic symptoms in FTD, including clinical characteristics, genetic and neuroimaging findings, and treatments, while exploring the relationship between FTD and schizophrenia. Finally, based on this potential relationship, we propose future directions for research regarding the mechanisms underlying psychosis in FTD. The overlap between FTD and schizophrenia may provide a unique opportunity to explore psychosis irrespective of disease context.

METHOD

PubMed, MEDLINE, EMBASE and references from relevant studies, review articles, and books were searched using the terms "frontotemporal dementia", "psychosis", "schizophreni*", "psychotic symptoms", "hallucinations", and "delusions." Only publications written in English pertaining to psychosis in FTD were selected. The search yielded 122 articles, which formed the empirical basis of this review. The last search was conducted on Aug 12, 2013. Cross-referencing of the identified publications was also performed. The literature search was conducted independently by two of the authors (S.S. and S.N.). The results were screened for relevance, and the bibliographies of these articles were additionally screened.

RESULTS

Symptomatic studies on psychosis in FTD

Several early studies exploring the symptomatology of FTD have reported psychosis in patients with FTD before the establishment of consensus diagnostic criteria for FTD [13, 14]. After the establishment of consensus criteria for FTD by the Lund and Manchester Group in 1994 [15], and Neary et al. in 1998 [16], many studies have been conducted to compare clinical features and behavioral changes, including psychosis, between FTD and other forms of neurodegenerative dementias such as AD [17–21]. New research criteria for behavior variant FTD and the primary progressive aphasia (PPA) forms of FTD have simplified and helped to define patient cohorts likely to suffer from this disease [22, 23]. According to the latest Diagnostic and Statistical Manual of Mental Disorders (DSM-5) published in 2013, FTD is defined as frontotemporal neurocognitive disorders (NCD) [24]. Although the DSM criteria have not played much role in research until now, it may further facilitate studies on psychosis in FTD. Among these diagnostic criteria, the core symptoms are behavioral changes including disinhibition, apathy, loss of sympathy or empathy, stereotypic behavior, and hyperorality.

In general, the prevalence of psychotic symptoms was reported to be lower in patients with FTD than in those with AD (the estimated rate of delusions was 36% and hallucinations was 18%) [25]. Several reports failed to find psychosis among patients with FTD [26–28]. Other investigators reported relatively larger prevalence rates of delusions than hallucinations in patients with FTD [19, 29–32].

These symptomatic studies used different methodologies, including a multivariate stepwise discriminant analysis [18], original structured questionnaire [21], the Positive and Negative Syndrome Scale (PANSS) [33], and the Neuropsychiatric Inventory (NPI) [34–37]. While the NPI is a comprehensive behavioral assessment scale to compare neuropsychiatric symptoms of patients with dementia, the PANSS was originally designed for patients with schizophrenia, not psychosis in the setting of dementia. The details of these reports are summarized in Table 1.

There are several studies with larger cohorts. Omar et al. suggested that delusions were an early, prominent, and persistent feature, and that paranoid and somatic delusions were frequent. Bilateral or right-sided atrophy was found in most of the participants ($n = 56$) [32]. Mendez et al. evaluated 86 patients with FTD and reported that only 2.3% of them had delusions and none had hallucinations, which was significantly lower than patients with early onset AD ($n = 23$; delusion = 17.4% and hallucination = 4.3%) [38]. They also reviewed other reports and emphasized that psychotic symptoms were rare in FTD. They suggested that psychotic

Table 1
Delusions and hallucinations in patients with clinically diagnosed FTD

Author	n	Control	Measurement	Delusions	Hallucinations	
Lopez et al., [29]	20	AD ($n=40$)	DSM-III-R and others	20%	0%	
Levy et al., [35]	22	AD ($n=30$)	NPI	7%	0%	
Swartz et al., [18]	19	AD ($n=19$), late-life depression ($n=35$)	SCAN	Occasional (bizarre, jealous, somatic),	Rare (auditory)	
Hirono et al., [27]	24	AD ($n=240$), DLB ($n=23$)	NPI	0%	0%	
Gregory et al., [26]	15	–	CPRS	0%	0%	
Bozart et al., [19]	13	AD ($n=37$), tvFTD ($n=20$)	original questionnaire	15%	8%	
Bathgate et al., [21]	30	AD ($n=75$), CVD ($n=34$)	Informant-based behavioral questionnaire	Suspiciousness 30%, Delusions of theft 10%, False belief that people in home 10%, Misidentification phenomena 30%, Visual hallucinations/ illusions 8%, Auditory hallucinations/illusions 10%		
Boone et al., [33]	27	AD ($n=7$)	PANSS	No description about subscore, AD and FTD did not differ in positive symptom score		
Liu et al., [36]	51	Normal control ($n=20$), AD ($n=22$)	NPI	22%	13%	
Silveri et al., [119]	11	AD ($n=29$)	SPAS and NPI	Psychotic symptoms: SPAS 36% NPI 63%		
Mourik et al., [37]	63	–	NPI	12.7%	6.3%	
Engelborghs et al, [30]	29	AD ($n=205$), mixed dementia ($n=39$), DLB ($n=23$)	BEHAVE-AD	17.2%	6.9%	
Le Ber et al., [31]	68	–	detailed behavioral inventory (original)	5%	2%	
Mendez et al., [28]	74	–	psychiatric checklist (original)	Psychotic symptoms	2.7%	
Mendez et al., [7]	86	EOAD ($n=23$)	original questionnaire	2.3%	0%	
Omar et al., [32]	56	–	DSM-IV	14% (paranoid and somatic)	9%	2 cases have pathological confirmation
Lillo et al., [120]	43	FTD-ALS ($n=18$)	DSM-IV	19%	12%	

