A Possibility of Simultaneous Treatment with the Multicomponent Drug, Ninjin'yoeito, for Anorexia, Apathy, and Cognitive Dysfunction in Frail Alzheimer's Disease Patients: An Open-Label Pilot Study

Makoto Ohsawa[a,*], Yukiko Tanaka[b], Yoshito Ehara[c], Setsuko Makita[a] and Kosuke Onaka[b]
[a]*Oido Clinic, Isesaki, Gunma, Japan*
[b]*Uchida Hospital, Numata, Gunma, Japan*
[c]*Toumou Keiai Hospital, Ota, Gunma, Japan*

Abstract. A recent classification analysis of neuropsychiatric symptoms in patients with Alzheimer's disease (AD) revealed a distinct cluster with apathy and eating problems including anorexia that exhibits frailty. The apathy and frailty are risk factors in the disease progresses. However, there is currently no effective drug for treating both anorexia and apathy in AD. Here, we conducted an open-label pilot study to determine whether ninjin'yoeito (NYT, TJ-108), a multicomponent drug, is effective for improving anorexia and apathy in patients with AD, and consequently their cognitive function. Trials were conducted at three sites in Japan. Twenty patients [4 men and 16 women, average age = 82.6 ± 7.7 (mean $\pm$ SD) years old], including 19 AD and 1 mixed dementia with anorexia/apathy, were examined. NYT (6–9 g/day) was administered for 12 weeks. The changes in scores for "anorexia" using the Neuropsychiatric Inventory (NPI) subcategory for eating disturbance (primary outcome measure), NPI including "apathy", the vitality index, Mini-Mental State Examination (MMSE), and physical and blood nutrition indices were evaluated at baseline (week 0), and weeks 4, 8 and 12. After week 4, significant improvements were observed in the scores for "anorexia" and "apathy" by NPI and meal ingestion amount. Vitality index and MMSE score were significantly improved by week 12. We propose that NYT, a multicomponent drug with several effects including dopamine modulation, is a new-type dementia therapeutic agent with low risk of adverse reactions that can improve simultaneously anorexia/apathy, as well as cognitive dysfunction in frail AD patients.

Keywords: Alzheimer's disease, anorexia, apathy, cognitive function, dementia, frailty, ninjin'yoeito

INTRODUCTION

Alzheimer's disease (AD), an age-associated brain neurodegenerative disorder, is among the most common diseases causing dementia. The first symptom of AD is memory loss, which in most cases becomes more serious as the disease progresses. In parallel

*Correspondence to: Makoto Ohsawa, MD, Oido Clinic, 4005-1 Higashiobokata-cho, Isesaki, Gunma 379-2234, Japan. Tel.: +81 270 62 3333; Fax: +81 270 63 2412; E-mail: ohsawa@mail.gunma.med.or.jp.

with this memory loss, mental and behavioral disturbances in the form of behavioral and psychological symptoms of dementia (BPSD), as defined by the International Psychogeriatric Association (IPA) in 1996, also occur as a serious and growing public health problem [1].

Apathy in AD, which is characterized by loss of interest and motivation in daily activities in the absence of depression or other mood changes, is among the most common BPSD, affecting up to 97% of Japanese [2], 76% of Irish [3], and 71% of American AD patients [4]. Apathy can also cause disuse atrophy and lead to a reversal of day and night activity levels due to reduced daily activity. As a direct result of apathy, dementia is aggravated [5] and the caregiver burden is further increased [6].

A recent classification analysis of BPSD in patients with AD revealed a distinct cluster of AD patients with apathy and eating problems including anorexia [7] that exhibits frailty. Researchers have suggested that these behavioral disturbances may be associated with a decrease in dopaminergic neurotransmission in the mesolimbic reward system. Cholinesterase inhibitors have been widely used to treat apathy in AD patients in clinical practice because there is currently no specific drug for this disorder. The effect of methylphenidate, a dopamine enhancer, has also been investigated in clinical trials in the US [8]; however, these drugs are often associated with adverse reactions, such as anorexia and weight loss. In elderly patients in particular, aggravation of frailty that is caused by anorexia or weight loss can lead to further worsening of cognitive dysfunction [9]. There is currently no effective drug with low risk of adverse reactions for treating an AD patient cluster with anorexia/apathy.

