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# Effect of acupuncture on Alzheimer's disease in hospitalization - Focusing on behavioral psychological symptoms -

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***Abstract***

[Objective]Acupuncture for patients with dementia definitely improves cognitive function in vascular dementia (VD) and young cases (mild), effects on Alzheimer's disease (AD), cognitive function in severe cases, activity of daily living, and behavioral and psychological symptoms of dementia (BPSD) are mostly uncertain. Accordingly, we report this research where acupuncture was provided for patients with AD requiring hospitalization in a medical institution, which imposes a great burden on patients with dementia, their families, and society, to study the effects of acupuncture on BPSD.

[Methods] Non-randomized controlled trial was performed by assigning patients to a group with usual treatment and care (usual treatment group, six cases) and a group treated with acupuncture in addition to the usual treatment and care (acupuncture group, six cases) to observe them separately. Acupuncture was administered about 15 times twice a week over two months. The treatment provided was San Jiao acupuncture (triple energizer acupuncture), which has been reported to be effective as acupuncture for dementia. The primary endpoint was the NPI-Brief Questionnaire Form (NPI-Q). The secondary endpoints were the ABC Dementia Scale and Mini-Mental State Examination (MMSE). These were assessed by the attending nurses at the initial treatment and two months later. the linear mixed model and the post-hoc test based on the Bonferroni correction were used to examine baseline results, main effect of changes from the baseline with time, and interactions.

[Results] Comprehensive assessment of severity (NPI-Q) noted no significant difference between the control group and the acupuncture group (interaction) ($p = 0.75$). A within-group comparison indicated significant improvement in the acupuncture group ($p = 0.03$). A comprehensive assessment of care burden (NPI-Q) noted no significant difference between the control group and the acupuncture groups (interaction) ($p = 0.72$). A within-group comparison indicated significant improvement in the acupuncture group ($p = 0.04$). Among NPI-Q, the psychological symptoms of excitation and depression had improvement or an improving trend in both severity and burden of care (severity: $p = 0.04$ and $p = 0.04$, respectively; burden of care: $p = 0.03$ and $p = 0.09$, respectively).

[Conclusion] It was presumed that needle stimulation or intervention by acupuncturists for AD patients stabilized the psychological aspects of mood and anxiety to alleviate any distress leading to a reduction in BPSD symptoms. In this study, suggesting that acupuncture treatment may be a nondrug therapy option depending on the status of onset of symptoms and severity.

***Key words:*** *Alzheimer's disease, in hospitalization ,BPSD , acupuncture， NPI-Q*

## I. Introduction

Japanese society continues to age with an increasing percentage of elderly people aged 65 years or older. The prevalence of dementia was estimated to be 15% (about 4.62 million patients) in 2012 but is expected to increase to 24.5% to 33.3% (about 8.50 to 11.54 million patients) by 2060[1,2)]. The most common primary disease of dementia is Alzheimer's disease (AD) and accounts for about 60% of the total.[3)] Similar trends are noted in the percentage of elderly people and the prevalence of dementia around the world, and the measures implemented in Japan with its advanced aging society, are attracting global attention.[1,2)]

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Dementia presents with the core symptoms of memory disorder, disorientation, apraxia, and agnosia, as well as various behavioral and psychological symptoms of dementia (BPSD) that include delirium, depression, excitation, wandering, sleep disorders, and delusions.[4] BPSD is identified as a problem in nursing care and treatment and is a major cause of hospitalization in patients with dementia.[5] Therefore, alleviation of dementia and BPSD is important in reducing the burden on patients with dementia, their families, and society.

For BPSD, the *Clinical Practice Guideline for Dementia* 2017 recommends improvements in possible causative physical conditions, nursing care and environment, and intervention with nondrug therapies and medication.[6] Because medication in elderly patients with dementia tends to induce adverse events, nondrug therapies are considered more effective.

Among nondrug therapies, while it has been identified that music therapy may be effective,[6] there have been few reports on other nondrug therapies at present.

Application of acupuncture has been extensively studied for dementia therapy in China both in basic science and in clinical practice as well.

Recent systematic reviews (SRs) have reported that acupuncture improves cognitive function and the activities of daily living in patients with vascular dementia (VD)[7] and improves cognitive function in AD,[8,9] although the research was considered of low quality. An SR on the efficacies of therapies for dementia reported that nondrug therapies, including VD symptomatic medication and acupuncture, were more effective in young patients with VD than other therapies.[10]

An SR on acupuncture for BPSD concluded that acupuncture used concomitantly with medication had a higher efficacy rate than medication alone,[11] but the result was unevaluable because of problems in the research quality (subject patients, number of cases, and study design). Furthermore, the cited articles included mild to moderate cases without severe cases requiring hospitalization. In Japan, although there have been some case reports on acupuncture and moxibustion for BPSD,[12] no controlled trial has been performed up to the present.