AD, Alzheimer's disease; BEHAVE-AD, Behavioral Pathology in Alzheimer's Disease Scale; CPRS, Comprehensive Psychopathological Rating Scale; CVD, cerebrovascular dementia; DLB, dementia with Lewy bodies; DSM, Diagnostic and Statistical Manual of Mental Disorders; EOAD, early onset Alzheimer's disease; FTD-ALS, frontotemporal degeneration with amyotrophic lateral sclerosis; NPI, Neuropsychiatric Inventory; PANSS, Positive and Negative Syndrome Scale; SCAN, Schedules for Clinical Assessment in Neuropsychiatry; SPAS, Subsets of Survey Psychiatric Assessment Schedule; tvFTD, temporal variant frontotemporal dementia.

symptoms in patients with AD involved the temporal limbic area, a region which links perception to emotional states [38], while patients with FTD have relative sparing of this system, resulting in their difference in rate of psychotic symptoms [39]. Finally, Velakoulis et al. reviewed 199 studies and reported that the prevalence of psychosis was 6.5% in 751 patients with FTD [40]. Patients with FTD with psychosis were younger than those without psychosis at the age of onset and experienced a longer delay between onset of psychosis and their subsequent presentation of apparent cognitive decline. Taken together, the evidence indicates that the prevalence rate of psychosis in patients with FTD is lower than in patients with AD. Delusions are relatively more common than hallucinations in patients with FTD and younger age may be a risk factor for psychosis in FTD.

However, most of symptomatic studies shown in Table 1 examined neuropsychiatric symptoms in patients with FTD and thus, few studies specifically focused on psychosis [40]. In addition, the definition of psychosis differed among these studies and some did not provide a detailed definition of psychosis. Moreover, most of the studies diagnosed FTD and examined psychotic symptoms only based on clinical symptoms. Patients with FTD may have made false statements based on their delusions or confabulations. A delusion is a systematic fixed belief formation that is false but firmly held, in contrast, confabulations production of fabricated, misinterpreted memories which is more isolated, fleeting, and variable. A retrospective chart survey by Mendez et al. demonstrated that 8.3% of patients with FTD ($n=48$) made false reports about their own experience [41]. They found that patients with FTD might have both fantastic and wish-fulfilling confabulations, and typical content-specific delusions. Both phenomena may be a result of disturbances in the ventromedial prefrontal cortex, an area highly implicated in FTD. The disturbances in these brain areas may result in deficits of source monitoring and in activating an automatic tagging for false reports.

Furthermore, in patients with FTD, behavioral and personality changes are the most prominent symptoms and usually precede their cognitive disabilities. Clinical symptoms, such as disinhibition, inappropriate social behaviors, repetitive compulsion behaviors, and lack of insight are very heterogeneous. The heterogeneity of these clinical characteristics of FTD may lead clinicians to misdiagnose FTD, not only as psychiatric disorders, such as late-onset schizophrenia, atypical psychosis, and depression [42], but also as neurologic diseases, such as cerebrovascular disorders [3, 7, 28, 42]. One study at a specialized clinic for neurodegenerative diseases revealed that patients with FTD received a prior inaccurate psychiatric diagnosis more often than patients with AD (FTD, 50.7% versus AD, 23.1%; $p<0.001$) [3]. There is also a problem with referral. For example, in a nationwide study examining reasons for referral to geriatric psychiatric hospitals, patients with FTD who had paranoid syndromes (3% out of 75 FTD patients) were more likely to be hospitalized rather than referred to memory clinics [43]. Thus, the clinical report of psychotic symptoms in FTD may have been potentially influenced by 1) misdiagnoses due to subjective false reports and confabulations, or caregivers' misunderstandings, 2) misdiagnoses due to their behavioral symptoms, as well as 3) referral bias to memory clinic or psychiatric hospital.

Research studies based only on clinical symptoms alone have potential confounds related to misdiagnosis, and also have the potential to underrepresent patients in whom psychosis is the diseases' earliest manifestation. Given that biological confirmation of disease pathology has become increasingly developed, clinico-pathological studies are required to accurately diagnose FTD and to clarify the prevalence of psychotic symptoms.

