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Effect of ferulic acid and *Angelica archangelica* extract on behavioral and psychological symptoms of dementia in frontotemporal lobar degeneration and dementia with Lewy bodies

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Aim: The behavioral and psychological symptoms of dementia place a heavy burden on caregivers. Antipsychotic drugs, though used to reduce the symptoms, frequently decrease patients' activities of daily living and reduce their quality of life. Recently, it was suggested that ferulic acid is an effective treatment for behavioral and psychological symptoms. We have also reported several patients with dementia with Lewy bodies showing good responses to ferulic acid and *Angelica archangelica* extract (Feru-guard). The present study investigated the efficacy of Feru-guard in the treatment of behavioral and psychological symptoms in frontotemporal lobar degeneration and dementia with Lewy bodies.

Methods: We designed a prospective, open-label trial of daily Feru-guard (3.0 g/day) lasting 4 weeks in 20 patients with frontotemporal lobar degeneration or dementia with Lewy bodies. Behavioral and psychological symptoms of dementia were assessed at baseline and 4 weeks after the start of treatment, using the Neuropsychiatric Inventory. The Neuropsychiatric Inventory scores were analyzed using the Wilcoxon rank sum test.

Results: Treatment with Feru-guard led to decreased scores on the Neuropsychiatric Inventory in 19 of 20 patients and significantly decreased the score overall. The treatment also led to significantly reduced subscale scores on the Neuropsychiatric Inventory ("delusions", "hallucinations", "agitation/aggression", "anxiety", "apathy/indifference", "irritability/lability" and "aberrant behavior"). There were no adverse effects or significant changes in physical findings or laboratory data.

Conclusion: Feru-guard may be effective and valuable for treating the behavioral and psychological symptoms of dementia in frontotemporal lobar degeneration and dementia with Lewy bodies. **Geriatr Gerontol Int 2011; 11: 309–314.**

Keywords: *Angelica archangelica*, behavioral and psychological symptoms of dementia, dementia with Lewy bodies, ferulic acid, frontotemporal lobar degeneration.

Introduction

Dementia is a degenerative or vascular disease in the brain that leads to progressive cognitive disability and a cluster of non-cognitive symptoms and behavioral disturbances. In 1999, the International Psychogeriatric

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Association Consensus Group defined the cluster as the behavioral and psychological symptoms of dementia (BPSD).[1] BPSD are an integral part of the disease process and are commonly associated with reduction in the quality of life (QOL) for the patients as well as their caregivers[2] and with increases in caregiver stress[3] and in the costs of care.[4] Frontotemporal lobar degeneration (FTLD) and dementia with Lewy bodies (DLB) are characterized by prominent behavioral and psychological symptoms in presenile or senile age.[5,6] BPSD in FTLD include aggression, disinhibition, stereotyped behavior, dietary changes and apathy, whereas those in DLB include visual hallucination, delusion, depression, anxiety and REM sleep behavioral disorder. Those symptoms in FTLD or DLB place a heavier burden on caregivers than do symptoms of Alzheimer's disease (AD) or vascular dementia. Although antipsychotic drugs are still used to reduce the symptoms, their adverse effects (e.g. arousal disturbance, ileus, tardive dyskinesia, malignant syndrome and rhabdomyolysis) decrease patients' ability to perform activities of daily living (ADL) and reduce their QOL. Therefore, establishing a safe therapy for BPSD without using antipsychotic drugs is highly necessary for patients and their caregivers. Although lavender aroma therapy and foot care using green tea paste have been investigated as ways to effectively mitigate BPSD,[7,8] whether these therapies can relieve severe BPSD in FTLD or DLB remains unclear.

Ferulic acid is a nutrient that exists in many kinds of grains and suppresses free radicals, chronic inflammation and aggregation of amyloid β-protein in the brain.[9–11] *Angelica archangelica*, a biennial plant from the umbelliferous family Apiaceae, inhibits acetylcholine esterase.[12] Recently, the possibility that ferulic acid is effective against BPSD was shown.[13] We also reported two patients with DLB showing good responses to ferulic acid and *A. archangelica* extract (Feru-guard, GLOVIA, Tokyo, Japan).[14] Given these results, we hypothesized that Feru-guard is useful for the treatment of serious BPSD in FTLD or DLB. To investigate this hypothesis, we designed a prospective, open-label study.