Ninjin'yoeito (NYT, TJ-108), a traditional Japanese medicine (Kampo medicine, granules), is a multicomponent drug, composed of 12 crude drugs (rehmannia root, Japanese angelica root, atractylodes rhizome, *Poria sclerotium*, ginseng, cinnamon bark, polygala root, peony root, citrus unshiu peel, astragalus root, glycyrrhiza and schisandra fruit). NYT has been approved as a prescription drug in Japan, where it was originally used to treat a decline in constitution after recovery from disease, fatigue, and anorexia; therefore, it was hypothesized to improve the symptoms of frail elderly patients. In 1992, Ozaki and Shimomura [10] reported first that NYT improves apathy in elderly patients, as well as having psychotropic effects and improving appetite. Over a decade later, Kudoh et al. [11]

reported that AD patients receiving donepezil and NYT treatment showed a significant improvement in cognitive function and depression compared to those who only received donepezil. However, the effects of NYT on anorexia and apathy in AD have yet to be investigated.

Here, we conducted an open-label pilot study to determine whether NYT treatment improves anorexia and apathy in patients with AD, and consequently improves cognitive function.

MATERIALS AND METHODS

Study design and overview

This was an open-label trial to test the efficacy and safety of NYT on AD patients with anorexia/apathy in a 12-week treatment period. Subjects visited the study site at screening (2 weeks before starting treatment), baseline (week 0), and weeks 4, 8, and 12. Three sites participated in this trial after obtaining approval from their local institutional review boards. Informed consent to participate in the study was obtained in writing from each subject or legally authorized representative, and the study partner cooperated efficacy evaluation. The data were collected from April 2015 to September 2016.

Subjects

Individuals diagnosed with possible or probable AD, as defined by criteria set out by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR; Washington DC: American Psychiatric Association, 2000) and National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) [12], were eligible if they met all the inclusion criteria. The main inclusion criteria were age ≥55 years, Neuropsychiatric Inventory (NPI) subcategory scores for "anorexia" and "apathy" >3 points, and Mini-Mental-State Examination (MMSE) score ≤26 points. Individuals were excluded if they had a cerebral infarction that may affect cognitive function, NPI subcategory score for "agitation/aggression" >6 points, major depression or bipolar disorder (DSM-IV-TR) within the previous year, and alcoholism, drug addiction, malignant tumor or other life-threatening diseases within the previous 2 years. Individuals were also

excluded if they had received typical or atypical neuroleptics, anxiolytics, prokinetic agents, stomachics, or Kampo medicine other than NYT within the previous 2 weeks. Continued use during the treatment period was allowed for hypnotics, antidepressants, anticonvulsants, therapeutic agents for dementia (cholinesterase inhibitors and memantine) started within the prior 12 weeks, and antiulcer agents started within the prior 2 weeks. At screening for entry patients, candidate had been chosen from patients with 2-3 kg of weight loss within prior 6 months.

Study medication

TSUMURA Ninjin'yoeito Extract Granules for Ethical Use (NYT, TJ-108; Tsumura & Co., Tokyo, Japan) were administered three times daily (3 g each, 9 g/day) during the 12-week treatment period. The dose of NYT could be reduced to 6 g/day twice daily depending on the subject's age and body weight, and response to the treatment, such as the occurrence of adverse events. NYT has been approved by the authorities in Japan as a prescription drug. On assessment for adverse events, we have judged causal relationship from adverse reactions in package insert of NYT and medical opinion for pathogenesis, and then we have received approval from institutional review boards.

Outcome measures

The primary outcome measure for this trial was the change in score for "anorexia" according to the NPI subcategory for eating disturbance. The score was derived as the product of the frequency ratings for four items and the severity ratings for three items. The NPI subcategory comprises a maximum 12-point scale, with higher scores indicating greater impairment [13].

Secondary outcome measures included changes in total NPI score; NPI subcategory scores, including for "apathy"; vitality index; total MMSE score [14]; number of meals; amount scoring of food ingested at meals; physical and blood nutrition indices (body weight, body mass index [BMI], limb circumference [the upper arm, thigh and calf], serum albumin level, total lymphocyte count, erythrocyte count and hemoglobin concentration) and safety assessments by week 12. In addition, demographic data, medical history and laboratory tests were examined.

Statistical analysis

The efficacy analysis set (full analysis set: FAS) included all patients. Changes occurring from week 0 to weeks 4, 8 or 12 of the treatment period were evaluated by calculating the summary statistics and Wilcoxon's signed rank-sum test (with two-sided type 1 error of 5%). No adjustment was made for multiple testing.