Clinico-pathological reports on psychosis in FTD

Recent reports on the clinico-pathological features of patients suspected of suffering from FTD have revealed that FTD is associated with a variety of pathological conditions. In general, patients with FTD can be subdivided into the following three subcategories, which are based on the presence of specific pathologies: 1) tau, 2) transactive response DNA binding protein 43 kDa (TDP-43) and 3) Fused in Sarcoma (FUS) [44]. Even today, a small number of patients diagnosed with FTD do not show any of these FTD-related specific pathologies. In these cases, other co-existing neurodegenerative diseases, including AD and DLB, may become apparent with microscopy, particularly in older patients. Changes in the pathological classification of FTD syndromes are still in progress [44, 45].

There have been relatively few studies of psychosis in FTD where the cohort had pathological confirmation. These studies suggest several underlying histopathological backgrounds for psychosis in FTD. However, some of the early studies of FTD with psychosis did not employ immunostaining methods or the latest classification of pathological changes in these FTD syndromes. Furthermore, there is a possibility that

pathological classification will be changing from now on.

The tau pathology

The tau pathology includes Pick's disease, FTD with MAPT mutations (FTDP-17), corticobasal degeneration (CBD), progressive supranuclear palsy (PSP), and argyrophilic grain disease. Several case reports noted that patients with FTD who presented with psychotic symptoms had the neuropathology of Pick's disease [46–48]. However, their ages at onset and clinical presentations differed. Cases with FTDP-17 will be described in a later section discussing genetics.

The TDP-43 pathology

Tartaglia et al. and Loy et al. reported that patients with FTD with psychosis had the neuropathology of TDP-43 [49, 50]. Later, Claassen et al. reported six patients with FTD presenting DLB-like visual hallucinations; two of them were diagnosed with the TDP-43 pathology [51]. Velakoulis et al. also reported that among 17 pathologically proven patients with early-onset FTD, 5 had presented with a psychotic illness (schizophrenia/schizoaffective disorder = 4, bipolar disorder = 1) an average of 5 years prior to the diagnosis of FTD. Further, these patients with schizophrenia exhibited neuropathological changes consistent with the TDP-43 pathology [40].

The FUS pathology

Urwin et al. reported that 36% of 34 patients with FTD with psychosis presented with the FUS pathology, a relatively high frequency [52].

Other reports

Rohrer et al. studied a pathologically ascertained cohort of 95 patients with FTD (51%, 44%, and 5% had the TDP-43, tau, and FUS pathology, respectively) [53]. They reported that delusions and hallucinations existed mostly among patients in the TDP-43 type A pathology group, one patient in the TDP-43 type B pathology group showed delusions, and one patient with Pick's pathology showed an alteration of visual perception.

By contrast, some clinico-pathological reports without genetic information found low frequencies of psychosis in patients with FTD. According to Passant et al. no delusions and hallucinations were found among 19 patients (corticobasal degeneration = 1, frontotemporal lobe degeneration = 16, and Pick's disease = 2) [42]. Liscic et al. also reported that 4 patients experienced delusions, but none presented with hallucinations among 48 patients with pathologically proven FTD (only FTD = 37, FTD + AD = 11) [54]. This study was limited in that the information utilized to classify patients' detailed neuropathologies, such as tau-positive or tau-negative, was insufficient, and the behavioral assessments employed were not focused on psychosis.

Mendez et al. examined the relationship between psychosis in FTD and pathologies among 107 patients with clinically diagnosed FTD [55]. Among them, 95 had definite pathological findings, including 23 tau-positive patients, 51 tau-negative patients, and 21 patients with the AD pathology; 17 patients studied presented with psychosis. They found that patients with the AD pathology were more likely to have psychosis than other pathologies (28% versus 15%) and speculated that patients with the AD pathology might be misdiagnosed with FTD if they have an early age at onset and prominent neuropsychiatric features. This study did not contain more detailed neuropathology-based classification (subtype of the tau-positive pathology or tau-negative pathology) and does not discuss genetic information.

As a whole, patients with FTD who have the TDP-43 type B pathology are more likely to show psychosis compared to those with other pathology subtypes. This is associated with linkage to genetic mutation of C9ORF72 described below. Patients with FTD who have FUS pathology may also likely show psychosis, although the underlying mechanisms still remain elusive. Further studies that include genetic information, along with structural and functional imaging information, will be required to elucidate the relationships with FTD.

Genetic reports on psychosis in FTD

Recent advances in genetic research have revealed that approximately 40% of patients with FTD have a positive family history of dementia, suggesting a strong genetic component contributing to FTD [56]. Genes recognized to play an important role in the autosomal dominant FTD include 1) MAPT, encoding the microtubule-associated protein tau, 2) GRN, encoding the protein progranulin, 3) C9ORF72, a recently identified hexanucleotide repeat expansion on chromosome 9 open reading frame 72 [57, 58], and 4) other minor mutations.

MAPT mutation

More than 40 mutations in the MAPT gene have been identified in families with FTD and parkinsonism