Methods

Subjects

Patients with FTLD or DLB were recruited from the outpatient clinic of the National Hospital Organization Kikuchi Hospital, Koshi, Japan, between April 2009 and February 2010. FTLD or DLB was diagnosed according to the clinical diagnostic criteria for FTLD[5] or consensus guidelines for the clinical and pathological diagnosis of DLB,[6] respectively. Exclusion criteria were: (i) delirium due to metabolic intoxication or drug use; (ii) alcoholism, stroke, depression, manic state or schizophrenia before the onset of FTLD or DLB; (iii) previous use of tranquilizers or antidepressants; or (iv) neoplastic disease or acute inflammation. Ten patients with FTLD (three men) and 10 patients with DLB (one man) were enrolled. The clinical data for the patients are shown in Table 1. Written informed consent was obtained from all patients or their relatives before entry, and patient anonymity was preserved.

Design of study

This was a 4-week, prospective, open-label study. Subjects were prescribed a dose of 3.0 g/day (b.i.d. [morning and evening]) Feru-guard. During the 4-week period, there were no changes in medication, rehabilitative regimen, hospitalization or care environment. The institutional review board of National Hospital Organization Kikuchi Hospital approved the study protocol. The study was conducted in accordance with the provisions of the Declaration of Helsinki (as revised in Tokyo 2004).

Measures

A trained psychologist evaluated BPSD using the Japanese version of the Neuropsychiatric Inventory (NPI)[15] at baseline and 4 weeks after the start of treatment. Caregivers were asked to rate 10 common symptoms of dementia (delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, euphoria, apathy/indifference, disinhibition, irritability/lability and aberrant motor behavior), using the NPI.

Clinical assessments

Physical examination (including bodyweight, body temperature and blood pressure measurements), laboratory tests and electrocardiography were conducted for assessments at baseline and 4 weeks after the start of treatment.

Statistical analysis

Neuropsychiatric Inventory scores were analyzed using the Wilcoxon rank sum test. We performed a Student's

Table 1 Characteristics of our 20 patients (four men)

	Age (years)	Length of education (years)	Duration of distress (years)	MMSE
Mean ± SD	81.6 ± 5.9	9.2 ± 2.7	2.6 ± 1.6	17.4 ± 7.3
Range	72–92	6–16	1–6	5–27

MMSE, Mini-Mental State Examination; SD, standard deviation.

t-test to clarify the difference in the NPI subscale scores between the FTLD group and the DLB group. A multiple regression analysis was used to predict the improvement of NPI scores based on factors related to the subjects. A two-tailed test revealed significance according to the level set in this study ($P < 0.05$).

Results

All patients completed the present trial without being lost to follow up. There were no adverse effects or significant changes in the physical findings or laboratory data. Treatment with Feru-guard led to decreased NPI scores in 19 (95.0%) of 20 patients and to significantly decreased NPI scores overall (Table 2). The treatment also led to significantly reduced NPI subscale scores ("delusions", "hallucinations", "agitation/aggression", "anxiety", "apathy/indifference", "irritability/lability" and "aberrant behavior" [Table 2]). Feru-guard treatment also significantly decreased NPI scores in both the FTLD and DLB groups (Table 2). Our analysis of the differences in the improvements in NPI subscale scores between the two groups revealed that "disinhibition", "irritability/lability" and "aberrant behavior" were more significantly improved in FTLD and "hallucinations" and "depression" were more significantly improved in DLB. A multiple regression analysis was performed among age, sex, education period, diagnosis, baseline Mini-Mental State Examination (MMSE) score and baseline NPI score as dependent variables and the improvement of the NPI score as the independent variable. The independent variable was selected by stepwise regression. Consequently, the baseline MMSE score was significantly positively correlated with the improvement of the NPI score (Pearson's correlation coefficient: $r = 0.466$, $P = 0.022$), and it predicted the improvement of NPI significantly ($\beta = 0.466$, $P = 0.044$) (Table 3).