Based on these findings, acupuncture for patients with dementia definitely improves cognitive function in VD and effects on AD in young cases (mild), cognitive function in severe cases, activities of daily living, but effects on BPSD are uncertain. It is not clear, in particular, the type of AD patients for whom acupuncture is indicated and which symptoms of BPSD are effective with acupuncture treatment. In this study, we report on acupuncture treatment for patients with AD requiring hospitalization in a medical institution, which imposes a great burden on patients with dementia, their families, and society, to study the effects of acupuncture on BPSD.

## II. Methods

### 1. Subjects

Subjects for this study were patients hospitalized at the Saitama Medical University Saitama Neuropsychiatric Institute within the period between July of 2019 to November of 2020 who met the following criteria: a) diagnosed with AD, b) unable to be cared for at home, and c) consent to the study obtained from the patient or family. Exclusion criteria were a) patient's qualification for long-term care level ≥5, and b) judgment by a physician that the patient's condition was inappropriate for acupuncture, such as when the patient could not stay still. The doctor decided whether hospitalization was necessary after comprehensively considering physical factors, mental factors, and long-term care factors.

This study was approved by the Ethics Board of Meiji University of Integrative Medicine (2018 - 030) and conducted after we explained the freedom of participation or withdrawal of consent in the study, and protection of privacy orally and in written form to the patients, families, or caregivers trusted by the patient and obtained consent from them.

### 2. Study design

Non-randomized controlled trial was performed by assigning 14 patients to a group with standard treatment and care (standard treatment group, six cases) and a group treated with acupuncture in addition to standard treatment and care (acupuncture group, eight cases). Informed consent was given by the subjects, and patients who consented to acupuncture treatment were put into the acupuncture group, and patients who consented only to the evaluation were put into the standard treatment group. During hospitalization, both groups were prescribed dementia treatments such as donepezil hydrochloride and memantine hydrochloride.

### 3. Acupuncture

Acupuncture was administered twice a week over two months for a total of 15 times. The treatment provided was San Jiao Acupuncture, or triple energizer acupuncture, which has been reported to be effective for dementia.[13]

Acupuncture points used were CV17 (*Danzhong*), CV12 (*Zhongwan*), CV6 (*Qihai*), TE5 (*Waiguan*), SP10 (*Xuehai*), and ST36 (*Zusanli*). *San Jiao* Acupuncture was less stressful for the elderly and relatively easy to perform as it was conducted in the supine position. Needles were each inserted into the acupuncture point at 5 to 20 ㎜ in depth to obtain *deqi* (needle sensation), and kept inserted for five minutes. The period of insertion was set to five minutes because it was easy for the patient to accept. When acupuncture was difficult due to body movement by the patient, the acupuncture needle was pulled out after obtaining *deqi*.

For individual physical complaints of constipation, abdominal pain, stiff neck, and pain in the back and lower extremities, the pathologies were identified based on findings from a medical interview, palpation, and manual inspection, and additional acupuncture treatments were provided.

The needles used were disposable stainless-steel needles (40 ㎜, No. 20, Seirin Corporation). If acupuncture was difficult because of the patient's condition on the day of treatment, non-needle compression was applied to stimulate the common acupuncture points without using a needle but a small bar.

4. Outcome measurement

The main method of evaluation used was the NPI-Brief Questionnaire Form (NPI-Q). In addition, the patients were evaluated by the ABC dementia scale and Mini-Mental State Examination (MMSE). These were assessed by the attending nurses at the initial treatment and two months later (at the completion of the acupuncture treatment).

(1) NPI-Brief Questionnaire Form (NPI-Q)

NPI-Q, which was used in the assessment of BPSD,[14,15] was assessed by caregivers for the severity of symptoms (hereinafter "severity") and the burden felt by caregivers (hereinafter "burden") of ten BPSD items: delusion, hallucinations, excitation, depression, anxiety, euphoria, indifference, disinhibition, irritability, and abnormal behaviors. Severity is evaluated on a scale of 0 to 3 and burden on a scale of 0 to 5. A higher score means higher severity and burden.

(2) ABC Dementia Scale

This scale was named "ABC" as the acronym of the three domains of AD: activity of daily living (ADL), behavioral and psychological symptoms of dementia (BPSD), and cognitive function.[16] The scale was developed in Japan to allow convenient and comprehensive assessments and consists of a total of 13 items each assessed on a scale of 1 to 9. The severer the functional disorder, the lower the score. The maximum total score of the 13 items is 117.

(3) Mini-Mental State Examination (MMSE)

In MMSE, patients are tested on 11 items regarding cognitive function. A score ≤23 out of 30 is suspected to be dementia, and a score ≤27 is suspected to be mild cognitive impairment (MCI).[17]

5. Statistical analysis

BPSD, ADL, and cognitive function were examined before and after intervention. In particular, scores by item and the total scores of NPI-Q, ABC Dementia Scale, and MMSE were calculated.

To measure the effect of the baseline score on subsequent changes, the linear mixed model and the post-hoc test based on the Bonferroni correction were used to examine baseline results, main effects of changes from the baseline with time, and interactions.