RESULTS

Subject flow, protocol alteration, and demographics

Data from a total of 20 patients, including 19 with AD and 1 with mixed dementia, were analyzed to assess the efficacy and safety of NYT treatment. Four patients withdrew from this trial due to adverse events. During the course of the trial, the protocol was altered to accelerate subject enrollment as follows: the upper age for inclusion was changed from 55–84 years of age to ≥ 55 years. The demographic and clinical characteristics of patients at baseline are shown in Table 1. The average age of patients was 82.6 ± 7.7 years. The FAST, NPI total score, and MMSE were 4.7 ± 0.9, 13.75 ± 1.54, and 17.32 ± 1.29 at baseline, respectively. The percentage of female subjects was much higher of the one of the male subjects in this study even considering general high percentage of female in AD patients. This bias may be characteristic of participated local site, however, there was no difference in efficacy between male and female (data not shown).

Primary outcome measure

The primary outcome measure is summarized in Fig. 1. Treatment with NYT resulted in a significant reduction in the score for "anorexia", according to the NPI subcategory for eating disturbances, by week 4 (baseline: 4.85 ± 0.58; 4 w: 3.06 ± 0.60, $p < 0.05$; 8 w: 1.50 ± 0.43, $p < 0.001$; 12 w: 1.00 ± 0.44, $p < 0.001$).

Secondary outcome measures

Figure 2 summarizes the meal ingestion amount score. A significant increase in ingested food was observed by week 4 (4 w: 0.61 ± 0.14, $p < 0.01$; 8 w: 0.94 ± 0.17, $p < 0.001$; 12 w: 0.94 ± 0.19, $p < 0.001$).

Table 1
Baseline characteristics and demographics of the subjects

Variable	$n = 20$ (19 AD and 1 mixed dementia)
Age, y	82.6 ± 7.7
Gender, M/F	4/16
Body weight, kg	45.5 ± 8.4
BMI	20.7 ± 2.9
Duration of dementia, y	4.4 ± 3.1
FAST	4.7 ± 0.9
Outpatients/inpatients	19/1
Allergy to medicines	0
Complications	17
Concomitant treatment	20
Vitality Index total	7.05 ± 0.43
NPI total	13.75 ± 1.54
MMSE	17.32 ± 1.29
Serum potassium, mEq/L	4.34 ± 0.11

Data indicated mean $\pm$ SD, except for the Vitality Index, NPI, MMSE, and Serum potassium that are shown as mean $\pm$ SE. AD, Alzheimer's disease; FAST, a Functional Assessment Staging Test; NPI, Neuropsychiatric Inventory; MMSE, Mini-Mental State Examination; Complications, the number of patients with complications; Concomitant treatment, patients administered medications for complications and AD.
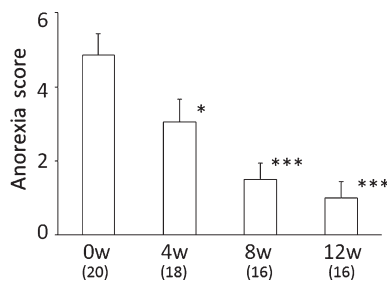

Fig. 1. Changes in score for "anorexia" in the NPI subcategory for eating disturbances after NYT treatment. The data represent mean $\pm$ SE. The number of patients is indicated in parentheses. $^*p < 0.05$, $^{***}p < 0.001$ versus 0 w (Wilcoxon's signed rank-sum test). The score was derived from the product of the frequency ratings for four items and the severity ratings for three items.

No significant change was observed in number of meals and the physical or blood nutrition indices (body weight, BMI, limb circumference, serum albumin level, total lymphocyte count, erythrocyte count and hemoglobin concentration; data not shown).

Total NPI score and NPI subcategory scores for "apathy" and "eating disturbance" had significantly decreased by week 4 (Table 2). No significant changes were observed in the other NPI subcategory scores, including "agitation/aggression" and "euphoria". A significant decrease was also observed in total caregiver distress scores, assessed by the NPI, from week 8. The total vitality index score was significantly increased in week 12 compared to baseline (Table 2),
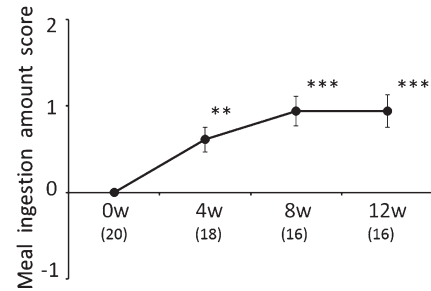

Fig. 2. Changes in meal ingestion amount score after NYT treatment. The data represent mean $\pm$ SE. The number of patients is indicated in parenthesis. $^{**}p < 0.01$, $^{***}p < 0.001$ versus 0 w (Wilcoxon's signed rank-sum test). The meal ingestion amount scoring by subjective caregiver's assessment consisted of five ratings (2: moderate or higher increase, more than approximately 50% increase; 1: mild increase, approximately 25% increase; 0: no change; –1: mild decrease, approximately 25% decrease; –2: moderate or higher decrease, more than approximately 50% decrease) compared with that at baseline (0 w). This was assessed by caregivers every day in diary, and then investigators have judged score by this diary.

as was the MMSE score (baseline: 17.32 ± 1.29, week 12: 19.44 ± 1.30, $p < 0.001$; Fig. 3).