Discussion

In the present study, treatment with Feru-guard led to significantly improved NPI scores in FTLD and DLB patients. The NPI is a clinical rating instrument that measures neuropsychiatric symptoms in demented patients and can characterize the effects of pharmacological treatment on these symptoms.[15,16] Our evaluation using NPI confirmed that Feru-guard treatment improved BPSD associated with FTLD or DLB. We investigated the differences between improvements in NPI subscale scores in the FTLD and DLB groups. This investigation showed more significant ameliorations of "disinhibition", "irritability/lability" and "aberrant behavior" in FTLD and of "hallucinations" and "depression" in DLB. Because these symptoms are characteristic of each of those respective dementias, Feru-guard treatment is considered to be more effective in treating characteristic symptoms of FTLD and DLB than other symptoms. Our multiple regression analysis indicates that the baseline MMSE score is associated with the improvement of the symptoms. Thus, we could anticipate a clinical response to Feru-guard in a patient by determining whether his or her baseline MMSE score was high.

Dealing with BPSD can cause caregiver distress and exhaustion. Antipsychotic drugs are still used to reduce the symptoms. The adverse effects of these drugs decrease patients' ADL and QOL; in addition, drug-induced gait disturbance and dizziness are likely to induce falls and bone injuries. A meta-analysis of randomized, placebo-controlled trials found a significantly higher risk of death due to atypical antipsychotic drug treatment for dementia,[17] leading to the recommendation from the US Food and Drug Administration that atypical antipsychotic drugs should not be prescribed for the control of BPSD. Because it was recently shown that donepezil, selective serotonin re-uptake inhibitors (SSRI) and Yokukansan were effective in treating BPSD,[18–22] these drugs have been used to treat BPSD instead of antipsychotic drugs. However, even these drugs cause various adverse effects in elderly patients. Donepezil induces gastrointestinal disturbance[23] and torsades de pointes with QT prolongation[24] and exacerbates chronic obstructive pulmonary disease[25] and psychotic symptoms.[26] SSRI cause gastric bleeding[27] and activation syndrome[28] and increase risks of incident clinical fragility fracture,[29] stroke[30] and diabetes.[31] Because SSRI decrease the activity of various isozymes of cytochrome P450 in the liver, affecting the metabolism and the clearance of different kinds of drugs, SSRI probably bring about unexpected adverse effects in elderly patients who may be taking several types of medication. A major ingredient of *Glycyrrhiza Radix* (licorice) in Yokukansan is glycyrrhizin, which occasionally induces pseudoaldosteronism.[32] Based on our clinical experience, Yokukansan causes hypokalemia and loss of appetite in demented patients.[22,26] These medicines as well as antipsychotic drugs might be especially harmful for demented patients who are 80 years old and over. In our subjects taking Feru-guard, there were no adverse effects or significant changes in the physical findings or laboratory data. The results suggest that Feru-guard treatment in FTLD or DLB might be safer than other pharmacological treatments.

An imbalance of neurotransmitters in the central nervous system putatively induces anxiety and excitement, and consequently induces BPSD. The mechanism by which treatment with Feru-guard improves BPSD in patients with FTLD or DLB remains uncertain. Ferulic acid suppresses free radicals, chronic inflammation, aggregation of amyloid β-protein and

Table 2 Changes in Neuropsychiatric Inventory scores 4 weeks after Feru-guard treatment in 20 patients with frontotemporal lobar degeneration or dementia with Lewy bodies