The statistical analyses were performed using SPSS Statics 26 (IBM Japan, Ltd.) with a significance level of 5% and a significance trend of 10%, and the results were expressed in means ± standard deviations. In addition, a boxplot of severity and care burden (NPI-Q), ABC dementia scale, and MMSE were created. A table was created to present the severity of NPI-Q, the burden of care, and the ABC dementia scale for each domain.

## III. Results

Twelve cases were analyzed, excluding two, from the fourteen cases enrolled, with one incapable of continuing acupuncture due to infection and one with a deviation from the protocol due to a referral to another hospital. The standard treatment group (hereinafter the "control group") included six cases (three males and three females), and the acupuncture group included six cases who successfully completed acupuncture treatment (three males and three females). The mean age of the participants (range) was 82 years (76 to 91 years), and the mean number of years after being diagnosed with dementia was three years (one to five years). The control group was 83 ± 5 years old, and the acupuncture group was 81 ± 5 years old.

1. Changes in NPI-Q

(1) Changes in Severity (Table 1, Figure 1)

Comprehensive assessment (total score) noted no significant difference between the control group and the acupuncture group (interaction) ($p$ = 0.75). A within-group comparison indicated significant improvement in the acupuncture group ($p$ = 0.03). No significant difference was observed in the control group ($p$ = 0.20).

For individual items, no significant difference was noted between the control group and the acupuncture group. A within-group comparison indicated significant improvements in excitation ($p$ = 0.04) and depression ($p$ = 0.04) in the acupuncture group and delusions in the control group ($p$ = 0.03).

Nevertheless, significant differences and trends were noted between the groups in the baseline comprehensive assessment ($p$ = 0.06), as well as baseline excitation ($p$ = 0.04), delusions ($p$ = 0.05), depression ($p$ = 0.08), disinhibition ($p$ = 0.05), and irritability ($p$ = 0.07) among the individual items.

(2) Changes in care burden (Table2, Figure2)

A comprehensive assessment (total score) noted no significant difference between the control group and the acupuncture group (interaction) ($p$ = 0.72). A within-group comparison indicated significant improvement in the acupuncture group ($p$ = 0.04). No significant difference was observed in the control group ($p$ = 0.28).

For individual items, no significant difference was noted between the control group and the acupuncture group. A within-group comparison indicated significant improvements and trends in excitation ($p$ = 0.03) and

Table 1. Evaluation for Severity (NPI-Brief Questionnaire Form: NPI-Q)
Shows the values for severity (NPI-Q) before and after intervention.

| | | Acupuncture Group | | | Control Group | | | |
|---|---|---|---|---|---|---|---|---|
| | | pre | post | *p* | pre | post | *p* | Difference between groups |
| delusion | mean | 0.5 | 0.5 | 1.00 | 1.0 | 0.7 | 0.03* | 0.05† |
| | S.D. | 1.2 | 1.2 | | 0.6 | 0.8 | | |
| hallucination | mean | 0.0 | 0.0 | 1.00 | 0.2 | 0.0 | 0.32 | 0.34 |
| | S.D. | 0.0 | 0.0 | | 0.4 | 0.0 | | |
| excitement | mean | 1.0 | 0.2 | 0.04* | 1.7 | 0.8 | 0.20 | 0.04* |
| | S.D. | 0.3 | 0.4 | | 1.0 | 0.8 | | |
| depression | mean | 0.8 | 0.3 | 0.04* | 0.2 | 0.0 | 0.32 | 0.08† |
| | S.D. | 0.8 | 0.5 | | 0.4 | 0.0 | | |
| anxiety | mean | 0.3 | 0.2 | 0.32 | 0.2 | 0.2 | 1.00 | 0.78 |
| | S.D. | 0.8 | 0.4 | | 0.4 | 0.4 | | |
| euphoria | mean | 0.0 | 0.0 | 1.00 | 0.2 | 0.2 | 1.00 | 0.34 |
| | S.D. | 0.0 | 0.0 | | 0.4 | 0.4 | | |
| indifference | mean | 0.5 | 0.3 | 0.56 | 0.7 | 0.7 | 1.00 | 0.24 |
| | S.D. | 0.5 | 0.5 | | 0.5 | 0.5 | | |
| disinhibition | mean | 0.0 | 0.0 | 1.00 | 0.7 | 0.7 | 1.00 | 0.05† |
| | S.D. | 0.0 | 0.0 | | 0.8 | 0.8 | | |
| irritability | mean | 0.2 | 0.2 | 1.00 | 1.0 | 0.7 | 0.16 | 0.07† |
| | S.D. | 0.4 | 0.4 | | 0.9 | 0.5 | | |
| abnormal behavior | mean | 0.3 | 0.2 | 0.32 | 0.5 | 0.5 | 1.00 | 0.40 |
| | S.D. | 0.8 | 0.4 | | 0.8 | 0.8 | | |
| total score | mean | 3.7 | 1.7 | 0.03* | 6.2 | 4.3 | 0.20 | 0.06† |
| | S.D. | 1.9 | 1.2 | | 3.3 | 3.5 | | |

