International Psychogeriatrics (2009), 21:3, 520–525 © 2009 International Psychogeriatric Association
doi:10.1017/S1041610209008631 Printed in the United Kingdom

Characteristics of eating and swallowing problems in patients who have dementia with Lewy bodies

Shunichiro Shinagawa,[1,2] Hiroyoshi Adachi,[2,3] Yasutaka Toyota,[2] Takaaki Mori,[2] Izumi Matsumoto,[4] Ryuji Fukuhara[2] and Manabu Ikeda[2,5]

[1] *Department of Psychiatry, Jikei University School of Medicine, Tokyo, Japan*
[2] *Department of Neuropsychiatry and Neuroscience, Ehime University Graduate School of Medicine, Ehime, Japan*
[3] *Osaka University Health Care Center, Osaka, Japan*
[4] *Department of Special Support School Education, Ehime University Graduate School of Education, Ehime, Japan*
[5] *Department of Psychiatry and Neuropathobiology, Faculty of Medical and Pharmaceutical Science, Kumamoto University, Kumamoto, Japan*

ABSTRACT

Background: Eating problems occur frequently in patients with dementia, and almost half of all patients with Parkinson's disease have such problems. It has therefore been assumed that eating problems are also common in patients with dementia with Lewy bodies (DLB). However, few systematic studies have investigated eating problems in DLB patients. The aim of this study was to clarify the frequency and characteristics of eating problems in patients with DLB.

Methods: We examined 29 consecutive patients with DLB and 33 with Alzheimer's disease (AD) in terms of age, sex, education, Mini-mental State Examination, clinical dementia rating (CDR), neuropsychiatric inventory (NPI), Unified Parkinson disease rating scale (UPDRS), fluctuations in cognition, and usage of neuroleptic drugs / antiparkinsonian drugs. We employed a comprehensive questionnaire comprising 40 items and compared the scores between the two groups.

Results: DLB patients showed significantly higher scores than AD patients for "difficulty in swallowing foods," "difficulty in swallowing liquids," "coughing or choking when swallowing," "taking a long time to swallow," "suffering from sputum," "loss of appetite," "need watching or help," and "constipation". Only the UPDRS score significantly affected the scores for "difficulty in swallowing foods," "taking a long time to swallow" and "needs watching or help" score, whereas only the NPI score affected the score for "loss of appetite." The scores for UPDRS, NPI and CDR significantly affected the scores for "difficulty in swallowing liquids." No significant independent variables affected the scores for "coughing or choking when swallowing," "suffering from sputum" and "constipation."

Conclusion: Although DLB patients show many eating problems, the causes of each problem vary, and the severity of dementia or Parkinsonism is not the only determinant.

Key words: dementia with Lewy bodies, eating problems, swallowing problems, extrapyramidal signs, autonomic dysfunction

Introduction

It is well known that eating problems occur in association with cognitive dysfunction, psychiatric problems, and decline of daily activity in individuals with dementia (Frissoni *et al.*, 1998; Holm and Soderhamn, 2003). It is also known that eating/swallowing problems are associated with extrapyramidal signs (EPS) in Parkinson's disease (PD), almost half of all patients having some kind of eating problem (Liberman *et al.*, 1980). Dementia with Lewy bodies (DLB) is a dementing disorder clinically characterized by marked fluctuations in cognition, visual hallucinations, EPS, and sensitivity to typical neuroleptics (McKeith *et al.*, 1996; 2006). As DLB is clinically and pathologically related to PD, eating/swallowing problems have been considered common in DLB patients because of their EPS, autonomic dysfunction, fluctuations in cognition, and psychiatric problems. In a recent report from the DLB Consortium, "eating and swallowing difficulties" are described as a part of autonomic dysfunction in supportive diagnostic features (McKeith *et al.*, 2005). For DLB patients

Correspondence should be addressed to: Shunichiro Shinagawa, Department of Psychiatry, The Jikei University School of Medicine, 3-25-8 Nishi-shinbashi, Minato-ku, Tokyo, 105-8461, Japan. Phone: +81 3 3433 1111 ext 3301; Fax: +81 3 3437 0228. Email: shinagawa@jikei.ac.jp. Received 10 Nov 2008; revision requested 1 Dec 2008; revised version received 24 Dec 2008; accepted 5 Jan 2009. First published online 4 March 2009.

and their caregivers, it is important to evaluate the clinical background to eating / swallowing problems.

DLB is the second most common form of dementia after Alzheimer's disease (AD), accounting for 15–20% of dementia cases in pathological studies (McKeith *et al.*, 1996). However, to our knowledge, only a few systematic studies have investigated eating/swallowing problems in DLB patients (McKeith *et al.*, 2006). The aim of the present study was to clarify the frequency and characteristics of eating/swallowing problems in DLB patients, and their relationship to other symptoms.

Methods

Subjects

The study participants comprised 29 consecutive outpatients attending the Higher Brain Function Clinic of the Department of Neuropsychiatry, Ehime University Hospital, Japan, with a diagnosis of probable DLB according to the international working group criteria (McKeith *et al.*, 1996), between June 2005 and September 2005. Thirty-three patients with AD were also selected, matched for age and Mini-mental State Examination (MMSE) score (Folstein *et al.*, 1975), clinical dementia rating (CDR) score (Hughes *et al.*, 1982), and education. Patients with AD satisfied the criteria for probable AD developed by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (McKhann *et al.*, 1984). All subjects with DLB and AD underwent magnetic resonance imaging (MRI) and HMPAO-SPECT. All subjects were evaluated by senior neuropsychiatrists and underwent both physical and neurological examinations, as well as standard psychiatric evaluation, to exclude major functional psychiatric disorders such as schizophrenia or mood disorders. We also employed the usual battery of screening blood tests including vitamin B_{12} and thyroid function assessment to exclude treatable causes of dementia. All of the subjects were living with reliable caregivers. After a complete description of the study was presented to all patients or their caregivers, written informed consent was obtained.

Patients were assessed using a comprehensive battery of neuropsychological and neuropsychiatric tests, including MMSE, digit span test, verbal fluency test, Raven's Coloured Progressive Matrices (Raven *et al.*, 1990), CDR, and neuropsychiatric inventory (NPI; Cummings *et al.* 1994). We used the Unified Parkinson Disease Rating Scale (UPDRS) Part 3 score (motor score) to evaluate the severity of extrapyramidal signs (Fahn *et al.*, 1987). Caregivers were also asked whether the patients had fluctuations in cognitive functioning, or used neuroleptic or antiparkinsonian drugs. Patients' present weights were also measured.

Assessment of eating problems

In order to assess the characteristics of eating/swallowing problems in DLB patients, we used a comprehensive questionnaire that had originally been designed to assess eating/swallowing problems in patients with frontotemporal dementia/AD (Ikeda *et al.*, 2002), and had been revised for DLB patients. The questionnaire comprised 40 items investigating the following five domains: swallowing problems, appetite change, food preferences, eating habits, and other oral behaviors. Revision of the eating/swallowing questionnaire was conducted by adding four new questions relating to DLB and deleting seven questions relating to frontotemporal dementia. For example, "Episodes of spontaneous vomiting" and "Episodes of self-induced vomiting" were unified into a single item, and items such as "Fluctuation in swallowing ability" were added. We confirmed the validity of the revised questionnaire items by piloting this version of the prototype with DLB and AD patients. Information was gathered from caregivers familiar with the patients' eating problems. It was emphasized that a "symptom" should reflect a substantive change from the patient's premorbid state and was not a longstanding eating habit. If caregivers endorsed a particular item, they were asked to rate the frequency (0 = never; 1 = occasionally, less than once per week; 2 = often, about once per week; 3 = frequently, several times per week but less than every day; 4 = very frequently, once or more per day or continuously); and severity (1 = mild, easily controlled; 2 = moderate, not easily controlled; 3 = marked, embarrassing or otherwise disturbing to the family). For each eating problem item, we derived a product score of frequency × severity analogous to the method applied in the NPI (Cummings *et al.* 1994). We compared the product scores (frequency × severity) for each item between the DLB and AD groups. The rater who administered the questionnaire was blind to the patients' diagnosis.

Statistical analyses

Data analyses were carried out using the SPSS-PC software package. The significance of differences in age and education between the two groups was analyzed using the t-test. The Mann-Whitney U test was used for the comparison of MMSE score, CDR

Table 1. Demographic variables of the two patient groups

	DLB	AD	p value
Age at examination (y)	80.3 ± 5.8	78.5 ± 7.0	0.277
Education (y)	8.9 ± 2.8	9.7 ± 2.7	0.262
Sex (male:female)	18:11	8:25	0.004
MMSE	18.0 ± 6.7	17.3 ± 7.1	0.697
CDR	1.4 ± 0.8	1.4 ± 0.9	0.821
UPDRS (Part 3)	22.6 ± 20.9	6.9 ± 8.1	0.000
NPI	15.4 ± 13.2	11.8 ± 11.8	0.268
Fluctuations (N:Y)	14:15	25:8	0.035
Neuroleptics (N:Y)	17:12	30:3	0.006
Antiparkinsonians (N:Y)	25:4	32:1	0.176

Mean ± SD or N; MMSE = Mini-mental State Examination; CDR = clinical dementia rating; UPDRS = Unified Parkinson disease Rating Scale; NPI = neuropsychiatric inventory.

score, UPDRS score, NPI, and product score for each item between the two groups.

After comparing the product score for each item between the two groups, multiple regression analysis was conducted in order to investigate factors that most affected each eating problem item. In the stepwise multiple regression analysis, we assumed each item score to be a dependent variable and assumed that age, sex, MMSE score, CDR score, NPI score, UPDRS score, fluctuation, and usage of neuroleptic drugs were independent variables.

Results

Demographic variables of the two patient groups are summarized in Table 1. There were significant differences in the sex ratio, UPDRS score, presence of fluctuations in cognitive functioning, and use of neuroleptic drugs between the two groups. All the neuroleptic drugs used in both groups were atypical neuroleptics such as quetiapine. There was no significant difference in present body weight between the two groups. The scores (frequency × severity) for each symptom items between the two groups are summarized in Table 2. DLB patients scored significantly higher in items for "difficulty in swallowing foods," "difficulty in swallowing liquids," "coughing or choking when swallowing," "taking a long time to swallow," "suffering from sputum," "loss of appetite," "needs watching or help," and "constipation." There were no items for which AD patients scored significantly higher than DLB patients.

Multiple regression analysis was conducted for each of the items in which DLB patients scored significantly higher than AD patients. The results of the stepwise multiple regression analysis are summarized in Table 3. The UPDRS score significantly affected the "difficulty in swallowing foods" score; the UPDRS score, NPI score and CDR score significantly affected the "difficulty in swallowing liquids" score; no significant independent variable affected the "coughing or choking when swallowing" score; and the UPDRS score significantly affected the "taking a long time to swallow" score. No significant independent variables affected the "suffering from sputum" scor; the NPI score significantly affected the "loss of appetite" score; the UPDRS score significantly affected the "needs watching or help" score; and no significant independent variable affected "constipation" score.