	Baseline (mean ± SD)	Follow up (mean ± SD)	*P*-value*
NPI total score			
FTLD + DLB	28.3 ± 9.6	17.7 ± 9.7	<0.001
FTLD	32.3 ± 11.1	22.0 ± 10.2	<0.01
DLB	24.2 ± 5.9	13.3 ± 7.3	<0.01
Delusions			
	2.2 ± 2.7	1.3 ± 2.1	<0.05
	2.4 ± 3.4	1.5 ± 2.7	NS
	1.9 ± 2.0	1.1 ± 1.3	NS
Hallucinations			
	2.8 ± 3.4	1.1 ± 2.1	<0.02
	0.0 ± 0.0	0.0 ± 0.0	NS
	5.5 ± 2.7	2.2 ± 2.5	<0.02
Agitation/aggression			
	4.6 ± 3.2	2.5 ± 1.9	<0.001
	6.4 ± 2.8	3.6 ± 2.0	<0.02
	2.7 ± 2.5	1.4 ± 1.1	<0.03
Depression/dysphoria			
	1.7 ± 2.9	1.2 ± 2.0	NS
	0.3 ± 0.9	0.3 ± 0.9	NS
	3.1 ± 3.5	2.0 ± 2.4	NS
Anxiety			
	1.9 ± 2.3	1.5 ± 2.0	<0.04
	1.6 ± 2.2	1.0 ± 1.4	NS
	2.1 ± 2.5	1.9 ± 2.4	NS
Euphoria			
	0.2 ± 0.9	0.2 ± 0.9	NS
	0.4 ± 1.3	0.4 ± 1.3	NS
	0.0 ± 0.0	0.0 ± 0.0	NS
Apathy/indifference			
	5.9 ± 2.4	3.3 ± 1.9	<0.001
	5.4 ± 2.7	3.6 ± 2.6	<0.03
	6.3 ± 2.2	3.0 ± 0.8	<0.02
Disinhibition			
	1.9 ± 3.1	1.8 ± 2.9	NS
	3.7 ± 3.6	3.5 ± 3.4	NS
	0.0 ± 0.0	0.0 ± 0.0	NS
Irritability/lability			
	4.0 ± 3.2	2.3 ± 2.0	<0.005
	5.7 ± 3.4	3.2 ± 2.3	<0.02
	2.3 ± 1.9	1.4 ± 1.2	NS
Aberrant behavior			
	3.4 ± 3.4	2.6 ± 2.7	<0.05
	6.4 ± 1.8	4.9 ± 1.8	<0.05
	0.3 ± 0.9	0.3 ± 0.9	NS

*Wilcoxon rank sum test, with $P < 0.05$ accepted as significant. DLB, dementia with Lewy bodies; FTLD, frontotemporal lobar degeneration; Feru-guard, ferulic acid and *Angelica archangelica* extract; NS, not significant; NPI, Neuropsychiatric Inventory; SD, standard deviation.

Table 3 Factor associated with improvement of Neuropsychiatric Inventory score

Dependent variable	B	SE	β	*t*	*P**
Baseline MMSE score	0.378	0.174	0.466	2.174	0.044

*Multiple regression analysis, with $P < 0.05$ accepted as significant. Adjusted $R^2 = 0.172$, $P = 0.044$. MMSE, Mini-Mental State Examination; SE, standard error.

neurotoxic action induced by amyloid β-protein in the brain.[9–11,33] *A. archangelica* extract inhibits acetylcholine esterase and increases acetylcholine in the synapse.[12] Free radical scavengers might theoretically be utilized as a therapy in FTLD,[34] and acetylcholinesterase inhibitors such as rivastigmine and donepezil could alleviate BPSD in DLB.[19,35] These findings may indicate that the suppression of free radicals and acetylcholinesterase derived from Feru-guard might lead to the amelioration of BPSD in FTLD or DLB.

Several limitations of the study should be considered. First, this study had an open-label design and no control group. Consequently, our results may have been partially due to a placebo effect. Second, our sample size was small. Third, this sample might not represent the whole population of patients with FTLD or DLB, because recruitment was from only one outpatient clinic. To overcome these limitations and establish Feru-guard as a useful treatment for FTLD or DLB, we propose doing double-blind, randomized studies with much larger samples.

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