S.D.: standard deviation.
significant difference †$p<0.10$ ＊$p<0.05$

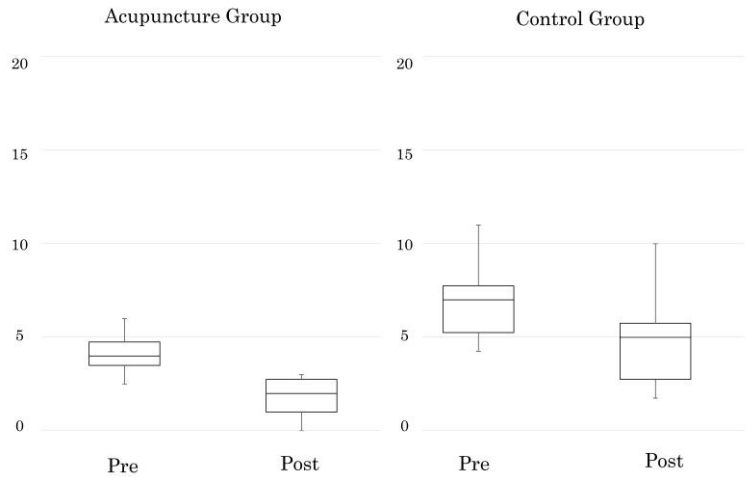


Figure. 1 Changes in severity (NPI-Brief Questionnaire Form: NPI-Q)
Shows a boxplot of severity (NPI-Q) before and after intervention. From the bottom, the sample minimum (smallest observation), the lower quartile or first quartile, the median (middle value), the upper quartile or third quartile, and the sample maximum (largest observation) are shown. The same applies to Figures 2-4.

Table 2 Evaluation for Care burden (NPI-Brief Questionnaire Form: NPI-Q)
Shows the values for care burden (NPI-Q) before and after intervention

| | | Acupuncture Group | | | Control Group | | | |
|---|---|---|---|---|---|---|---|---|
| | | pre | post | *p* | pre | post | *p* | Difference between groups |
| delusion | mean | 0.5 | 0.3 | 0.32 | 1.2 | 0.5 | 0.09† | 0.17 |
| | S.D. | 0.8 | 0.5 | | 0.8 | 0.8 | | |
| hallucination | mean | 0.0 | 0.0 | 1.00 | 0.0 | 0.0 | 1.00 | 1.00 |
| | S.D. | 0.0 | 0.0 | | 0.0 | 0.0 | | |
| excitement | mean | 1.2 | 0.3 | 0.03* | 1.3 | 0.7 | 0.16 | 0.23 |
| | S.D. | 0.8 | 0.5 | | 0.5 | 0.8 | | |
| depression | mean | 0.7 | 0.3 | 0.09† | 0.2 | 0.0 | 0.32 | 0.16 |
| | S.D. | 0.8 | 0.5 | | 0.4 | 0.0 | | |
| anxiety | mean | 0.3 | 0.2 | 0.32 | 0.2 | 0.2 | 1.00 | 0.78 |
| | S.D. | 0.8 | 0.4 | | 0.4 | 0.4 | | |
| euphoria | mean | 0.0 | 0.0 | 1.00 | 0.2 | 0.2 | 1.00 | 0.34 |
| | S.D. | 0.0 | 0.0 | | 0.4 | 0.4 | | |
| indifference | mean | 0.2 | 0.0 | 0.32 | 0.0 | 0.2 | 0.32 | 0.85 |
| | S.D. | 0.4 | 0.0 | | 0.0 | 0.4 | | |
| disinhibition | mean | 0.0 | 0.0 | 1.00 | 0.5 | 0.5 | 1.00 | 0.08† |
| | S.D. | 0.0 | 0.0 | | 0.8 | 0.8 | | |
| irritability | mean | 0.0 | 0.0 | 1.00 | 1.2 | 0.3 | 0.10 | 0.02* |
| | S.D. | 0.0 | 0.0 | | 1.2 | 0.5 | | |
| abnormal behavior | mean | 0.2 | 0.0 | 0.32 | 0.3 | 0.5 | 0.32 | 0.27 |
| | S.D. | 0.4 | 0.0 | | 0.5 | 0.8 | | |
| total score | mean | 3.0 | 1.2 | 0.04* | 5.0 | 3.0 | 0.28 | 0.09† |
| | S.D. | 1.3 | 1.0 | | 3.3 | 3.2 | | |