Adverse events

Serious adverse events were noted in three patients. However, a causal relationship with NYT was excluded for all three patients, who developed deteriorated consciousness levels with hypotension (death; withdrawal), worsened backache (hospitalization; withdrawal), and a fracture from falling (hospitalization; withdrawal). Two patients exhibited non-serious adverse reactions that were suspected to be associated with NYT treatment: elevated γ-GTP levels (continuation) and vomiting (withdrawal).

DISCUSSION

In AD patients with apathy, significant improvement in the primary outcome, NPI score for "anorexia", was observed with NYT treatment by week 4. Although the number of meals consumed by patients did not change, with almost all patients eating three meals a day at baseline, meal ingestion amount score, which was estimated by caregivers, was significantly increased by week 4. It is well known that ginseng, atractylodes rhizome, *Poria sclerotium*, citrus unshiu peel and glycyrrhiza, the components of NYT, improve anorexia [15]. However, no significant changes were observed in the physical and blood

Table 2
Changes in NPI and vitality index scores after NYT treatment

Test	0 w	4 w	8 w	12 w
Subjects (n)	20	18	16	17
NPI				
Total	13.75 ± 1.54	9.06 ± 1.36***	6.69 ± 1.09***	5.88 ± 0.96*** (1)
Delusion	0.20 ± 0.16	0.17 ± 0.12	0.13 ± 0.09	0.18 ± 0.10
Hallucination	0.10 ± 0.07	0.00 ± 0.00	0.06 ± 0.06	0.00 ± 0.00
Agitation/Aggression	0.35 ± 0.17	0.33 ± 0.14	0.31 ± 0.18	0.29 ± 0.17
Dysphoria	0.80 ± 0.49	0.61 ± 0.45	0.13 ± 0.13	0.06 ± 0.06
Anxiety	0.30 ± 0.16	0.11 ± 0.08	0.19 ± 0.19	0.24 ± 0.24
Euphoria	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Apathy	5.85 ± 0.65	4.00 ± 0.57***	3.38 ± 0.54***	3.31 ± 0.51*** (1)
Disinhibition	0.10 ± 0.10	0.06 ± 0.06	0.13 ± 0.13	0.12 ± 0.12
Irritability/Lability	0.10 ± 0.07	0.06 ± 0.06	0.00 ± 0.00	0.00 ± 0.00
Aberrant motor activity	0.45 ± 0.25	0.44 ± 0.27	0.44 ± 0.24	0.44 ± 0.27 (1)
Night-time Disturbance	0.45 ± 0.22	0.22 ± 0.17	0.13 ± 0.13	0.25 ± 0.19 (1)
Eating Disturbance	5.05 ± 0.60	3.06 ± 0.60***	1.81 ± 0.56***	0.94 ± 0.43*** (1)
Distress Total	5.35 ± 0.91	4.33 ± 0.79	2.69 ± 0.58**	2.56 ± 0.57*** (1)
Vitality Index				
Total	7.05 ± 0.43	7.17 ± 0.37	7.75 ± 0.37	7.94 ± 0.39* (1)

Data indicate mean $\pm$ SE. The number of patients with missing data is shown in parenthesis. NYT, Ninjin'yoeito; NPI, Neuropsychiatric Inventory. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ versus 0 w (Wilcoxon's signed rank-sum test).
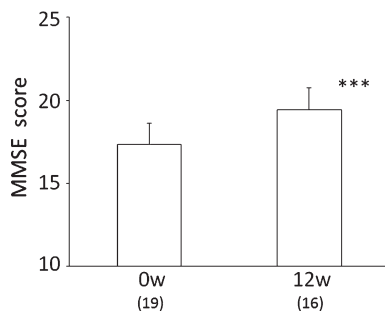

Fig. 3. Changes in MMSE score after NYT treatment. The data represent mean $\pm$ SE. The number of patients is indicated in parentheses. ***$p < 0.001$ versus 0 w (Wilcoxon's signed rank-sum test).

nutrition indices until week 12. We hypothesize that improvements in anorexia and meal ingestion amount may not necessarily be reflected in physical and blood nutrition indices due to the age-related reduction in absorption from epithelial cells in small intestinal villi [16]. Elicitation of physical and blood nutrition changes may require a longer study period.