Discussion

Our results indicated that DLB patients showed a higher incidence of eating/swallowing problems than AD patients, when matched for age, MMSE score, CDR score and education. As expected, most of the problems were involved in the swallowing domain: "difficulty in swallowing foods," "difficulty in swallowing liquids," "coughing or choking when swallowing," "taking a long time to swallow," "suffering from sputum," along with some problems in other domains such as "loss of appetite," "needs watching or help," and "constipation." Except for "needs watching or help", no problems in the eating habits domain and food preference domain were noted.

"Difficulty in swallowing foods" was affected only by UPDRS score, whereas "difficulty in swallowing liquids" was affected by UPDRS score, NPI score, and CDR score. This difference between swallowing foods (solid) and swallowing liquids (fluid) may reflect the difference in the underlying mechanism. Liquid has a shorter oral stage than solids, and the speed of flow into the pharynx

Table 2. The scores (frequency × severity) for each symptom domain in the two groups

	DLB	AD	p value
Swallowing problems			
Difficulty in swallowing food	1.71	0.03	0.002
Difficulty in swallowing liquids	0.61	0.03	0.043
Coughing or choking when swallowing	0.96	0.24	0.013
Taking a long time to swallow	1.57	0.00	0.000
Placing food in mouth but not chewing it	0.29	0.00	NS
Chewing food but not swallowing it	0.04	0.03	NS
Suffering from sputum	0.86	0.12	0.011
Fluctuation in swallowing ability	0.18	0.00	NS
Appetite change			
Loss of appetite	1.79	0.15	0.000
Increase in appetite	0.04	0.33	NS
Seeking out food between meals	0.00	0.64	NS
Overeating at meal time	0.07	0.03	NS
Reporting hunger or requesting more food	0.04	0.03	NS
Reporting being overfull	0.00	0.00	NS
Needs to limit food	0.00	0.12	NS
Fluctuation in appetite	0.64	0.03	NS
Food preference			
Preferring sweet foods more than before	0.07	0.18	NS
Drinking more soft or sweet drinks	0.07	0.06	NS
Drinking more tea/coffee or water	0.18	0.24	NS
"Taste" in food changed in some way	0.00	0.00	NS
Adding more seasoning to their food	0.04	0.00	NS
Developing other food fads	0.00	0.00	NS
Hoarding foods	0.00	0.00	NS
Drinking more alcohol	0.11	0.00	NS
Eating habits			
Wanting to cook or eat the same food every day	0.04	0.21	NS
Tending to eat foods in the same order	0.00	0.03	NS
Wanting to eat at the same time every day	0.00	0.00	NS
Decline in table manners	0.36	1.12	NS
Eating with hands	0.18	0.52	NS
Taking a long time to eat	1.32	0.42	NS
Getting drowsy at meal time	0.39	0.03	NS
Needs watching or help	2.32	0.00	0.000
Other eating behaviors			
Tending to overfill mouth	0.00	0.24	NS
Chewing or sucking without trying to eat	0.00	0.00	NS
Eating non-edible foodstuffs	0.25	0.18	NS
Tending to snatch or grasp any food items	0.00	0.27	NS
Becoming a heavier smoker or taking up smoking	0.00	0.00	NS
Episodes of vomiting	0.04	0.00	NS
Fever with a meal	0.21	0.00	NS
Constipation	3.39	0.21	0.000

is fastter (Logemann, 1988). Initiation of the deglutition reflex is likely to be delayed when swallowing liquids. It is difficult to swallow if the flow speed is faster than the swallowing movement. Difficulty in swallowing liquids is likely to occur in neuromuscular disease and pharyngeal disease (Feinberg and Ekberg, 1994). Our results for the relationship between NPI/CDR score and difficulty in swallowing liquids may suggest problems at the anticipatory stage in DLB patients. This idea is supported by the view that patients with attention disturbances have problems at the anticipatory stage and tend to develop swallowing difficulties (Feinberg *et al.*, 1992). The "difficulty in swallowing foods" item scored higher than the "difficulty in swallowing liquids" item indicating that problems in swallowing foods are more common than problems in swallowing liquids. However, swallowing liquids may require more accurate control of muscles and nerves than swallowing solids. Clinicians should

Table 3. Factors affecting each eating questionnaire item

DEPENDENT VARIABLES	SIGNIFICANT INDEPENDENT VARIABLES	β	p value
Difficulty in swallowing foods	UPDRS	0.501	0.009
Difficulty in swallowing liquids	UPDRS	0.72	0.000
	NPI	0.62	0.001
	CDR	−0.53	0.009
Coughing or choking when swallowing	–		
Taking a long time to swallow	UPDRS	0.435	0.026
Suffering from sputum	–		
Loss of appetite	NPI	0.435	0.027
Needs watching or help	UPDRS	0.529	0.001
Constipation	–		

CDR = clinical dementia rating; UPDRS = Unified Parkinson disease Rating Scale; NPI = neuropsychiatric inventory.

be aware of this difference in the mechanism, and should ask caregivers which problems are dominant when managing DLB patients.

It was noteworthy that only the NPI score affected "appetite loss." Visual hallucinations, which are the most common psychiatric symptom in DLB, may lessen a patient's appetite. It has been pointed out that visual hallucinations disturb patients' concentration while eating food (Kindell, 2002), which may explain why the NPI score affected "appetite loss." However, future assessment of the mechanism whereby psychiatric symptoms according to the NPI affect patients' appetite is required.

Multiple regression analysis demonstrated no significant independent variables affecting the "coughing or choking when swallowing" and "suffering from sputum" scores. EPS, psychiatric symptoms and severity of dementia did not affect these scores, and they may reflect some other mechanism such as autonomic dysfunction. No significant independent variables affected the "constipation" score, because constipation may be the direct result of autonomic dysfunction (Thaisetthawatkul *et al.*, 2004). A previous study noted that 83% of patients with pathologically confirmed DLB showed constipation (Horimoto *et al.* 2003), and our results also support this high frequency of constipation in DLB patients.

There are a few methodological issues that should be taken into consideration when interpreting our results. First, although we compared DLB and AD patients, we did not compare DLB and patients with Parkinson's disease without dementia. Therefore, it is still unclear whether our results are DLB-specific problems or problems common to both PD and DLB. Secondly, significantly more neuroleptic drugs were used in DLB patients. As DLB patients are very sensitive to such drugs, which may produce EPS and other adverse reactions (McKeith *et al.*, 1996; Ballard *et al.*, 1998), this use of neuroleptic drugs may result in a high frequency of swallowing and eating problems in DLB patients. However, use of neuroleptic drugs did not affect any items in the multiple regression analysis, and did not provoke severe neuroleptic sensitivity reactions under close supervision. For accuracy, we need to conduct further research comparing DLB and AD patients who do not use any drugs and their swallowing and eating problems, although it would be very difficult in a clinical and hospital-based setting. Thirdly, longitudinal changes in patients' weight were not recorded, and therefore we cannot discuss the difference in weight loss between the two groups in this study.

In conclusion, eating and swallowing problems were more frequent in patients with DLB than in patients with AD. Eating problems were relatively few in AD patients, at least at the mild stage, and this result is consistent with previous studies (Bozeat *et al.*, 2000; Ikeda *et al.*, 2002). Although DLB patients show many eating problems, the causes of each problem vary, and are not solely dependent on the severity of dementia or parkinsonism. It is necessary to be cautious about swallowing and eating problems in order to prevent accidents when managing DLB patients. For caregivers, it may be more difficult to understand eating/swallowing problems in neurodegenerative disorders than those related to vascular disease. Education of family caregivers and care staff about eating/swallowing problems in DLB patients is also important for clinicians.

Conflict of interest

None.

Description of authors' roles

S. Shinagawa collected the data, carried out the statistical analysis, and wrote the manuscript. H.

Adachi, Y. Toyota and T. Mori collected the data. I. Matsumoto and R. Fukuhara provided critical comments on an earlier draft of the paper. M. Ikeda designed the study and provided critical comments for an earlier draft of the paper.

Acknowledgments

We would like to thank the late Professor H.Tanabe for his encouragement and helpful suggestions on our research.

References

Ballard, C. *et al.* (1998). Neuroleptic sensitivity in dementia with Lewy bodies and Alzheimer's disease. *Lancet*, 351, 1032–1033.

Bozeat, S. *et al.* (2000). Which neuropsychiatric and behavioural features distinguish frontal and temporal variants of frontotemporal dementia from Alzheimer's disease? *Journal of Neurology, Neurosurgery and Psychiatry*, 69, 178–186.

Cummings, J. L. *et al.* (1994). The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. *Neurology*, 44, 2308–2314.

Fahn, S., Elton, R. and Members of the UPDRS Development Committee (1987). *Recent Developments in Parkinson's Disease*, Vol 2. Florham Park: Macmillan Health Care Information.

Feinberg, M. J. and Ekberg, O. (1994). Videofluoroscopy in elderly patients with aspiration: importance of evaluating both oral and pharyngeal stage of deglutition. *American Journal of Roentgenology*, 156, 293–296.

Feinberg, M. J. *et al.* (1992). Deglutition in elderly patients with dementia: findings of videofluorographic evaluation and impact on staging and management. *Radiology*, 183, 811–814.

Frissoni, G. B. *et al.* (1998). Overcoming eating difficulties in the severely demented. In L. Volicer and A. Hurley (eds.), *Hospice Care for Patients with Advanced Progressive Dementia* (pp. 48–67). New York: Springer Publishing Company.

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

Holm, B. and Soderhamn, O. (2003). Factors associated with nutritional status in a group on any early stage of dementia. *Clinical Nutrition*, 22, 385–389.

Horimoto, Y. *et al.* (2003). Autonomic dysfunctions in dementia with Lewy bodies. *Journal of Neurology*, 250, 530–533.

Hughes, C. P. *et al.* (1982). A new clinical scale for the staging of dementia. *British Journal of Psychiatry*, 140, 566–572.

Ikeda, M. *et al.* (2002). Changes in appetite, food preference, and eating habits in frontotemporal dementia and Alzheimer's disease. *Journal of Neurology, Neurosurgery and Psychiatry*, 73, 371–376.

Kindell, J. (2002). *Feeding and Swallowing Disorders in Dementia*. Oxford: Speechmark Publishing Ltd.

Liberman, A. N. *et al.* (1980). Dysphagia in Parkinson's disease. *American Journal of Gastroenterology*, 74, 157–160.

Logemann, J. A. (1998). *Evaluation and Treatment of Swallowing Disorders*, 2nd edn. 2nd edn. San Diego, CA: College Hill Press.

McKeith, I. G. *et al.* (1996). Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): report of the consortium on DLB international workshop. *Neurology*, 47, 1113–1124.

McKeith, I. G. *et al.* (2005). Diagnosis and management of dementia with Lewy bodies. Third report of the DLB consortium. *Neurology*, 65, 1863–1872.

McKeith, I. G. *et al.* (2006). More severe functional impairment in dementia with Lewy bodies than Alzheimer disease is related to extrapyramidal motor dysfunction. *American Journal of Geriatric Psychiatry*, 14, 582–588.

McKhann, G. *et al.* (1984). 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*, 34, 939–944.

Raven, J. C., Court, J. H. and Raven, J. (1990). *Manual for Raven's Coloured Progressive Matrices*. Oxford: Oxford Psychologists Press.

Thaisetthawatkul, P. *et al.* (2004). Autonomic dysfunction in dementia with Lewy bodies. *Neurology*, 62, 1804–1809.

syndromes with known serum antibodies, such as relapsing polychondritis and Sjögrens, have been subsequently diagnosed in patients presenting with subacute encephalopathy.