S.D.: standard deviation.
significant difference †$p<0.10$ ＊$p<0.05$

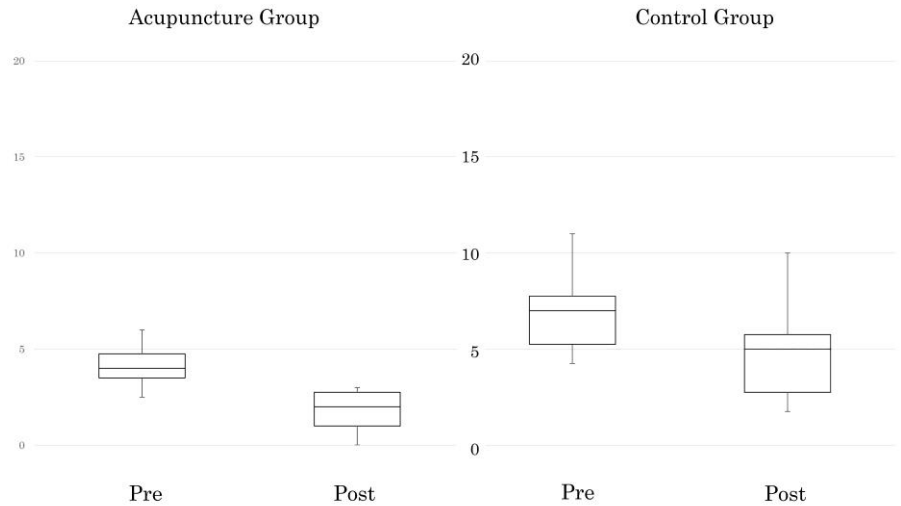


Figure 2 Changes in degree of care burden (NPI-Brief Questionnaire Form: NPI-Q)
Shows a boxplot of the care burden (NPI-Q) before and after intervention.

depression ($p$ = 0.09) in the acupuncture group and delusions in the control group ($p$ = 0.09).

Nevertheless, significant differences and trends were noted between the groups in the baseline comprehensive assessment ($p$ = 0.09), as well as baseline delusions ($p$ = 0.08), and irritability ($p$ = 0.02) among individual items.

2. Changes in ABC Dementia Scale (Table3, Figure3)

A comprehensive assessment (total score) noted no significant difference between the control group and the acupuncture group (interaction) ($p$ = 0.61). A within-group comparison noted no significant difference either. For domains (subcategories), no significant difference (interaction) was noted between the control group and the acupuncture group for ADL, BPSD, and cognitive function ($p$ = 0.11, p = 0.75, and p = 0.24, respectively). A within-group comparison noted significant worsening ($p$ = 0.03) in the cognitive function of the acupuncture group.

Nevertheless, significant differences and trends were noted between the groups in the baseline comprehensive assessment (total score) ($p$ = 0.02), as well as the baselines of ADL ($p$ = 0.07) and cognitive function ($p$ = 0.01) domains (subcategories).

3. Changes in MMSE (Figure 4)

A comprehensive assessment (total score) noted no significant difference (interaction) between the control group and the acupuncture group ($p$ = 0.55). A within-group comparison noted no significant difference either.

4. Safety

Although six of the eight subjects receiving acupuncture treatment had no past experience with acupuncture, none of the subjects had difficulty in continuing the treatment due to acupuncture. No adverse event, such as worsening of symptoms, was noted.

## IV. Discussion

1. About this study

Frequent BPSD symptoms included excitation, indifference, irritability, and delusions. Of these, excitation, irritability, and delusions imposed a greater burden of care, exhibiting a strong correlation with each other.[18] BPSD develops on the basis of cognitive dysfunction in response to the effects of physical condition, changes in living environment, care situation, anxiety, depression, and psychological conditions of the premorbid character.[6] While cognitive function, severity or the burden of care for BPSD exhibit a weak correlation, it was reported that some patients had high severity and a high burden of care regardless of cognitive function.[18] Thus, the severity of BPSD symptoms were related not only to cognitive function but also to physical condition, mental status, and living environment, and patients with dementia imposing a high burden of care should be hospitalized.

The cognitive functions of the subjects with dementia in this study were moderate to severe (MMSE: 15.2 ± 5.3 in the standard treatment group and 21.5 ± 8.9 in the acupuncture group). Among the NPI items, severity and

Table.3 Evaluation of ABC dementia scale
Shows the values of the ABC dementia scale before and after intervention.

| | | | Acupuncture Group | | | Control Group | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | pre | post | $p$ | pre | post | $p$ | Difference between groups |
| Domain A | ADL | mean | 41.3 | 43.2 | 0.42 | 31.7 | 27.5 | 0.23 | 0.07† |
| | | S.D. | 13.8 | 10.9 | | 9.5 | 9.4 | | |
| Domain B | BPSD | mean | 22.5 | 23.2 | 0.60 | 19.0 | 20.8 | 0.34 | 0.21 |
| | | S.D. | 4.3 | 1.8 | | 6.6 | 5.3 | | |
| Domain C | Cognitive function | mean | 18.2 | 15.2 | 0.03* | 7.5 | 6.5 | 0.20 | 0.01* |
| | | S.D. | 6.9 | 6.7 | | 1.4 | 1.6 | | |
| total score | | mean | 82.0 | 79.8 | 0.50 | 58.2 | 54.8 | 0.60 | 0.02* |
| | | S.D. | 22.8 | 15.5 | | 16.4 | 12.7 | | |

