The purpose of this study was to evaluate the effect of keishibukuryogan (KB) against the cognitive symptoms associated with silent brain infarction in a prospective cohort study. The subjects were 93 patients with silent brain infarcts who visited the Department of Japanese Oriental Medicine, University of Toyama, and its allied hospitals. They consisted of 24 males and 69 females, mean age (± S.E.) 70.0±0.8. Group SK (n=51) consisted of patients who used KB extract for more than 6 months per year. Group SC (n=42) consisted of patients who did not use Kampo formulas. The NS group (n=44) consisted of elderly subjects who had no silent brain infarction, 21 males and 23 females, with a mean age (± S.E.) of 70.7±0.7 years. Among the three groups, the revised version of Hasegawa’s dementia scale, apathy scale and self-rating depression scale were compared between the study start and after three years. In the SK and SC groups, these scores, and the subjective symp-
無症候性脳梗塞患者に対する桂枝茯苓丸を主体とした漢方薬の効果を3年間にわたり前向き研究により検討した。対象は富山大学附属病院ならびに関連病院を受診した無症候性脳梗塞患者93名で男性24名、女性69名、平均年齢70.0 ±0.8才である。桂枝茯苓丸エキスを1年あたり6カ月以上内服した51名をSK群、漢方薬を内服せずに経過を観察した42名をSC群とし、MRI上明らかな無症候性脳梗塞を認めない高齢者44名、平均年齢70.7±0.7才をNS群とした。3群間において、開始時と3年経過後の改訂版長谷川式痴呆スケール、やる気スコア（apathy scale）、自己評価式うつ状態スコア（self-rating depression scale）を比較した。また、SK群とSC群においては自覚症状（頭重感、頭痛、めまい、脳凝り）の経過も比較検討した。その結果、3群間の比較では、自己評価式うつ状態スコアにおいて開始時SK群とSC群は、NS群に比べて有意にスコアが高かった。しかし、3年経過後にはNS群は開始時より有意に上昇したが、SK群は有意に減少した。さらに無症候性脳梗塞にしばしば合併する自覚症状の頭重感において桂枝茯苓丸は有効であった。以上の結果から、無症候性脳梗塞患者の精神症状と自覚症状に対して桂枝茯苓丸が有効である可能性が示唆された。

キーワード：桂枝茯苓丸、無症候性脳梗塞、うつ症状、改訂版長谷川式痴呆スケール、やる気スコア、自己評価式うつ状態スコア

I. Introduction

Silent brain infarction is diagnosed by magnetic resonance imaging (MRI) and computed tomography (CT) as small cerebral infarctions without neurological symptoms. Silent brain infarction is thought to have a vascular origin and is frequently seen in neurologically asymptomatic elderly patients. It was recently reported that cerebral stroke and vascular dementia are related to silent brain infarction

Silent brain infarction is characterized by the mental symptoms of lowering of the function of acknowledgment and a state of depression. In terms of prevention by Western medicine, anticoagulant therapy was not able to suppress its advance, and the only treatment available is the control of blood pressure to prevent cerebral infarction by hypertension.

Keishibukuryogan (KB) is a Kampo (Japanese herbal) formula that improves the microcirculation. Clinically, KB has been reported to have strong hemorheological and anti-coagulative effects. KB was also demonstrated to have an antioxidant effect and a hypotensive effect in spontaneously hypertensive rats. Taken together, it is suggested that KB has a salutary effect on silent brain infarction. In an earlier study, we demonstrated that KB affected mental symptoms of silent brain infarction in the short term. Therefore, in this study we present the results of a prospective cohort study that examined the long-term effects of KB on mental symptoms compared to patients with silent brain infarction but not treated with Kampo formulas and to healthy elderly subjects without silent brain infarction.

II. Subjects

Patient selection:

1) Neurologically normal patients were diagnosed with silent brain infarction based on high-intensity lesions greater than 3 mm in size on T1-weighted images that coincided with low-intensity lesions on T2-weighted images on MRI.

2) Patients who had severe dementia, complications from other severe diseases, or who were judged inappropriate for this study by the investigators were excluded from entry. Informed consent was obtained from all patients prior to enrollment according to our institutional guidelines.