The aetiology of a humourally mediated central nervous system condition may require initial compromise of the blood–brain barrier. This could expose the brain to serum factors, such as antibodies, resulting in central nervous system damage after the development of serum antibodies. Such serum antibodies could have been initially raised against skin tissue in our patient, and subsequently cross-react with neurons to mediate cognitive deterioration.

The autoantigens BP180 and BP230 are structural components of dermal hemi-desmosomes and are known to be targeted by antibodies in BP. Recent work has shown that BP230 also exists in human CNS neurons, with prominent expression within hippocampal neuronal somae and axons, providing a theoretical common antigen binding site.[5] Furthermore, IgG from our patient bound to hippocampal somae and axons during the peak of the illness, at a time when the skin biopsy demonstrated features consistent with basement zone IgG deposition. This suggests the concomitant presence of skin and neural antibodies during disease onset. However, serum analysis for BP180 and BP230 was negative in our patient. Hence, our patient may have antibodies to an antigenic target which is common to both skin and brain but is not BP180 or BP230.

This is the first study to directly link the clinical entities of encephalitis and BP through an antibody-based mechanism. It also emphasises the importance of recognising autoimmune encephalopathies and the benefits of prompt immunotherapy.

A Soni,[1] S R Irani,[2] B Lang,[2] K Taghipour,[3] R Mann,[4] A Vincent,[2] D Collins[4]

[1] Department of Rheumatology, Great Western Hospital, Swindon, UK; [2] Neurosciences Group, Department of Clinical Neurology, John Radcliffe Hospital, Oxford, UK; [3] Department of Dermatology, Churchill Hospital, Oxford, UK; [4] Department of Dermatology, Great Western Hospital, Swindon, UK

Correspondence to: Dr D Collins, Department of Rheumatology, Great Western Hospital, Marlborough Road, Swindon SN3 6BB, UK; david.collins@smnhst.nhs.uk

Acknowledgements: We thank St John's immunodermatology laboratory for performing the skin immunofluorescence.

Funding: SRI is supported by the National Institute of Health Research, Department of Health, UK.

Competing interests: AV receives royalties and payments for VGKC and other antibody assays.

Patient consent: Obtained.

AS and SRI contributed equally to the work.

Provenance and peer review: Not commissioned; externally peer reviewed.

Received 20 October 2008
Revised 5 April 2009
Accepted 6 April 2009

J Neurol Neurosurg Psychiatry 2009;**80**:1412–1413.
doi:10.1136/jnnp.2008.165894

REFERENCES

1. **Graus F,** Keime-Guibert F, Rene R, *et al.* Anti-Hu-associated paraneoplastic encephalomyelitis: analysis of 200 patients. *Brain* 2001;**124**:1138–48.
2. **Stinco G,** Codutti R, Scarbolo M, *et al.* A retrospective epidemiological study on the association of bullous pemphigoid and neurological diseases. *Acta Derm Venereol* 2005;**85**:136–9.
3. **Ances BM,** Vitaliani R, Taylor RA, *et al.* Treatment-responsive limbic encephalitis identified by neuropil antibodies: MRI and PET correlates. *Brain* 2005;**128**:1764–77.
4. **Vincent A,** Buckley C, Schott JM, *et al.* Potassium channel antibody-associated encephalopathy: a potentially immunotherapy-responsive form of limbic encephalitis. *Brain* 2004;**127**:701–12.
5. **Seppanen A,** Autio-Harmainen H, Alafuzoff I, *et al.* Collagen XVII is expressed in human CNS neurons. *Matrix Biol* 2006;**25**:185–8.

Characteristics of abnormal eating behaviours in frontotemporal lobar degeneration: a cross-cultural survey

Frontotemporal lobar degeneration (FTLD) is characterised by behavioural changes, including loss of insight, disinhibition, apathy, mood changes, stereotypic behaviour and abnormal eating behaviour.[1 2] Although many studies have highlighted the high prevalence of alterations in food preference and eating habits in FTLD and described loss of appetite in dementia represented by Alzheimer disease (AD),[3] there have been few systematic studies comparing FTLD subgroups, or contrasting AD and FTLD.[1 2 4] Eating behaviours are modulated by many factors including personal habits, ethnic culture and climate, such that alteration in eating behaviour in dementias may be confounded by ethnic or cultural factors. Food culture, meal styles and customs differ substantially between Western countries and Japan. People in the UK consume considerably more sweets, and total daily calorific intakes are higher than they are for the Japanese. (Data derived from the Food and Agriculture Organization of the United Nations; http://faostat.fao.org/.) Therefore, it is unclear whether altered eating behaviours of FTLD in Western cohorts are an entirely disease-specific effect or whether they are modulated by ethnic–cultural factors. The aims of this study were to investigate changes in eating behaviours in Japanese FTLD and AD patients and to compare the profile of abnormal eating behaviours in Japanese and Western patients using the same instruments.

A total of 163 patients were involved: 72 from Ehime, Japan (18 frontotemporal dementia (FTD), 11 semantic dementia (SD) and 43 AD), and 91 from Cambridge, UK (23 FTD, 25 SD, 43 AD) (fig 1). A detailed description of British patients has been reported previously;[5] all were of white European ethnicity. All patients were living at home. Patients in the FTD and SD groups fulfilled consensus criteria for FTLD. FTD with motor neuron disease patients were excluded. The diagnosis of probable AD was made according to the NINCDS-ADRDA criteria. All underwent comprehensive investigation including MRI and/or HMPAO-SPECT, a battery of screening blood tests, neuropsychological and psychiatric evaluations, mini-mental state examination (MMSE) and clinical dementia rating (CDR).

The care-giver-based questionnaire consisted of 36 items investigating five domains: swallowing, appetite, food preference (including sweet food preference and food fads), eating habits (including stereotypic eating behaviours and decline in table manners) and other oral behaviours (including food cramming and indiscriminate eating). It was emphasised that a "symptom" should reflect a substantive change from a patient's premorbid state. If care givers endorsed a particular item, they were asked to rate the frequency and severity, to derive a frequency×severity score.[5] Patients' present weights were measured, and patients' premobid weights were ascertained from their previous check-up to estimate the amount of weight change.

As demographic variables, there were no significant differences between patients in Japan and in the UK in age, education and CDR grade. There were significantly more females in the Japanese cohort, and the mean MMSE score of Japanese patients was significantly lower. Figure 1 shows the total scores (frequency×severity) for each domain in the three patient groups in Japan and UK. For all five domains, two-way ANOVAs showed a significant main effect of diagnosis only, no significant main effect of patients' nationality and no interaction between diagnosis and nationalities. In all instances, FTD patients scored significantly higher than AD patients. For appetite change, food preference and eating habits, SD patients also scored significantly higher than AD patients. A weight gain of more than 7.5 kg was found in 30% of the FTD cases and 36% of SD cases in UK, compared with 5.6% of FTD cases and 9.1% of SD cases in Japan.

Patients with FTD and SD presented similar abnormal eating behaviours both in Japan and in the UK. Changes in eating behaviours in Japanese patients with both of the FTLD subtypes were significantly more common than AD patients, as was the case in the UK. Therefore, it is clear that patients with FTD and SD exhibit similar abnormal eating behaviours, as is the case with other behavioural and psychiatric symptoms.[1 2] Changes in eating behaviours in FTLD groups appear to be universal, and although ethnic-cultural factors might modulate these changes to some extent, they are likely to be a direct consequence of the pathology of FTLD. Changes in food preference and eating habits were the main alteration in SD. The FTD group also showed changes in appetite and oral behaviours. These findings are in keeping with prior reports.[2] The

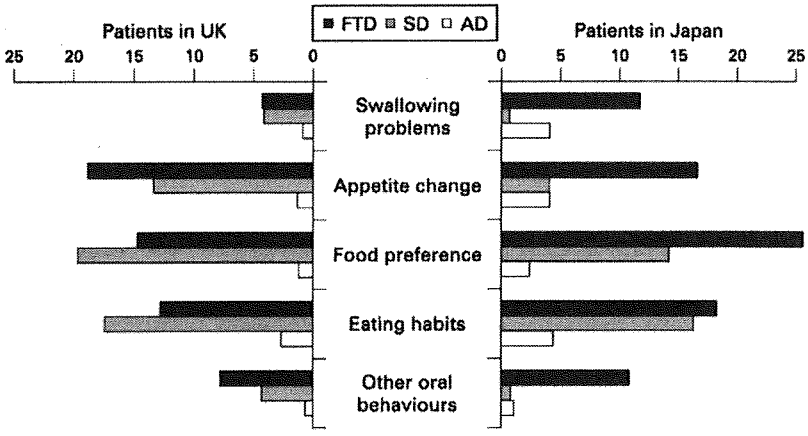

Figure 1 Score (frequency×severity) for each symptom domain in three patient groups in UK and Japan. Frequency: 1, occasionally, less than once per week; 2, often, about once per week; 3, frequently, several times per week but less than every day; 4, very frequently, once or more per day or continuously. Severity: 1, mild, easily controlled; 2, moderate, not easily controlled; 3, marked, embarrassing or otherwise disturb family. FTD, frontotemporal dementia (Japan: n = 18, age 65.5 (SD 7.0) years, F/M 9/9, mini-mental state examination (MMSE) 16.1 (9.4); UK: n = 23, age 61.1 (6.6), MMSE 22.9 (7.4)). SD, semantic dementia (Japan: n = 11, age 66.8 (7.6) years, F/M 7/4, MMSE 15.7 (10.8); UK: n = 25, age 65.1 (7.0), MMSE 17.2 (8.3)). AD, Alzheimer disease (Japan: n = 43, age 70.1 (9.8) years, F/M 30/13, MMSE 13.7 (7.9); UK: n = 43, age 68.3 (7.7), MMSE 20.6 (5.7)).

higher rate of appetite change in British SD may reflect the more advanced disease of the British: four out of 11 Japanese patients were moderate or severe demented cases (CDR≥2), whereas 16 out of 25 were moderate or severe in the UK cohort.

It appears that some abnormal eating behaviours such as appetite increase are modulated by cultural factors. A weight gain of more than 7.5 kg was found in 30% of FTD and 36% of SD cases in the UK, while it was found in less than 10% of FTD and SD cases in Japan. As described above, sugar intake and total calorie consumption differ significantly across Japan and the UK. We suggest that Japanese FTLD patients did not manifest such severe weight gain, because their eating behaviours are not amplified by cultural factors.

The current results highlight the stability of abnormal eating behaviours in FTLD across cultures with significantly different dietary habits and reinforce the view that changes in eating behaviour are diagnostically useful in detecting FTLD.[1 5]

S Shinagawa,[1,2] M Ikeda,[3,4] P J Nestor,[5] K Shigenobu,[6] R Fukuhara,[1] M Nomura,[7] J R Hodges[8]

[1] Department of Neuropsychiatry, Ehime University Graduate School of Medicine, Ehime, Japan; [2] Department of Psychiatry, Jikei University School of Medicine, Tokyo, Japan; [3] Department of Psychiatry and Neuropathobiology, Faculty of Medical and Pharmaceutical Sciences, Kumamoto University, Kumamoto, Japan; [4] Division of Clinical Research, Kikuchi National Hospital, Kikuchi, Japan; [5] University of Cambridge Neurology Unit, Addenbrooke's Hospital, Cambridge, UK; [6] Asakayama General Hospital, Osaka, Japan; [7] Department of Nursing, Ehime Prefectural University of Health Science, Ehime, Japan; [8] Prince of Wales Medical Research Institute, Sydney, Australia

Correspondence to: Professor M Ikeda, Department of Psychiatry and Neuropathobiology, Faculty of Medical and Pharmaceutical Sciences, Kumamoto University, Kumamoto, Japan, 1-1-1, Honjo, Kumamoto 860-8556, Japan; mikeda@kumamoto-u.ac.jp

Competing interests: None.