S.D.: standard deviation.
significant difference †$p < 0.10$ ＊$p < 0.05$

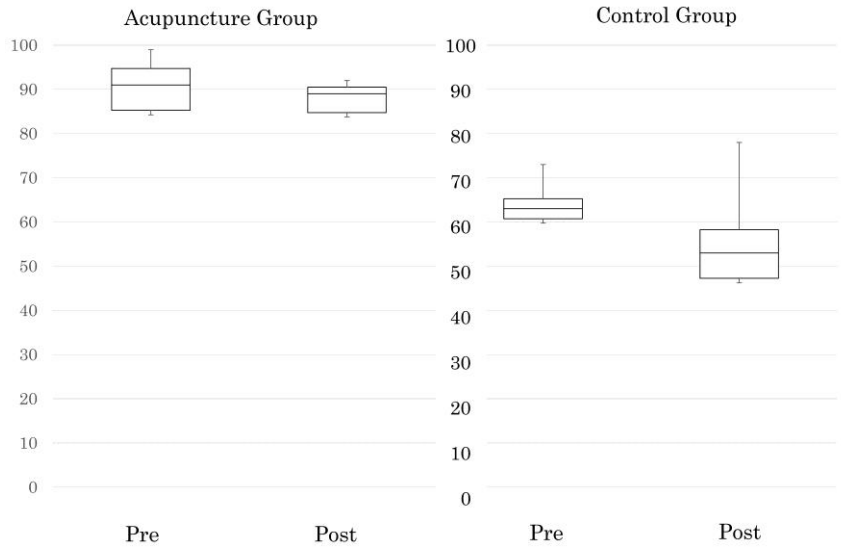


Figure.3 Changes in the ABC dementia scale
Shows a boxplot of the ABC dementia scale before and after intervention.

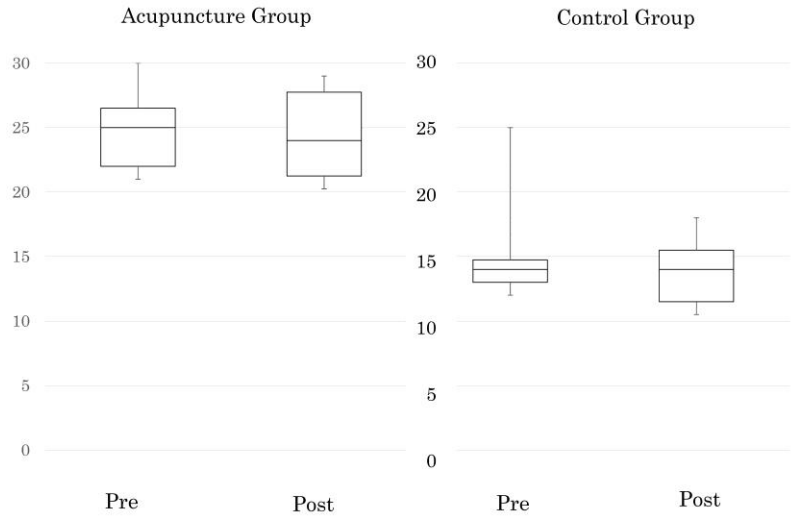


Figure.4 Changes in the Mini-Mental State Examination (MMSE)
Shows a boxplot of the MMSE before and after intervention.

burden of care were high for symptoms of excitation, irritability, and delusions (in descending order) in the standard treatment group and in excitation, depression, and delusions (in descending order) in the acupuncture group. Hence, the BPSD status of the subjects with dementia in this study showed high severity and a high burden of care requiring hospitalization, similar to a report from Yamaguchi, et al.[18)]

It has been reported that acupuncture treatment for BPSD was provided to patients at home[19)] and patients with mild to moderate dementia.[20)] However, there has been no reports of acupuncture treatment on patients with severe symptoms requiring hospitalization or inpatients imposing a high burden of care. In this regard, the results of this study could be invaluable.

2. Acupuncture for BPSD

In this study, no between-group differences (interaction) were observed in NPI-Q (severity and burden of care) or the BPSD domain of the ABC Dementia Scale ($p$ = 0.75, 0.72, and 0.75, respectively). Because this study was performed with a small number of subjects with AD requiring hospitalization that satisfied the criteria, and many of the pre-intervention assessment results had intergroup differences, within-group comparisons were conducted for further investigation.

In this study, NPI-Q (severity and burden of care) was significantly reduced ($p$ = 0.03 and $p$ = 0.04, respectively). An SR by Kwon, et al.[11)] reported that medication with concomitant acupuncture treatment had a significantly higher efficacy rate for BPSD than that of medication alone, which supported our results. However, Jia, et al.[25)] provided San Jiao Acupuncture, which was the same as our method, in patients with mild to moderate AD and reported that NPI had no significant change compared with those under medication only. Accordingly, the significant improvement in NPI-Q was considered to be because acupuncture treatment was provided concomitantly with the standard treatment instead of providing acupuncture alone.

SRs on cerebrovascular dementia and AD demonstrated that adverse events of acupuncture were mild, and acupuncture treatment was safe for patients with dementia exhibiting BPSD. In this study, acupuncture treatment was provided periodically in an inpatient ward in cooperation with other medical professionals, and the acupuncture group showed a decreasing trend in both severity and burden of care in total NPI-Q score, suggesting that acupuncture treatment may be a nondrug therapy option, depending on the status of onset of symptoms and severity.