III. Methods

1) Study protocol:

We selected the SK group according to our previous study. It was composed of patients for whom administration of KB had previously shown favorable results. SK subjects used KB for more than 6 months per year and were free of side effects. The
SC group was composed of patients who had silent brain infarction but did not receive Kampo treatments. They visited the Department of Japanese Oriental Medicine, University of Toyama, and its allied hospitals. The NS group consisted of elderly subjects who had no silent brain infarction and had been observed for 3 years in a health-screening program of the brain at the Shimane Institute of Health Science. Patients in the SK group were administered KB extract (made by Tsumura & Co. 7.5 g/day : n=33, made by Kanebo LTD. 6.0 g/day : n=18) between meals three times a day. The revised version of Hasegawa’s dementia scale (HDS-R), apathy scale and self-rating depression scale (SDS) were assessed by the investigators at the beginning and after 3 years of medication administration. In the SK and SC groups, subjective symptoms (headache, dizziness or vertigo, stiff shoulder) were evaluated by the investigators at the beginning and after 3 years of medication administration by means of a 5-point rating scale (0=no symptoms, 1=very slightly affected, 2=slightly affected, 3=moderately affected, 4=severely affected). Further, in the SK group, Terasawa’s Oketsu score was evaluated at the beginning and at 3 years.

**2) Trial period:** June 1999 to May 2006.

**3) Statistical analysis:** Data are shown as mean ± S.E. Two-way repeated-measures ANOVA, Mann-Whitney U test and Student’s t-test were used for statistical analysis, and p<0.05 was considered significant.

**IV. Results**

**Patient characteristics (Table 1)**

The total enrollment consisted of 127 subjects with silent brain infarctions. 74 patients were treated

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Patient characteristics</th>
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<tbody>
<tr>
<td>Group</td>
<td>SK</td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
</tr>
<tr>
<td></td>
<td>Female</td>
</tr>
<tr>
<td>Age</td>
<td>(Years, mean ± S.E.)</td>
</tr>
<tr>
<td>Complication</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Hypertension</td>
</tr>
<tr>
<td></td>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td></td>
<td>Hyperlipidemia</td>
</tr>
<tr>
<td>Number of high intensity areas of brain by MRI</td>
<td>Single</td>
</tr>
<tr>
<td></td>
<td>Multiple</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Revised version of Hasegawa’s dementia scale (HDS-R), apathy scale and self-rating depression scale (SDS)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Beginning point</td>
</tr>
<tr>
<td>HDS-R</td>
<td>SK</td>
</tr>
<tr>
<td></td>
<td>SC</td>
</tr>
<tr>
<td></td>
<td>NS</td>
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<tr>
<td>Apathy scale</td>
<td>SK</td>
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<tr>
<td></td>
<td>SC</td>
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<tr>
<td></td>
<td>NS</td>
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<tr>
<td>SDS</td>
<td>SK</td>
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<tr>
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<td>SC</td>
</tr>
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<td></td>
<td>NS</td>
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* p<0.01 and †p<0.05 vs. corresponding beginning point; ‡ p<0.01 vs. NS group in beginning point.
with keishibukuryogan (SK group) and 53 patients were treated without the use of Kampo formulas (SC group). In the 3-year study period, none of the patients in either group had a stroke. Discounting the patients who dropped out or whose various scores could not be assessed at 3 years, 51 patients in the SK group and 42 patients in the SC group were finally analyzed. The SK patients took KB extract for 11.1±0.2 months/year on average. There were no statistical differences between the SK and SC groups in terms of gender, age, complications and degree of infarction. The NS group consisted of 44 subjects, 21 males and 23 females (Table 1).

Revised version of Hasegawa’s dementia scale (Table 2)
Mean HDS-R was 27.3±0.3 at the beginning and 27.4±0.3 at 3 years in the SK group, and 27.5±0.4 at the beginning and 27.8±0.3 at 3 years in the SC group. Mean HDS-R was 26.8±0.5 at the beginning and 27.5±0.4 at 3 years in the NS group. There was no statistical significance among the three groups.

Apathy scale (Table 2)
The mean apathy scale in the SK group was 11.4±0.9 at the beginning and 10.7±0.9 at 3 years, and in the SC group 12.8±1.4 at the beginning and 12.6±1.5 at 3 years. In the NS group, the mean apathy scale was 13.8±0.7 at the beginning and 13.8±0.8 at 3 years. There was no statistical significance among the three groups.