Ethics approval: Ethics approval was provided by Ehime University School of Medicine Ethical Committee.

Patient consent: Obtained.

Provenance and peer review: Not commissioned; externally peer reviewed.

Received 14 October 2008
Revised 17 February 2009
Accepted 19 February 2009

J Neurol Neurosurg Psychiatry 2009;**80**:1413–1414. doi:10.1136/jnnp.2008.165332

REFERENCE

1. **Bozeat S,** Gregory CA, Ralph MA, *et al.* Which neuropsychiatric and behavioural features distinguish frontal and temporal variants of frontotemporal dementia from Alzheimer's disease? *J Neurol Neurosurg Psychiatry* 2000;**69**:178–86.
2. **Snowden JS,** Bathgate D, Varma A, *et al.* Distinct behavioural profiles in frontotemporal dementia and semantic dementia. *J Neurol Neurosurg Psychiatry* 2001;**70**:323–32.
3. **Morris CH,** Hope RA, Fairburn CG. Eating habits in dementia: A descriptive study. *Br J Psychiat* 1989;**154**:801–6.
4. **Miller BL,** Darby AL, Swartz JR, *et al.* Dietary changes, compulsions and sexual behavior in frontotemporal degeneration. *Dementia* 1995;**6**:195–9.
5. **Ikeda M,** Brown J, Holland AJ, *et al.* Changes in appetite, food preference, and eating habits in frontotemporal dementia and Alzheimer's disease. *J Neuro Neurosurg Psychiatry* 2002;**73**:371–6.

Posterior circulation strokes without systemic involvement as the presenting feature of Fabry disease

Fabry disease is a multisystem lysosomal storage disorder with serious effects including cardiomyopathy and renal failure. Although neurological involvement at presentation is unusual, it is increasingly recognised that Fabry disease may present with ischaemic strokes and may be responsible for up to 5% of cryptogenic strokes in young men.[1] Early recognition is vital to permit early therapeutic intervention and family screening, and could prevent clinical progression and recurrent stroke. We report a patient who presented with recurrent brainstem ischaemic strokes due to Fabry disease, with no evidence of systemic manifestations at presentation. Fabry disease should be considered in cases of cryptogenic stroke (especially young men with vertebrobasilar territory symptoms) even without multisystem involvement.

CASE REPORT

In January 2007, a 24-year-old man was admitted with sudden rotatory vertigo and nausea. He reported three previous similar episodes. In 2004, he had diplopia for 5 days; later that year, he experienced transient vertigo and gait ataxia. The third episode occurred in February 2005, when he suffered the abrupt onset of unsteadiness, nausea, slurred speech and right-sided weakness. An MRI scan of the brain at this time showed a lesion of high signal on T2-weighted images in the left pons; MR angiography, carotid duplex scan and transoesophageal echocardiogram (TOE) were normal. Demyelination was considered, but when a cerebrospinal fluid (CSF) examination failed to show oligoclonal bands, a diagnosis of probable cryptogenic stroke was made. He made a good recovery over several weeks and remained symptom-free on aspirin and simvastatin until the present admission.

His general and neurological examinations were unremarkable. His only known vascular risk factor was smoking; there was no history of drug abuse, family history of stroke or premature vascular disease. He did not report painful acroparaesthesias during childhood. Pulse and blood pressure were normal. Routine haematology, biochemistry and cholesterol levels were normal. Detailed thrombophilia and vasculitic screens were negative. T2-weighted MRI of the brain revealed the old lesion in the left pons and a new lesion in the right midbrain compatible with ischaemia (fig 1), but an extensive battery of investigations (including repeat MR angiography and TOE) failed to reveal any cause. There was no signal abnormality in the thalamic pulvinar on T1-weighted images. However, plasma and leucocyte alpha-galactosidase A activity were very

認知症薬（周辺症状）

水上　勝義*
みずかみ　かつよし

- 周辺症状に対する薬物療法は安全性を優先する．また薬剤の副作用に留意する．
- 易怒性や攻撃性に対しては，抗精神病薬のほかに抑肝散やタンドスピロンなどの選択肢がある．
- DLB の薬物療法は特に注意が必要である．DLB の幻視に対してドネペジルや抑肝散が奏功する場合がある．
- せん妄に対しては原因検索と原因の除去をまず行う．症状が強い場合，少量の抗精神病薬を夜間に投与する．
- 抑うつ状態にはおもに SSRI や SNRI が用いられる．アパシーは抑うつ状態に類似するが，抗うつ薬の効果はあまり期待できない．

Key Words　周辺症状，抗精神病薬，漢方薬，抗不安薬，抗うつ薬

認知症の症状は，認知機能障害（中核症状），behavioral psychological symptoms of dementia（BPSD）あるいは周辺症状，そして，神経身体症状の3つに大別される．本稿のテーマである周辺症状は，認知症の経過中およそ8割の患者に出現し，患者や介護者の QOL を低下させ，介護者の心理，身体，経済的な負担を増加させ，患者の施設入所を促進させる一因である．したがって周辺症状に適切に対応することが，認知症の在宅介護を続けるうえで鍵となる．周辺症状に対しては，まず非薬物的対応がなされる．しかし，非薬物的対応で症状が改善しない場合が少なくない．その場合，薬物療法が併用される．認知症高齢者に対する薬物療法では副作用が生じやすく，薬物選択や投与量に注意が必要である．

□ 周辺症状の薬物療法に関する一般的留意点[1)]

認知症高齢者では，抗コリン作用による認知機能障害の悪化やせん妄の誘発，鎮静や起立性低血圧によるふらつきや転倒，さらに循環系への副作用などに十分注意が必要である．薬剤の開始量は成人の 1/2〜1/3 の量が目安になる．また，他科を受診している患者の場合，他科の処方を常にチェックし，薬物相互作用に対しても注意が必要である．

□ 各症状に対する薬物療法

周辺症状といっても症状は多岐にわたり，使用される薬剤も症状によって異なる．以下に代表的な症状とそれらに対する薬物療法について述べる．

1．易怒性，攻撃性

易怒性や攻撃性（暴言や暴力）に対する薬物療法では，抗精神病薬が用いられることがあるが，安全性の配慮から，まず代替薬を用いるのも治療選択肢の一つである．抑肝散は，比較的多数例を対象とした検討で，その有効性が示されている．われわれが行ったクロスオーバー試験においても，認知症高齢者の認知機能や ADL に影響を与えることなく，易怒性，攻撃性を改善した[3)]．ときに消化器症状や低カリウム血症などの副作用を認める．通常1日 7.5 g 投与するが，小柄な高齢者の場合 5 g 投与であっても効果が得られることがある．より体力の低下がめだつ患者に対しては，抑肝散の加味方である抑肝散加陳皮半夏が適応である．

抗不安薬が易怒性や攻撃性に有効な場合もある．われわれのオープンスタディによる検討[4)]では，タンドスピロン 10〜30 mg/日が有効であった．抑肝散もタンドスピロンもセロトニン 1A 受容体のパーシャルアゴニスト作用を有しており，この作用が周辺症状に効果を発揮したと考えられる．なおベンゾジアゼピン系抗不安薬は，眠気や筋弛

*筑波大学大学院人間総合科学研究科　精神病態医学

0913-7963/09/¥800/論文/JCLS

緩作用などの副作用を認めるうえに，せん妄のリスクもあるため，日中の使用は控えるべきである．

抗精神病薬のなかでは，チアプリドは認知症高齢者にしばしば用いられる．特に脳血管障害にみられる攻撃性，興奮，徘徊，多動などに対する有効性が報告されている．150 mg まで使用可能であるが，25～50 mg の低用量で改善をみる例も多いため，少量から開始する．これらの薬剤で効果が得られない場合，非定型抗精神病薬（リスペリドン，オランザピン，クエチアピン，ペロスピロン，アリピプラゾール，ロナセン®）を用いることがある．リスペリドンの易怒性，攻撃性に対する効果は，いくつかの二重盲検試験によって検討されている[5,6]．0.25～0.3 mg/日（分 2 朝，夕，不眠をともなえば就眠前 1 回投与）から開始し，1 mg/日を超える使用は控える．低用量でも使用を続けていると次第に活動性の低下や錐体外路症状が出現するので，その場合漸減，中止する．なお，レビー小体型認知症（DLB）は周辺症状を高頻度に認めるが，抗精神病薬に対する過敏性のため低用量でも重篤な副作用が出現しやすい．したがって DLB に対してはできる限り抗精神病薬の使用は控える．認知症に対して非定型抗精神病薬は適応外処方である．また非定型抗精神病薬服用中の認知症患者は非服用者に比して高い死亡率を示すことが報告されている[7]．たしかに非定型抗精神病薬を使わざるをえない場合もあるが，非定型抗精神病薬使用の際には，適否の見極めや使用に当たり説明が大切である．困難例では専門医に相談することが望ましい．

2．幻覚，妄想状態

認知症疾患ではときに幻聴，幻視，体感幻覚などの幻覚症状を認める．興奮をともなわない幻覚であればそのまま経過をみることが可能である．DLB では幻視が高頻度に見られ診断基準にもあげられている．DLB の幻視の場合は，抗精神病薬よりも塩酸ドネペジル[8]や抑肝散[9]のほうが安全性の面から望ましい．脳血管性認知症の幻覚，妄想状態には二重盲検試験の結果から釣藤散の効果も示されている[10]．

認知症の妄想としては，物盗られ妄想や被害妄想が多い．興奮をともなう物盗られ妄想に対してはリスペリドンなど少量の非定型抗精神病薬が用いられる．

3．せん妄

せん妄状態は，意識障害が背景にあり，夕方から夜間にかけて悪化し，しばしば幻覚，妄想，滅裂な言動，興奮状態などを認める．せん妄の多くは何らかの身体的あるいは心理・環境的誘因がみいだせる．薬剤が誘因となる場合もある．せん妄の治療はまずは原因を取り除くことである．通常せん妄は一過性であるが，興奮や混乱が続く場合，全身状態に配慮しながら慎重に薬物療法が行われる．チアプリド 25～50 mg の投与や，興奮が強い場合にリスペリドン内用液 0.5～1 ml やクエチアピン 25～50 mg を夕食後あるいは就眠前に投与する．日中は覚醒レベルを上げる必要があるため，原則としてこれらの薬剤は投与しない．脳血管性認知症のせん妄に釣藤散が有効との報告がある[10]．