Next, subjects with BPSD symptoms in which acupuncture and the acupuncturist's intervention were effective, were studied because BPSD develops on the basis of cognitive dysfunction in response to physical, environmental, and psychological factors. Among NPI-Q, the psychological symptoms of excitation and depression showed improvement or an improving trend in both severity and burden of care (severity: $p$ = 0.04 and $p$ = 0.04, respectively; burden of care: $p$ = 0.03 and $p$ = 0.09, respectively).

On the other hand, the ABC Dementia Scale (BPSD) showed no change, which was presumably due to its characteristics of mainly assessing behavioral symptoms.

Kase, et al.[21)] analyzed the details of BPSD and effective intervention actions and reported that Group 1 (activity and aggressiveness) required medication adjustment/ management and intervention to make the patients calm; Group 2 (confusion and disorientation with underlying anxiety and restlessness) required intervention to attempt stimulation of the patient's abilities, such as ensuring sufficient time for conversation and to adjust the pace of living for the patient; Group 3 (visual hallucinations, resistance, and physiological causes, such as resistance to care) required intervention to achieve daily life with some changes to avoid conflicts, and Group 4 (persecutory delusion and hearing loss) required intervention for reduced visual and hearing functions.

Focusing on between-group differences, the categories of delusions, excitation, disinhibition, irritability, severity, and burden of care were higher in the control group, and hallucinations, disinhibition, and euphoria were excluded from the subjects of the acupuncture group. This is because intervention is difficult in patients with severe hallucinations (seeing or hearing what does not really exist), and disinhibition (talking to a stranger as if the person was an acquaintance and saying something offensive to others).

In addition, Fujimura, et al.[22)] assessed responses and changes in elderly people with dementia who received rubbing acupuncture (*sakka-shin*) based on observation records, care records, and interviews with caregivers and concluded that acupuncture and the patients' relationship to acupuncturists led to comfort, reduced pain, communication, acquisition of sociality, and outlet for complaints. Furthermore, mood, improved anxiety,[23)] and improved sleeping disorders[24)] were reported among patients with dementia who received acupuncture treatment.

Based on these findings, it was presumed that needle stimulation or intervention by acupuncturists for AD patients stabilized the psychological aspects of mood and anxiety to alleviate distress leading to a reduction in BPSD symptoms. Consequently, standard medical care should be prioritized for Group 1 and concomitant use of acupuncture treatment is desirable for Group 2.

3. Acupuncture for cognitive function and ADL

This study noted no significant improvement in MMSE or the ABC Dementia Scale (cognitive function) in either the between-group comparison or the within-group comparison (ABC Dementia Scale [cognitive function]: there was significant worsening in the acupuncture group

[within-group comparison]). On the ABC Dementia Scale (activities of daily living), the between-group comparison noted no significant difference, while the within-group comparison showed a decrease in the control group (31.7 to 27.5) but an increasing trend in the acupuncture group (41.3 to 43.2).

For cognitive function, while it was reported that acupuncture treatment alone or acupuncture treatment used concomitantly with medication improved cognitive function in both cerebrovascular dementia and AD,[25-27] others reported that they did not improve cognitive function.[19,23] They also reported an improvement in ADL,[25-27] while others reported no improvement in ADL.[19]

When an elderly person with dementia is admitted to a medical institution, the person is at high risk for deliriums, decrease in cognitive and physical functions, and other symptoms, and there was a report that the hospitalization period was prolonged as well.[28] The expected result was not obtained in the assessment of cognitive function because of the effect of these factors.

Although the number of cases was small without a significant difference, in situations of hospitalization, it was reported that cognitive function and activities of daily living decreased and that cognitive function correlated with BPSD symptoms. However, the acupuncture group in this study had a reduction in cognitive function, but activities of daily living showed improvement. This was considered to be because acupuncture stabilized the psychological aspects of BPSD. Based on these findings, further studies should be conducted on acupuncture treatment as a safe and secure nondrug therapy for patients with BPSD requiring hospitalization.

4. About acupuncture and moxibustion treatment

The points of *San Jiao* Acupuncture provided in this study used common acupuncture points in the thoracoabdominal region, upper extremities, and lower extremities.

*San Jiao* Acupuncture was expected to regulate "*Yiqitiaoxue and Fubenpeiyuan*" and to delay the aging process through the upper (heart and lungs), the middle (spleen and stomach), and the lower (liver and kidneys) energizers.[25] *San Jiao* Acupuncture was originally described as an anti-aging procedure that delays the aging process. This acupuncture treatment is based on the idea that the deterioration of *San Jiao* is the fundamental mechanism of aging.

For treatment sites, an SR on cerebrovascular dementia reported that acupuncture points used frequently were GV20 (*Baihui*), Sishenzong, GV24 (*Shenting*), GV28 (*Yinjiao*), PC06 (*Neiguan*), GV26 (*Renzhong*), ST36 (*Zusanli*), SP6 (*Sanyinjiao*), KI3 (*Taixi*), and GB13 (*Benshen*), most of which are in the head.[25] Patients with mild dementia and dementia, were provided with various acupuncture treatments, including manual acupuncture, electrical needle stimulation, head acupuncture, and ear acupuncture. It was reported that there was no difference between manual acupuncture treatment and electrical needle stimulation[25]. The treatment sites of acupuncture in this study were different from those reported in the SRs, and this is an issue to be studied in the future.