The vitality index, an assessment of motivation, was significantly improved in week 12. This change was induced by the improvement in the subcategory for meal (appetite, baseline: 1.35 ± 0.11; 12 w: 1.81 ± 0.10, mean $\pm$ SE, $p < 0.05$). Another assessment of motivation, NPI subcategory score for "apathy", which is not associated with meal and appetite, was also significantly improved by week 4 in accordance with above-mentioned improvement in anorexia. Apathy has been linked to anorexia in AD

patients along with dopaminergic neuron dysfunction in the mesolimbic reward system [7]. Very recently, scientists generated a novel apathy-like murine model induced by water immersion that exhibited reduced food intake and nesting behaviors (apathy-like behaviors) [17]. Both reduced food intake and nesting behaviors were restored by administration of pargyline, an inhibitor of the dopamine-degrading enzyme MAO-B, providing evidence that anorexia/apathy-like behaviors in this animal model were associated with dopaminergic dysfunction. NYT restored the reduced food intake and nesting behaviors, and their effects disappeared completely by co-administered with a dopamine D2 receptor antagonist. Further, there has been recent interest in the finding that instrumental motivation is impaired by dysfunction of dopamine D2 receptor expression in the ventrolateral striatum [18]. We therefore propose that improvements in anorexia/apathy by NYT treatment in AD patients may result from the activation of dopaminergic function via the dopamine D2 receptor. NYT improved anorexia/apathy without aggravating agitation and euphoria. We also clarified that caregiver distress was attenuated by these improvements.

A noteworthy result of this study was the significant increase in MMSE score after treatment with NYT for 12 weeks. Although cholinesterase inhibitors, the standard therapeutic agent for dementia, are known to increase MMSE score, which peaks after 12 weeks of administration, subsequent cognitive function gradually declines in spite of continuous administration of these drugs [19]. Nevertheless,

continued administration is thought to attenuate the cognitive decline and the treatment is very important to maintain their cognitive function as long as possible. Although almost all patients enrolled in the present study had been taking therapeutic agents for dementia, we set an entry criteria that a patient stably taken therapeutic agent for dementia more than 12 weeks at least after completion dose increasing. Therefore, the present significant increase in MMSE score may have resulted from either the co-administration of these therapeutic agents with NYT or as a result of NYT alone [Three patients had not taken therapeutic agent for dementia. However, increase in MMSE score was also observed in these 3 patients (3 points increase, 2 points increase, and no data due to withdrawal, respectively)]. Improvement in cognitive function by NYT administration has been previously reported [11], with AD patients showing improved cognitive function following a 2-year treatment period with donepezil and NYT. NYT and its components have also been studied for their role in cognitive function in the following basic animal research. NYT and citrus unshiu peel, a component of NYT, reversed age-induced demyelination, leading to an acceleration of axonal remyelination in the brain [20]. Polygala root, another important component of NYT, enhanced choline acetyltransferase activity in basal forebrain cells and nerve growth factor secretion in astrocytes [21]. Furthermore, polygala root contains 1, 5-anhydro-D-fructose, a newly identified natural sugar that has antioxidant [22] and anti-inflammatory effects [23], and attenuates iNOS expression [24]. Deoxyshizandrin isolated from the Schisandra fruit, a component of NYT, ameliorated amyloid-β (Aβ) 1–42-induced memory impairment in mice [25]. Further, dopamine D2 receptor in the hippocampus is well known for playing an important role in memory and learning [26]. These actions of several components of NYT may additively or synergistically improve cognitive function in AD patients. NYT has a beneficial effect to strengthen the cognitive improvement effect of standard therapeutic agents for dementia.

On the close relationship between anorexia that exhibits frailty or apathy and AD, the frailty/apathy and cognitive impairment can affect each other and accelerate the disorder [5, 9, 27]. Frailty and apathy do not usually restore over the stage of disease progress. Therefore, early treatment for frailty/apathy may be of importance for AD patients. Here, we propose that NYT, a multicomponent drug with several effects including dopamine modulation, is a new-type dementia therapeutic agent that improves simultaneously anorexia/apathy, as well as cognitive dysfunction in frail AD patients. Moreover, given that NYT also improves cerebral blood flow [28] involving both suppression of Aβ production via beta-site APP cleaving enzyme-1 (BACE1) [29] and acceleration of Aβ excretion from the brain, it may also have beneficial effects in patients with mild cognitive impairment with apathy and white matter changes [30] or cognitive frail patients, namely in the prevention of dementia. These findings should be confirmed in randomized and placebo controlled trials with a larger sample size and longer treatment period in the future.

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CONFLICT OF INTEREST

All authors declare that they have no financial or any other kinds of personal conflicts regarding this article.

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