4．抑うつ状態

抑うつ状態とは，意欲が低下し，それまでの趣味や楽しみにも関心を示さず，問うと「気分が晴れ晴れしない」，「つらい」などの抑うつ気分を訴える状態である．認知症の抑うつ状態においても抗うつ薬の治療を行うが，三環系抗うつ薬は抗コリン作用が強いため使用を控える．SSRI（フルボキサミン，パロキセチン，セルトラリン）や SNRI（ミルナシプラン）が比較的安全である．ただし SSRI は CYP450 のアイソザイムの阻害作用があるため，併用薬に注意が必要である．また抗うつ薬服用によってかえって落ち着きがなくなる activation syndrome と呼ばれる状態が見られたり，急に中止すると頭痛，感冒様症状などの退薬症状が見られることがあるので注意する．AD の抑うつ状態に対してセルトラリンの効果について報告がある[11]．またわれわれのオープンスタディでは AD の抑うつ状態に対してミルナシプランの効果が示された[12]．少量から開始し 40 mg/日程度で効果が得られる場合が多かった．ただしミルナシプランの副作用として排尿障害に注意する．また塩酸ドネペジルも AD の抑うつ，不安状態に有効である[13]．抑うつ状態と類似の状態にアパシーという状態がある．自発性，意欲，

関心などが低下するが，抑うつ気分はみられず，本人はあまり苦痛を感じていないことが特徴である．アパシーに対しては抗うつ薬の効果はあまり期待できず，むしろドネペジルのほうが有効である[13]．

おわりに

認知症の周辺症状に対する薬物療法について概説した．薬物療法の使用目的は，周辺症状を改善し，家庭生活が維持できるように援助することである．薬物療法では認知機能や身体機能の低下をきたすことがあるため，十分な注意が必要である．福祉サポートなどの非薬物的アプローチを活用しながら，安全で効果的な薬物療法に留意したい．

文　献

1) 水上勝義：精神疾患．高齢者の安全な薬物療法ガイドライン 2005．日本老年医学会編，メジカルビュー，東京，pp. 40-60，2005
2) Iwasaki K, Satoh-Nakagawa T, Maruyama M, et al : A randomized, observer-blinded, controlled trial of the traditional Chinese medicine *Yi-Gan* San for improvement of behavioral and psychological symptoms and activities of daily living in patients with dementia. J Clin Psychiatry 66 : 248-252, 2005
3) Mizukami K, Asada T, Kinoshita T, et al : A Randomized Crossover Study of a Traditional Japanese Medicine (Kampo) "Yokukansan" in the Treatment of the Behavioral and Psychological Symptoms of Dementia. Int J Neuropsychopharmacol 2008 (in press)
4) Sato S, Mizukami K, Asada T : A preliminary open-label study of serotonin 1A partial agonist tandospirone for behavioral and psychological symptoms associated with dementia. Int J Neuropsychopharmacol 10 : 281-283, 2007
5) De Deyn PP, Rabheru K, Rasmussen A, et al : A randomized trial of risperidone, placebo, and haloperidol for behavioral symptoms of dementia. Neurology 53 : 946-955, 1999
6) Katz IR, Jeste DV, Mintzer JE, et al : Comparison of risperidone and placebo for psychosis and behavioral disturbances associated with dementia : a randomized, double-blind trial. Risperidone Study Group. J Clin Psychiatry 60 : 107-115, 1999
7) Schneider LS, Dagerman KS, Insel P : Risk of death with atypical antipsychotic drug treatment for dementia : meta-analysis of randomized placebo-controlled trials. J Am Med Assoc 294 : 1934-1943, 2005
8) Mori T, Ikeda M, Fukuhara R, et al : Correlation of visual hallucinations with occipital rCBF changes by donepezil in DLB. Neurology 66 : 935-937, 2006
9) Iwasaki K, Maruyama M, Tomita N, et al : Effects of the traditional Chinese medicine Yi-Gan San for cholinesterase inhibitor-resistant visual hallucinations and neuropsychiatric symptoms in patients with dementia with Lewy bodies. J Clin Psychiatry 66 : 1612-1613, 2005
10) Terasawa K, Shimada Y, Kita T, et al : Choto-san in the treatment of vascular dementia : a double-blind, placebo-controlled study. Phytomedicine 4 : 15-22, 1997
11) Lyketsos CG, DelCampo L, Steinberg M, et al : Treating depression in Alzheimer disease. Arch Gen Psychiatry 60 : 737-746, 2003
12) Mizukami K, Tanaka Y, Asada T : Efficacy of milnacipran of depressive state in the patients with in Alzheimer's disease. Prog Neuropsychopharmacol Biol Psychiatry 30 : 1342-1346, 2006
13) Gauthier S, Feldman H, Hecker J, et al : Efficacy of donepezil on behavioral symptoms in patients with moderate to severe Alzheimer's disease. Int Psychogeriatr 14 : 389-404, 2002

Decreased Ventilatory Response to Hypercapnia in Dementia with Lewy Bodies

Katsuyoshi Mizukami, MD,[1] Toshiaki Homma, MD,[2] Kazutaka Aonuma, MD,[3] Toru Kinoshita, MD,[4] Kenji Kosaka, MD,[5] and Takashi Asada, MD[1]

A systematic autonomic dysfunction observed among patients with dementia with Lewy bodies (DLB) has recently attracted close attention. Here, we compare cardiovascular and pulmonary autonomic functions among patients with DLB, patients with Alzheimer's disease, and healthy control subjects. All 15 DLB patients demonstrated severely low ventilatory response to hypercapnia, whereas none of the other subjects demonstrated abnormal results. The majority of the DLB patients showed impaired heart rate variability, low uptake on ^{123}I-metaiodobenzylguanidine myocardial scintigraphy, and orthostatic hypotension. Ventilatory response to hypercapnia as a marker of respiratory autonomic function is a promising diagnostic tool for DLB.

Ann Neurol 2009;65:614–617

Dementia with Lewy bodies (DLB) is regarded as the second-most common degenerative dementia after Alzheimer's disease (AD).[1] The clinical criteria for DLB alone can separate many patients with DLB from other related disorders including AD. However, despite high diagnostic specificity, such criteria have lower sensitivity, and improved methods of case detection are required.[2] Several articles have emphasized that patients with DLB have autonomic physical symptoms, such as syncope, orthostatic hypotension, urinary incontinence, and constipation.[3–5] These autonomic symptoms, as well as a low uptake on ^{123}I-metaiodobenzylguanidine myocardial scintigraphy,[6,7] are included as a supportive feature of the criteria of the Consortium on DLB.[8] Accordingly, autonomic assessment may prove useful to

From the [1]Department of Psychiatry, University of Tsukuba, Tsukuba City; [2]Division of Respiratory Diseases, Teikyo University Chiba Medical Center, Ichihara; [3]Department of Cardiology, University of Tsukuba, Tsukuba City; [4]Kodama Clinic, Tokyo; and [5]Yokohama Hoyu Hospital, Yokohama, Japan.

Address correspondence to Dr Mizukami, Department of Psychiatry, Institute of Clinical Medicine, University of Tsukuba, 1-1-1 Tennodai, Tsukuba City, Ibaraki 305-8575, Japan. E-mail: mizukami@md.tsukuba.ac.jp

Potential conflict of interest: Nothing to report.

Received May 23, 2008, and in revised form Nov 13. Accepted for publication Nov 14, 2008.

Published in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/ana.21613

distinguish DLB from other dementing diseases including AD. However, to date, there is only our prior report, in a pilot study examining the diagnostic utility of impairment in ventilatory response to hypercapnia (VRH) in patients with DLB.[9] In this study, we evaluated additional neurologically impaired and healthy control subjects to examine the utility of the decreased VRH for the diagnosis of DLB.

Subjects and Methods

From a consecutive series of hospitalized dementia cases in our university hospital for their clinical evaluation between January 2006 and December 2007, we recruited 15 patients with probable DLB (6 male and 9 female patients; mean age, 68.8 years [standard deviation (SD), 7.3]), and 7 patients with AD (2 male and 5 female patients; mean age, 76.1 years [SD, 8.6]). We also recruited 12 community-dwelling healthy volunteers as control subjects (6 male and 6 female subjects; mean age, 69.3 years [SD, 4.7]). A diagnosis of probable DLB was made according to the latest clinical criteria.[8] In addition, 12 of 15 patients with DLB (80.0%) showed a reduction in cerebral blood flow in the occipital lobe on single-photon emission computerized tomography, and 11 of 15 patients (73.3%) showed low uptake on ^{123}I-metaiodobenzylguanidine myocardial scintigraphy. Both types of imaging have been reported to be useful in making a diagnosis of DLB.[8] The mean scores of the Mini-Mental State Examination of the DLB, AD, and control subjects were 18.9 (SD, 5.8), 20.6 (SD, 5.1), and 29.3 (SD, 1.0), respectively. The mean duration of the illness of DLB and AD patients was 3.6 (SD, 2.0) and 3.7 (SD, 2.2) years, respectively. None of the DLB or AD patients and only 1 of the 12 control subjects smoked. Some participants had hypertension and received antihypertensives. Otherwise, none of the subjects took medicine affecting autonomic function during the evaluations.

We evaluated respiratory autonomic functions by means of VRH, as well as arterial blood gas, percentage vital capacity, and forced expiratory volume in 1 second. To evaluate cardiovascular autonomic function, we tested for orthostatic hypotension and heart rate variability. This study protocol was approved by the Internal Ethical Review Board of the University of Tsukuba. Patients and their caregivers provided written, informed consent for study participation.

Evaluations

VENTILATORY RESPONSE TO HYPERCAPNIA. VRH was assessed using the dual control system for oxygen and carbon dioxide (Duograph KAY-100; CHEST, Tokyo, Japan). End-tidal oxygen partial pressure ($PETO_2$) was kept constant at 180 Torr during the procedure. VRH was expressed as the slope of the regression line relating ventilation (L/min) to changes in end-tidal carbon dioxide partial pressure ($PETCO_2$), corrected by body surface area (m^2) ($\Delta VE/PETCO_2/BSA$) ($L/min/Torr/m^2$).[9]

HEART RATE VARIABILITY. Twenty-four-hour Holter monitoring was performed with a three-channel recorder (8000T; Marquette Electronics, Milwaukee, WI) to evaluate heart rate variability. Frequency domain indices, that is, low frequency (LF; range, 0.04– 0.15Hz) and high frequency (HF; range, 0.15–0.40Hz), were analyzed using a commercially available software algorithm (MARS; Marquette Electronics). HF is considered to be a marker of parasympathetic activity, whereas LF is considered to be a marker of sympathetic activity.[10,11]

ORTHOSTATIC HYPOTENSION. Orthostatic hypotension, evaluated using a head-up tilt table, is defined as a reduction in systolic blood pressure of at least 20mm Hg or diastolic blood pressure of at least 10mm Hg within 3 minutes of standing.[12] Autonomic testing was performed blind to clinical diagnosis.

Fisher's exact test was used to determine the effect of antihypertensives on the results of orthostatic hypotension, and also was used to determine the significance of the difference between the number of the patients showing decreased parameters among DLB, AD, and control groups. Analysis of variance was used to compare autonomic responses among the three groups, and pairwise comparison was performed by using the Tukey–Kramer test for adjusting for multiple comparisons. Pearson's correlation coefficient was used to examine correlations between age and VRH, HF, or LF from each group, and also to examine a correlation between VRH and clinical data, such as the scores of Mini-Mental State Examination, Barthel index, duration of the disease, and Hoehn and Yahr stage in the DLB patients. In addition, Student's t test was used to examine the differences between VRH, HF, or LF for male and female subjects, and between patients with and without treatment with antihypertensives. Statistical analysis was performed with the use of R as statistical software.[13] p values < 0.05 were considered statistically significant.