Self-rating depression scale (Table 2)
The mean SDS scale in the SK group was 39.2±1.4 at the beginning and 36.2±1.4 at 3 years, and in the SC group 41.5±1.7 at the beginning and 41.9±1.9 at 3 years. In the NS group, mean SDS was 32.2±1.1 at the beginning and 35.5±1.2 at 3 years. At the beginning, mean SDS values of the SK and SC groups were significantly higher than that of the NS group (p<0.01). After 3 years, mean SDS of the SK group was significantly lower than at the beginning (p<0.05), and among the three groups, mean SDS of the SK group was also significantly decreased compared with that of the SC and NS groups (p<0.05).

Subjective symptoms (Figure 1)
The patients with silent brain infarction often have combined symptoms of heaviness of head, headache and dizziness. Progression of the symptoms was compared between the SK and SC groups. In the SK group, heaviness of head was improved after 3 years compared to the beginning point. Headache, dizziness or vertigo and stiff shoulder did not change over 3 years in either group, and there were no statistical significance in the two groups. Terasawa’s Oketsu score was 34.0±3.4 at the beginning and 36.7±3.7 at 3 years in the SK group, not a significant change.

V. Discussion and conclusion
In an earlier study, we demonstrated that KB had short-term effects on mental symptoms in silent
brain infarction\textsuperscript{10,17}. Herein, we examined the long-term effects of KB on mental symptoms over 3 years, and compared to the subjects without Kampo treatment. After 3 years, we also compared the results against those of elderly subjects who were observed by a health-screening program of the brain for 3 years.

On the function of acknowledgement, HDS-R did not change among the three groups between the beginning and after 3 years. There were some reports about the possible relationship of silent brain infarction with the cognitive function, with the disagreement in their results being ascribed to age differences of the subjects, extent of infarction, and examination method of the cognitive function. It was reported that silent brain infarction and the cognitive function are more frequent in elderly people\textsuperscript{25} and are also related to a higher degree of ventricular hyperintensity\textsuperscript{10}. We examined these values with clinical assessments in the current study.

For emotional disorders, we studied the apathy scale, an index of the lowering of desire, and SDS, an index of the depressive state. For the apathy scale, there was no difference among the three groups at the beginning and after 3 years. This scale reflects neuronal degeneration, shows that reduction after a stroke\textsuperscript{12} is independent of the depressive state\textsuperscript{28}, and is related to decreased blood flow in the frontal lobe\textsuperscript{30}. Therefore, patients with a slight lesion like silent brain infarction were not differentially recognized compared with elderly subjects.

On SDS, it is reported that silent brain infarction is related to a tendency toward depression\textsuperscript{31}. In this study, the mean SDS values of the SK and SC groups were significantly higher than that of NS group at the beginning of the study. After 3 years, mean SDS of the elderly had worsened significantly, but that of the SK group had improved significantly compared with the value at the beginning. Thus, comparing SK patients with the other groups, SDS of the former improved significantly after 3 years. As for the anti-depression effect of KB, firstly, it has been suggested to work by causing improvement in blood circulation\textsuperscript{13}, as decreases in cerebral blood circulation causes silent brain infarction\textsuperscript{20}. Secondly, there are some reports that KB exerts favorable effects on the mental state directly\textsuperscript{21}, so the depressive state is thought to improve.

Concerning subjective symptoms, silent brain infarction is reportedly related to non-specific symptoms such as headache, etc.\textsuperscript{22}. In the present study, 50-70\% of the patients had non-specific symptoms. KB was useful for improving some symptoms complicating silent brain infarction. Especially in regard to heaviness of head, KB showed improvement compared with the subjects treated without Kampo formulas.

The Oketsu score did not show a significant change after 3 years. Because this score worsens by aging, it is thought to need a comparison with control subjects. Further, as this score was scattered among the institutions in this study, this point is thought to be a problem awaiting solution in the future.

Finally, KB may be useful against depression and subjective symptoms, especially heaviness of head, in relation to silent brain infarction. It is clear that future investigations will need to study the functional mechanisms of KB and to focus on much larger study populations as well as on longer-term longitudinal studies to confirm the protective effects of KB against cerebral attack and vascular dementia.

\section*{Acknowledgement}
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