5. Mechanism of action of acupuncture

The mechanism of onset of AD has characteristics of amyloid β-protein accumulation and acetylcholinesterase inhibitors that act as anti-dementia drugs, which have a protective effect against the toxicity of the amyloid β protein. Somaesthetic stimuli that includes acupuncture make the brain's cholinergic vasodilation system act to increase blood flow in the cerebral cortex and hippocampus and are, therefore, expected to prevent delayed neuronal death due to ischemia.[29, 30]

Han, et al . showed a 20% increase in lifespan in senescence-accelerated mice.[26] These mice apparently showed clear cognitive improvements in the Morris water maze test, including functions like spatial memory, relearning, thinking and analytical judgment abilities. Their neuropathological study indicated that acupuncture inhibits withdrawal of hippocampal neurons, suppresses reactive proliferation of glial cells while maintaining a neuronal/glia cell balance.[27,31] Following acupuncture treatment for AD and VD patients, activities of daily living improved significantly compared to those of patients who received anti-cholinesterase medication. Memory retention, orientation, and calculating ability became apparently better in the VD group than in the control group prescribed with Hydergine. Marked and sustained therapeutic effects were maintained especially in patients with mild levels of VD.[32]

Acupuncture provided once a week for three months, 12 times in total, increases Aβ sequester proteins (ApoAl) to suppress the neurotoxicity of Aβ, suggesting that cognitive function may improve in elderly people with MCI.[33]

It has been reported that BPSD symptoms were related to the prefrontal cortex (orbital and dorsolateral regions), anterior cingulate cortex, islet, and temporal lobe.[34] It has also been reported that acupuncture to the Zusanli: ST36 of AD model rats for 30 days activated the brain regions of the orbitofrontal cortex, medulla oblongata, and raphe nucleus.[35] Many serotonergic neurons exist in the raphe nucleus, and stimulation with acupuncture and moxibustion was reported to have an effect on the serotonergic nervous system.[36,37]

Excitation and depression, which showed decreases in severity and burden of care, are frequent symptoms in AD,[38,39] and the affectional segment that includes depression and excitation are known to be closely related to serotonin. Additionally, as dopamine is also closely related to the segment for pleasure and affection called the reward system, it is considered an important substance in the control of motivation and emotion.

*Yokukansan* is reported to be effective for BPSD in AD,[40,41] and its mechanism of action is considered to involve serotonin, dopamine, and norepinephrine in the prefrontal cortex.[42]

A report on anesthetized rats explained that noxious skin stimuli in the extremities increased the release of serotonin from the cerebral cortex.[43] Another report described animals whose serotonin levels increased mainly in the dorsal raphe nucleus and striatum after acupuncture, and where the dopamine level increased mainly in the nucleus accumbens and striatum,[44] and these mechanisms are presumed to be related.

These facts suggest that reductions in BPSD, excitation, and depression in patients who undergo acupuncture are related to the serotonergic nervous system, such as the orbitofrontal cortex, medulla oblongata, and raphe nucleus. We would like to further study clinical application from basic research (translational research) in the future.

6. Range of application and limitation of this study

Because continued treatment for AD patients requiring hospitalization may be difficult, depending on their cognitive function and symptoms, it is important to provide explanations not only for patients but also for their families to ensure understanding. Therefore, acupuncture was provided only in a small number of patients (applicable patients) with a reduced number of cases. For cases to be treated, criteria for AD patients for whom acupuncture treatment is indicated should be prepared based on the present results. In addition, there is a limit to increasing the number of cases where acupuncture treatment can be provided continuously within a predetermined period of hospitalization in a single institution. Because this study suggested that acupuncture treatment for BPSD may be provided safely and effectively, studying such treatments in multiple institutions is a future issue.

For treatment method and duration, while San Jiao Acupuncture was provided in this study, the method uses acupuncture points different from those in the SRs on acupuncture for vascular dementia and AD. In addition, the treatment duration was two months, twice weekly for about 15 times in total. Therefore, duration and method of treatment should also be examined.

This is the first study examining the effect of acupuncture on BPSD in patients with AD, requiring hospitalization in a medical institution, which imposes burdens on the patients with dementia, their families, and society. In the future, research should be advanced based on the results of our present study.

## V. Conclusion

In AD patients requiring hospitalization, acupuncture treatment was attempted twice weekly for two months to observe decreasing trends in NPI-Q severity and burden of care, as well as severity of depression. On the other hand, if hallucinations and disinhibition were noted, it was difficult to continue the acupuncture treatment. Although it was suggested that acupuncture treatment for AD patients in inpatient wards may be a nondrug therapy option, development of BPSD has variations according to the patient, and indications should, therefore, be considered depending on the pathology.

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**Conflict of interest**

There is no conflict of interest in this study.

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