Results

The use of antihypertensives was not significantly different among the three groups, and their use showed no significant effect on any results of autonomic assessments. All patients among the three groups showed normal arterial blood gas analysis, percentage vital capacity, and forced expiratory volume in 1 second. However, the indices of VRH of the DLB patients, AD patients, and control subjects were 0.156 (SD, 0.10), 0.431 (0.04), and 0.466 (0.09), respectively. VRH in DLB patients was significantly lower than that of AD ($p < 0.001$) patients and the control subjects ($p < 0.001$), whereas there was no statistical difference between AD patients and the control subjects (Table and Fig 1). All DLB patients demonstrated abnormally low VRH (reference range: male patients, 0.34–1.20; female patients, 0.39–0.95), whereas all of the AD or control subjects had normal VRH. In DLB patients, there was no correlation between VRH and the scores of Mini-Mental State Examination, Barthel index, disease duration, or Hoehn and Yahr stage.

The number of subjects who showed a decrease from

Table. **Comparisons of Respiratory and Cardiovascular Functions**

Items	DLB	AD	Control	
Ventilatory response to hypercapnia	0.156 ± 0.097 (mean ± SD)	0.431 ± 0.040	0.466 ± 0.094	DLB vs control ($p < 0.001$), DLB vs AD ($p < 0.001$), AD vs Control (NS)[a]
n/total (%)[b]	15/15 (100%)	0/7 (0%)	0/12 (0%)	$p < 0.001$[c]
Heart rate variability				
High Frequency (mean ± SD)	36.8 ± 32.2	115.4 ± 54.1	121.7 ± 102.7	DLB vs Control ($p = 0.016$), DLB vs AD (NS), AD vs Control (NS)[a]
n/total (%)[b]	9/13 (69.2%)	1/6 (16.7%)	4/12 (33.3%)	NS[c]
Low Frequency (mean ± SD)	132.6 ± 149.2	208.4 ± 141.9	279.2 ± 173.5	DLB vs control (NS), DLB vs AD (NS), AD vs control (NS)[a]
n/total (%)[b]	9/13 (69.2%)	3/6 (50.0%)	4/12 (33.3%)	NS[c]
Orthostatic hypotension	10/15 (66.7%)	2/7 (28.6%)	2/12 (16.7%)	$p < 0.05$[c]

[a]Results by Tukey–Kramer test.
[b]n = number of the patients showing decreased parameter; total = total patients in group.
[c]Results by Fisher's exact test.
DLB = dementia with Lewy bodies; AD = Alzheimer's disease; SD = standard deviation.

the 95% confidence limits of HF (56.5–186.9) and LF (168.9–389.4) were 9 of 13 and 9 of 13 in DLB patients, 1 of 6 and 3 of 6 in AD patients, and 4 of 12 and 4 of 12 in control subjects, respectively (see the Table). Notably, several DLB patients showed extremely low HF and LF values (Fig 2). The average values of HF in DLB patients, AD patients, and control subjects were 36.8 (32.2) msec^2, 115.4 (54.1) msec^2, and 121.7 (102.7) msec^2, respectively. The average value of HF in the DLB group was significantly lower than that in the control group ($p = 0.016$) (see the Table and Fig 2). Likewise, the average values of LF in DLB patients, AD patients, and control subjects

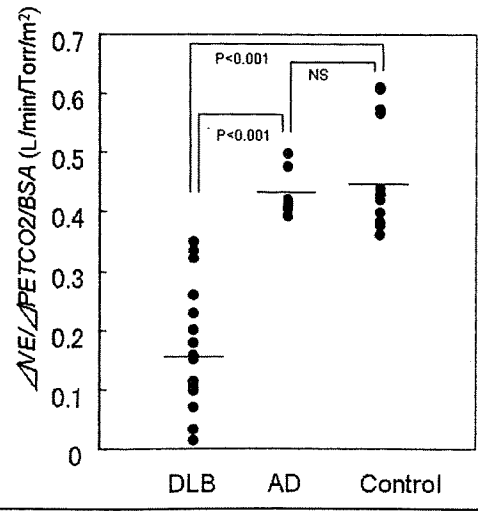

Fig 1. Ventilatory response to hypercapnia for patients with dementia with Lewy bodies (DLB), patients with Alzheimer's disease (AD), and control subjects. $\Delta VE/PETCO_2/BSA$ = slope of the regression line relating ventilation to changes in end-tidal carbon dioxide partial pressure, corrected by body surface area; NS = not significant.

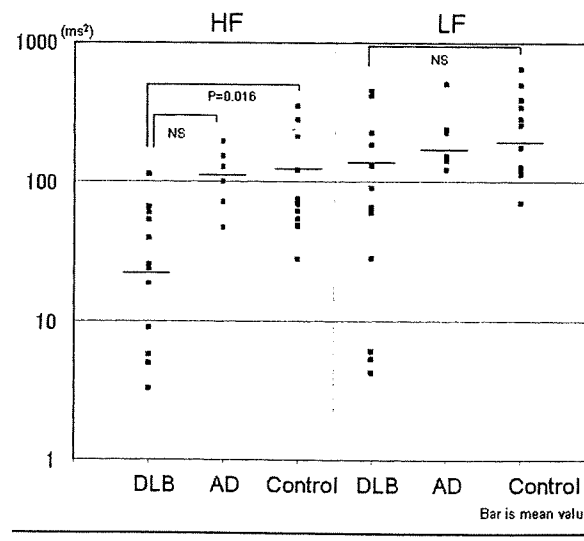

Fig 2. High frequency (HF) and low frequency (LF) of heart rate variability for patients with dementia with Lewy bodies (DLB), patients with Alzheimer's disease (AD), and control subjects. NS = not significant.

were 132.6 (149.2) $msec^2$, 208.3 (141.9) $msec^2$, and 279.2 (173.5) $msec^2$, respectively, and LF in DLB was lower than those in the AD group and control group, although the difference did not reach significance (see the Table and Fig 2).

There were no significant correlations between age and VRH, HF, or LF in any group. In addition, there were no differences in VRH, HF, or LF between the male and female subjects of each group. In 10 of 15 patients with DLB, orthostatic hypotension was observed, whereas only 2 of 7 AD patients and 2 of 12 control subjects showed orthostatic hypotension.

Discussion

In this study, the majority of DLB patients demonstrated abnormal findings in all the examinations of cardiovascular autonomic functions, and the results of the respiratory autonomic function assessments were significantly worse for DLB patients than for AD patients and control subjects. The greater rate of low heart-to-mediastinum (H/M) ratios of ^{123}I-metaiodobenzylguanidine myocardial scintigraphy and orthostatic hypotension in patients with DLB examined in our study is consistent with the results of previous studies.[5–7,14] In addition, our DLB group showed lower values of HF and LF than those in the AD and control groups. To date, only one study has reported HF and LF findings in patients with DLB.[14] Allan and colleagues[14] demonstrated that HF and LF were lower in their patients with DLB than in those with AD and control subjects. All of the earlier mentioned results appear to support the findings of this study.

In addition, all our 15 DLB patients showed abnormally low VRH. Although it is possible that smoking and chronic obstructive pulmonary disease[15] can affect VRH, this has not yet been reported in any study to our knowledge. Only one control subject in our study was a smoker, and no subject in this study suffered from respiratory disease including chronic obstructive pulmonary disease, making these unlikely to have influenced our results.

It remains open whether a low VRH will be proved to be a unique finding in DLB among various neurodegenerative diseases. Two prior studies have reported that patients with neurodegenerative disease involving the autonomic nervous system, such as multiple system atrophy and Parkinson's disease, showed reduced ventilatory response to hypoxia but normal sensitivity to hypercapnia.[16,17] Thus, VRH appears to be a promising diagnostic method for differentiating DLB from AD and possibly other neurological diseases. Finally, decreased VRH may have clinical significance in that patients with DLB may be more susceptible to respiratory compromise.

We thank Drs T. Kakuma and D. Darby for useful comments on the manuscript.

References

1. McKeith I, Galasko D, Kosaka K, et al. Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): report of the consortium on DLB international workshop. Neurology 1996;47:1113–1124.
2. McKeith IG, Burn DJ, Ballard CG, et al. Dementia with Lewy bodies. Semin Clin Neuropsychiatry 2003;8:46–57.
3. Horimoto Y, Matsumoto M, Akatsu H, et al. Autonomic dysfunctions in dementia with Lewy bodies. J Neurol 2003;250: 530–533.
4. Kaufmann H, Nahm K, Purohit D, et al. Autonomic failure as the initial presentation of Parkinson disease and dementia with Lewy bodies. Neurology 2004;63:1093–1095.
5. Thaisetthawatkul P, Boeve BF, Benarroch EE, et al. Autonomic dysfunction in dementia with Lewy bodies. Neurology 2004; 62:1804–1809.
6. Watanabe H, Ieda T, Katayama T, et al. Cardiac 123I-metaiodobenzylguanidine (MIBG) uptake in dementia with Lewy bodies: comparison with Alzheimer's disease. J Neurol Neurosurg Psyhchiatry 2001;70:781–783.
7. Yoshita M, Taki J, Yokoyama K, et al. Value of ^{123}I-MIBG radioactivity in the differential diagnosis of DLB from AD. Neurology 2006;66:1850–1854.
8. McKeith IG, Dickson DW, Lowe J, et al. Diagnosis and management of dementia with Lewy bodies. Third report of the DLB consortium. Neurology 2005;65:1863–1872.
9. Homma T, Ogawa R, Kikuchi N, et al. Respiratory chemosensitivity in dementia with Lewy bodies. J Jpn Resp Soc 2007;45: 297–300.
10. Pagani M, Lombardi F, Guzzetti S, et al. Power spectral analysis of heart rate and arterial pressure variabilities as a marker of sympatho-vagal interaction in man and conscious dog. Circ Res 1986;59:178–193.
11. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heart rate variability: standards of measurement, physiological interpretation, and clinical use. Circulation 1996;93:1043–1065.
12. The Consensus Committee of the American Autonomic Society and the American Academy of Neurology. Consensus statement on the definition of orthostatic hypotension, pure autonomic failure, and multiple system atrophy. Neurology 1996;46:1470.
13. R Development Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria, 2008. Available at: http://www.R-project.org. Accessed May 1, 2008.
14. Allan LM, Ballard CG, Allen J, et al. Autonomic dysfunction in dementia. J Neurol Neurosurg Psychiatry 2007;78: 671–677.
15. Calverley PMA: Ventilatory control and dyspnea. In: Calverley PMA, et al, eds. Chronic obstructive pulmonary disease. London: Chapman and Hall, 1995:205–242.
16. Onodera H, Okabe S, Kikuchi Y, et al. Impaired chemosensitivity and perception of dyspnea in Parkinson's disease. Lancet 2000;356:739–740.
17. Tsuda T, Onodera H, Okabe S, et al. Impaired chemosensitivity to hypoxia is a market of multiple system atrophy. Ann Neurol 2002;52:367–371.

International Journal of Neuropsychopharmacology (2009), 12, 191–199. Copyright © 2008 CINP
doi:10.1017/S146114570800970X

ARTICLE

CINP

A randomized cross-over study of a traditional Japanese medicine (kampo), yokukansan, in the treatment of the behavioural and psychological symptoms of dementia

Katsuyoshi Mizukami[1], Takashi Asada[1], Toru Kinoshita[2], Katsuaki Tanaka[3], Kazuki Sonohara[3], Ryuhei Nakai[4], Kiyoshi Yamaguchi[5], Haruo Hanyu[6], Kiyoshi Kanaya[7], Tetsuya Takao[8], Masakatsu Okada[9], Sumio Kudo[10], Hayato Kotoku[11], Masahiko Iwakiri[12], Hirofumi Kurita[13], Toshihiro Miyamura[14], Yosuke Kawasaki[15], Koji Omori[16], Kazumasa Shiozaki[17], Toshinari Odawara[17], Tatsuya Suzuki[18], Shizuru Yamada[19], Youichi Nakamura[20] and Kenji Toba[3]

[1] *Department of Psychiatry, Institute of Clinical Medicine, University of Tsukuba;* [2] *Kodama Clinic;* [3] *Department of Geriatric Medicine, Kyorin University, School of Medicine;* [4] *Kikyogahara Hospital;* [5] *Department of Geriatric Medicine, Graduate School of Medicine, the University of Tokyo;* [6] *Department of Geriatric Medicine, Tokyo Medical University;* [7] *Geriatric Medicine, Hachioji Medical Center of Tokyo Medical University;* [8] *Hospital Bando;* [9] *Hitachi Umegaoka Hospital;* [10] *Hitachi Sakura Clinic;* [11] *Luria-mental Clinic;* [12] *Ishizaki Hospital;* [13] *Kurita Hospital;* [14] *Health Care Center, University of Yamanashi;* [15] *Kyosai Hospital;* [16] *Gunma Prefectural Psychiatric Medical Center;* [17] *Psychiatric Center, Yokohama City University Medical Center;* [18] *Division of Geriatric Medicine, Nippon Medical School;* [19] *Geriatric Facilities Mahoroba-no-sato;* [20] *Nakamura Clinic, Japan*

Abstract

The effectiveness and safety of yokukansan (TJ-54), a traditional Japanese medicine (kampo) for the treatment of the behavioural and psychological symptoms of dementia (BPSD), were evaluated in 106 patients diagnosed as having Alzheimer's disease (AD) (including mixed-type dementia) or dementia with Lewy bodies. Patients were randomly assigned to group A (TJ-54 treatment in period I and no treatment in period II; each period lasting 4 wk) or group B (no treatment in period I and TJ-54 treatment in period II). BPSD and cognitive functions were evaluated using the Neuropsychiatric Inventory (NPI) and the Mini-Mental State Examination (MMSE), respectively. Activities of daily living (ADL) were evaluated using Instrumental Activities of Daily Living (IADL) in outpatients and the Barthel Index in in-patients. For the safety evaluation, adverse events were investigated. Significant improvements in mean total NPI score associated with TJ-54 treatment were observed in both periods (Wilcoxon test, $p=0.040$ in period I and $p=0.048$ in period II). The mean NPI scores significantly improved during TJ-54 treatment in groups A and B ($p=0.002$ and $p=0.007$, respectively) but not during periods of no treatment. Among the NPI subscales, significant improvements were observed in delusions, hallucinations, agitation/aggression, depression, anxiety, and irritability/lability. The effects of TJ-54 persisted for 1 month without any psychological withdrawal symptoms in group A. TJ-54 did not show any effect on either cognitive function or ADL. No serious adverse reactions were observed. The present study suggests that TJ-54 is an effective and well-tolerated treatment for patients with BPSD.

Received 13 March 2008; Reviewed 13 June 2008; Revised 24 September 2008; Accepted 3 November 2008; First published online 11 December 2008

Key words: Behavioural and psychological symptoms of dementia, traditional Japanese medicine (kampo), yokukansan.

Introduction

It has been reported that the behavioural and psychological symptoms of dementia (BPSD), including aggression, agitation, screaming, wandering, hallucinations, and delusions occur in 20–80% of patients with dementia (Lawlor, 2004). These symptoms impair the activities of daily living (ADL) in patients with dementia, impose great burdens on caregivers, hasten hospital admission (Steele *et al.* 1990), and increase care costs (Beeri *et al.* 2002). Although some atypical antipsychotic agents have been used for the treatment of BPSD (Herrmann & Lanctôt, 2006), adverse

Address for correspondence: K. Mizukami, M.D., Ph.D., Department of Psychiatry, Institute of Clinical Medicine, University of Tsukuba, 1-1-1, Tennodai Tsukuba City, Ibaraki, 305-8575, Japan.
Tel.: +81-29-853-3182 *Fax*: +81-29-853-3182
Email: mizukami@md.tsukuba.ac.jp

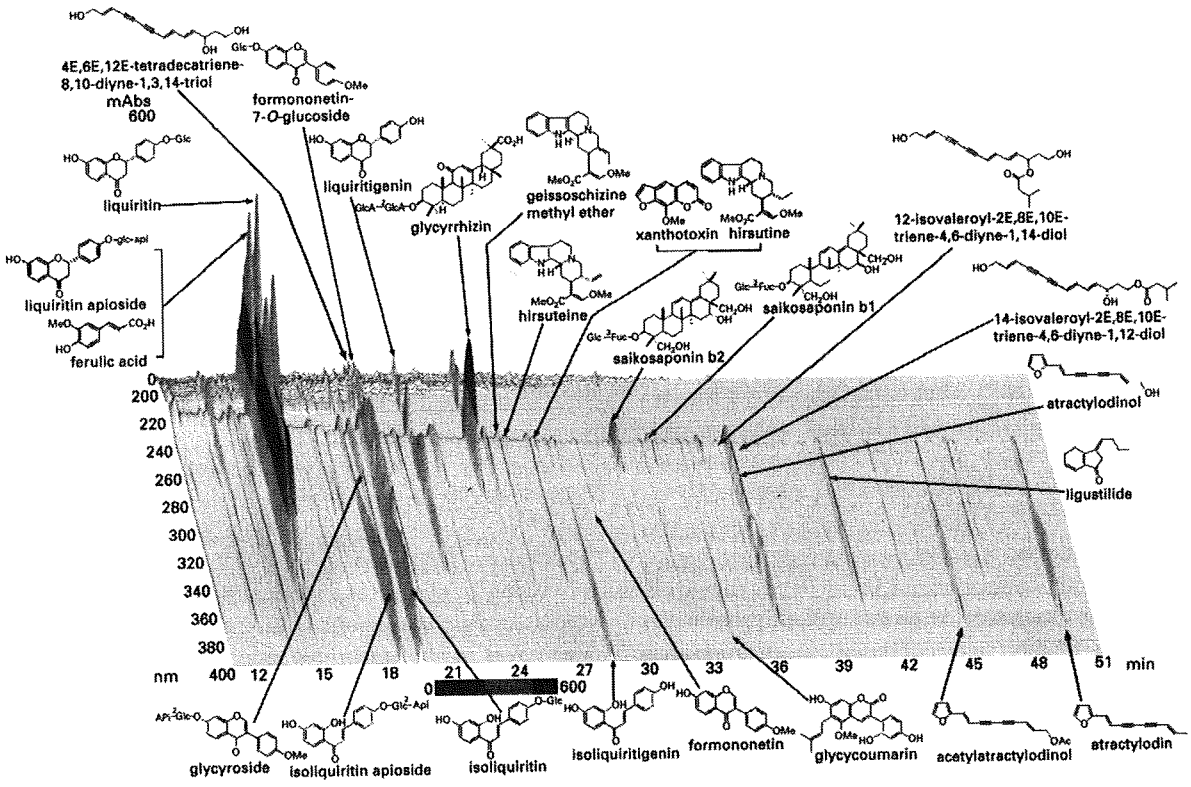

Fig. 1. Chemical profile of TJ-54 analysed by three-dimensional HPLC. Each peak of TJ-54 in the HPLC profile was identified by comparison of the retention times and UV spectra of chemically defined standard compounds.

reactions such as deterioration of cognitive function, somnolence, extrapyramidal symptoms, and gait disturbance are often present (Schneider *et al.* 2006). Recently, an increased mortality rate was reported in elderly patients with dementia who were using atypical antipsychotic agents (Schneider *et al.* 2005) as well as in such patients who were using conventional antipsychotic agents (Wang *et al.* 2005). There is therefore an urgent need to develop or find an effective BPSD treatment regimen that can be used more safely.

Kampo is the name given to Japanese traditional herbal medicine. Around the 5th century, Chinese herbal medicines were first introduced into Japan. Since then, through the accumulation of a vast body of clinical experience, kampo has developed and has been systematized. Kampo has attracted attention due to its purported ability to effectively treat disease while maintaining a favourable quality of life (QoL). More specifically, some papers have highlighted the efficacy of kampo in the treatment of dementia (Iwasaki *et al.* 2004; Terasawa *et al.* 1997; Yamaguchi *et al.* 2004).

Yokukansan (*yi-gan san* in Chinese) extract (TJ-54, Tsumura Co., Japan) is a kampo medicine containing JP Atractylodes lancea rhizome, JP poria sclerotium, JP Cnidium rhizome, JP Uncaria hook, JP Japanese angelica root, JP Bupleurum root, and JP Glycyrrhiza (JP: Japanese Pharmacopoeia) (Fig. 1). It has been prescribed for the treatment of emotional distress and agitation in infants. Recently, Iwasaki and colleagues reported that TJ-54 alleviates BPSD and problems with ADL in patients with dementia (Iwasaki *et al.* 2005*a*, *b*) and proposed its utilization as a new remedy to treat BPSD. We conducted this study in order to evaluate further the effectiveness and safety of TJ-54.

Methods

Subjects

We recruited patients aged 55–85 yr who met the diagnostic criteria for Alzheimer's disease (AD) using DSM-IV criteria (APA, 1994) and the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association criteria (NINCDS/ADRDA; McKhann *et al.* 1984), regardless of co-existence of vascular lesions (so-called mixed-type dementia). We also

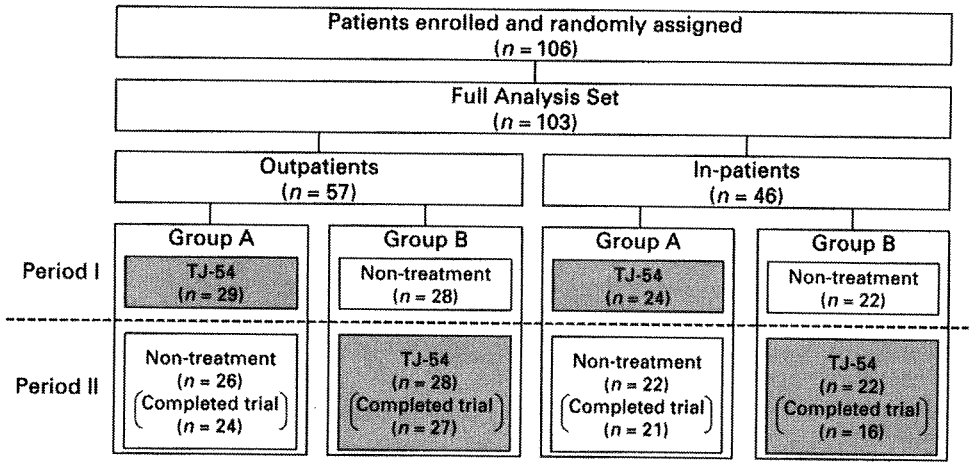

Fig. 2. Flow chart of the study.

recruited patients who were diagnosed as having dementia with Lewy bodies (DLB) ('probable DLB' based on the diagnostic criteria of McKeith *et al.* 1996). They were further selected based on an additional inclusion criterion that they showed, in the Neuropsychiatric Inventory (NPI, 10 items; Cummings *et al.* 1994), a score of $\geqslant 6$ for at least one of ten items at baseline. Patients with serious physical conditions or patients with delirium caused by a disease other than dementia were excluded.

The concomitant drugs prohibited in this study were antipsychotic agents, mood stabilizers, anxiolytic agents (other than benzodiazepine anxiolytic agents) and kampo other than the study drug.

This study was carried out in compliance with the ethical principles embodied in the Helsinki Declaration (1975). The study protocol was approved by the internal review board at each study site. Written informed consent was obtained from each patient (if capable of giving consent) or his/her proxy consent provider prior to participation in this study.

Study design

This study was conducted using a cross-over method, with a 4-wk treatment period (TJ-54 7.5 g t.i.d.) and a 4-wk non-treatment period. The subjects were randomly assigned, using a central registration method, into group A (TJ-54 treatment in period I and non-treatment in period II) or goup B (non-treatment in period I and TJ-54 treatment in period II) (Fig. 2). A total of 106 subjects were randomized to either group A ($n=54$) or group B ($n=52$) according to a randomization schedule using outpatient/in-patient as a stratification factor and the institution as a block factor. This study was conducted at 20 Japanese medical institutions from October 2005 to April 2007. The physician in charge at each institution made a diagnosis and evaluated the clinical state, and the assessment was carried out by a rater independent of the physician.

This study was conducted as an open-label study since it was impossible to prepare a suitable placebo due to the unique flavor and odour of TJ-54.

Outcome measurement

The subjects were assessed three times, at baseline, at 4 wk (at the end of period I), and at 8 wk (at the end of period II) after starting the study. BPSD and cognitive functions were assessed using the NPI (10 items) and the Mini-Mental State Examination (MMSE; Folstein *et al.* 1975). Assessment of ADL was performed using the Instrumental Activities of Daily Living (IADL; Mahoney & Barthel, 1965) in outpatients, and using the Barthel Index (Lawton & Brody, 1969) in in-patients. Regarding NPI, the test–retest reliability was evaluated by intra-class correlation (ICC) calculated via a fitting linear mixed-effect model for the observations at each visit (Verbeke & Molenberghs, 2000).

Since pseudoaldosteronism has previously been reported as an adverse reaction to TJ-54, in addition to a routine survey of adverse events during the study, serum potassium levels and the degree of leg oedema were determined at baseline, at the end of period I, and at the end of period II.

Statistical analysis

The analysis set (full analysis set; FAS) included all the enrolled subjects except those who did not return

Table 1. Demographic data of the subjects

	Outpatients			In-patients		
	Group A ($n=29$)	Group B ($n=30$)	Total ($n=59$)	Group A ($n=25$)	Group B ($n=22$)	Total ($n=47$)
Age (yr), mean (±S.D.)	80.6 (±3.9)	76.9 (±6.1)	78.7 (±5.4)	78.9 (±6.9)	78.0 (±6.7)	78.5 (±6.7)
Gender (M/F)	13/16	7/23	20/39	8/17	11/11	19/28
Diagnosis, *n* (%)						
Alzheimer's disease	21 (72.4%)	25 (83.3%)	46 (78.0%)	15 (60.0%)	17 (77.3%)	32 (68.1%)
Mixed dementia	1 (3.4%)	1 (3.3%)	2 (3.4%)	8 (32.0%)	3 (13.6%)	11 (23.4%)
DLB	7 (24.1%)	4 (13.3%)	11 (18.6%)	2 (8.0%)	2 (9.1%)	4 (8.5%)
Mean baseline score (±S.D.)						
NPI	25.5 (±12.0)	28.6 (±13.3)	27.1 (±12.7)	22.1 (±13.2)	26.4 (±16.3)	24.2 (±14.8)
MMSE	17.4 (±6.3)	14.9 (±5.6)	16.1 (±6.0)	9.8 (±6.9)	9.4 (±6.7)	9.6 (±6.8)

DLB, Dementia with Lewy bodies; NPI, Neuropsychiatric Inventory; MMSE, Mini-Mental State Examination.

to the study site after their first visit (subjects with no available data) and those whose drug-taking compliance appeared to be poor. Inter-group comparisons were performed according to the standard 2 × 2 cross-over method, using the change after cross-over as the response (Jones & Kenward, 1989). The changes throughout period I were also analysed and compared between the two groups. Where data were missing, the last observation carried forward (LOCF) method was used.

The Wilcoxon test (with continuity correction) was applied for efficacy evaluation using a two-sided type I error of 5%. The 95% confidence interval (CI) for each efficacy parameter was estimated by analysis of covariance (ANCOVA) using the baseline value and the category of outpatient/in-patient as covariates. In addition, for descriptive purposes, the intra-group changes in periods I and II were analysed by the signed-rank sum test using a two-sided type I error of 5%. No adjustment for multiplicity was performed.

Results

Subjects

The patients' backgrounds for all of the 106 subjects enrolled are shown in Tables 1 and 2. The average age was 78.7±5.4 yr for outpatients and 78.5±6.7 yr for in-patients. AD was the most common type of dementia in both outpatients and in-patients. The mean total NPI score at baseline was 27.1±12.7 and 24.2±14.8 for outpatients and in-patients, respectively. The mean MMSE score at baseline was 16.1±6.0 and 9.6±6.8 for outpatients and in-patients, respectively.

The FAS comprised 103 subjects and three subjects were excluded. One subject did not return to the study site after their first visit, and two subjects were excluded based on the physician's judgement regarding compliance.

Efficacy

Of the subjects who completed the study, 45 were in group A and 43 were in group B (Fig. 2). After cross-over (in period II), a significant difference was observed in the NPI score between TJ-54 treatment and non-treatment ($p=0.048$; point estimate of treatment effect: −1.4, 95% CI −3.0 to 0.2). Also in period I, the changes in NPI score were significantly different between TJ-54 treatment and non-treatment ($p=0.040$; point estimate of treatment effect: −5.2, 95% CI −10.1 to −0.3). The NPI score improved significantly in the TJ-54 treatment period in both groups (group A: from 24.0 to 19.7, $p=0.002$; group B: from 28.6 to 23.5, $p=0.007$), while no significant improvement was seen in the non-treatment period (Table 2). No rebound phenomenon of BPSD after the last dose of TJ-54 was seen in group A. The ICC of NPI was estimated as 0.731.

Among the subscales of NPI, agitation/aggression and irritability/lability were alleviated significantly by TJ-54 treatment in both groups, while delusions, hallucinations, depression, and anxiety were alleviated significantly in only one of the two groups (Table 3).

In subgroup analysis in terms of disease type, no significant difference was observed, but a significant alleviation of BPSD by TJ-54 treatment was seen in

Table 2. Baseline data of the subjects

	Group A TJ-54 treatment to non-treatment				Group B Non-treatment to TJ-54 treatment				Group A *vs.* group B	
	n	Mean	S.D.	*p* value	*n*	Mean	S.D.	*p* value	ΔI–Baseline	ΔII–I
NPI (total)										
Baseline	53	24.0	12.6	$p=0.002$	50	27.9	14.6	$p=0.414$	$p=0.040$	$p=0.048$
Period I	48	19.7	14.7	$p=0.807$	50	28.6	20.8	$p=0.007$		
Period II	45	18.9	11.6		45	23.5	20.0			
NPI (AD+mix)										
Baseline	44	23.4	13.3	$p=0.032$	44	26.7	14.6	$p=0.723$	$p=0.076$	$p=0.154$
Period I	39	20.3	16.2	$p=0.574$	44	28.3	21.6	$p=0.028$		
Period II	37	18.9	12.6		41	24.0	20.9			
NPI (DLB)										
Baseline	9	26.7	8.3	$p=0.023$	6	36.8	12.5	$p=0.344$	$p=0.479$	$p=0.114$
Period I	9	16.8	4.1	$p=0.563$	6	30.7	15.0	$p=0.250$		
Period II	8	18.8	6.2		4	18.3	5.7			
MMSE										
Baseline	51	13.8	7.6	$p=0.821$	48	12.6	6.7	$p=0.112$	$p=0.112$	$p=0.104$
Period I	48	13.7	8.0	$p=0.671$	50	13.2	7.6	$p=0.056$		
Period II	43	13.4	7.8		43	14.5	8.1			
Barthel Index										
Baseline	24	52.3	30.3	$p=0.242$	22	47.0	30.8	$p=0.430$	$p=0.961$	$p=0.770$
Period I	22	57.7	29.2	$p=0.047$	21	46.7	32.0	$p=0.121$		
Period II	21	54.5	28.4		18	46.4	33.9			
IADL (male)										
Baseline	13	2.9	1.6	$p=0.672$	6	1.7	1.5	n.a.	$p=0.799$	$p=0.571$
Period I	12	2.9	1.2	$p=1.000$	6	1.7	1.5	$p=1.000$		
Period II	12	2.8	1.0		6	1.8	1.5			
IADL (female)										
Baseline	15	4.2	1.9	$p=0.984$	22	4.7	1.9	$p=0.516$	$p=0.533$	$p=0.551$
Period I	14	4.4	1.8	$p=0.672$	22	4.5	1.9	$p=0.781$		
Period II	12	4.4	1.7		22	4.6	1.9			

NPI, Neuropsychiatric Inventory; AD, Alzheimer's disease; DLB, Dementia with Lewy bodies; MMSE, Mini-Mental State Examination; IADL, Instrumental Activities of Daily Living.

the AD subgroup (including patients with mixed-type dementia) (Table 2). In patients with DLB, a significant alleviation by TJ-54 treatment was only seen in group A (Table 2), but when the two groups were combined, the NPI score decreased in 11/13 patients with DLB (Fig. 3). No significant differences after TJ-54 treatment were seen in the MMSE, IADL, or Barthel Index (Table 2).

Safety

Throughout the study period, adverse events for which a causal relationship with TJ-54 could not be ruled out (adverse reactions) were noted in six subjects. Three subjects developed gastrointestinal symptoms (vomiting/diarrhoea, nausea, epigastric distress), and these patients stopped taking TJ-54. Thereafter, their symptoms disappeared immediately. Glycyrrhiza contains glycyrrhizin, which has a facilitating action on potassium excretion in the renal tubules but there is a risk that hypokalaemia may be induced. In fact, following TJ-54 treatment, the average serum potassium level in the subjects decreased by 0.20 mequiv/l, although the value remained within the normal range. Two subjects developed hypokalaemia (3.8→3.4, 4.1→2.2 mequiv/l), and one of the two also showed sedation. In these two patients, however, the potassium level quickly returned to the