Vascular Depression

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Abstract: In recent years, a close correlation between cerebrovascular disease and depression in the elderly has become apparent, leading some researchers to advocate for a new entity called “vascular depression (VDep)”. Interest in this type of depression has been increasing in Japan. Alexopoulos et al. have asserted from the clinical point of view that depression in elderly individuals who have vascular risk factors alone should also be included in the category of VDep. This issue, however, remains controversial. In terms of the mechanisms of onset, one hypothesis based on research into post-stroke depression attributes late-life depression to local lesions, such as left frontal lobe lesions, while the threshold hypothesis explains the onset of depression in patients with silent cerebral infarction in terms of the accumulation of cerebrovascular lesions. However, considering the differences in mechanisms of onset, it would appear desirable to distinguish these two conditions from each other through studies of their pathology. The main treatment is antidepressant therapy, particularly with selective serotonin reuptake inhibitors (SSRIs) and serotonin and noradrenaline reuptake inhibitors (SNRIs) whose safety and usefulness have been reported. Meanwhile, the prevention and treatment of vascular disease are critical. Also important in this aging society is an understanding of the pathological features and treatment of VDep from the aspect of comprehensive medicine.

Key words: Vascular depression; Post-stroke depression; Late-life depression; Antidepressant therapy

Introduction

Although depression can occur at any age, it is generally considered that the number of elderly individuals with depression will increase sharply as society continues to age. Depression in the elderly is thought to occur through a combination of socio-psychological, organic, and functional factors. In the arena of organic factors, morphological imaging studies that...
employ MRI or other imaging techniques led in 1997 to the proposed concept of vascular depression, to describe depression related to cerebrovascular disease. This paper introduces the concept of vascular depression and outlines its treatment.

### Concept of Vascular Depression

It has long been indicated that organic factors play a greater role in depression in the elderly. In the 1980s, advances in diagnostic imaging techniques, particularly magnetic resonance imaging (MRI), enabled detailed examination of such involvement, and Krishnan et al.\(^1\) reported in 1988 that deep white matter lesions, detected as areas of hyperintensity in MRI studies, were more common in elderly patients with depression than in unaffected elderly individuals. Similar corroborating evidence was obtained by others in the field. In Japan, Fujikawa et al.\(^2\) reported a high frequency of silent cerebral infarction in patients with presenile or senile major depression. In 1997, through discussion based on these findings, Krishnan and Alexopoulos proposed that such depression associated with organic cerebrovascular factors be designated “vascular depression,” in accord with the concept of vascular dementia prescribed in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), published by the American Psychiatric Association.\(^3\)

Krishnan et al.\(^3\) reported depression accompanied with cerebrovascular lesions as determined by MRI and not accompanied with neurological signs to be MRI-defined vascular depression. They demonstrated that older age, late age at onset (60 years or older), non-psychotic subtype, absence of family history of mental disorders, loss of pleasure, and functional disability occurred more often in patients with this type of depression.

Alexopoulos et al.\(^4\) investigated patients with depression who were 60 years old or older at onset and who had a history or clinical findings of hypertension or transient cerebral ischemic attack, as a group of elderly patients

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**Table 1**  Diagnostic Criteria for Vascular Depression Proposed by Steffens and Krishnan (1998)

<table>
<thead>
<tr>
<th>Specify vascular subtype (can be applied to the current or most recent major depressive episode in major depressive disorder or bipolar disorder) if A and either B1 or B2 or B3:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A.</strong> Major depression occurring in the context of clinical and/or neuroimaging evidence of cerebrovascular disease or neuropsychological impairment.</td>
</tr>
<tr>
<td><strong>B1.</strong> Clinical manifestations may include history of stroke or transient ischemic attacks, or focal neurologic signs or symptoms (e.g., exaggeration of deep tendon reflexes, extensor plantar response, pseudobulbar palsy, gait disturbance, weakness of an extremity).</td>
</tr>
<tr>
<td><strong>B2.</strong> Neuroimaging findings may include white or gray matter hyperintensities (Fazekas et al. 1988 criteria &gt;2; or lesion &gt;5 mm in diameter and irregular in shape), confluent white matter lesions, or cortical or subcortical infarcts.</td>
</tr>
<tr>
<td><strong>B3.</strong> Cognitive impairment manifested by disturbance of executive function (e.g., planning, organizing, sequencing, abstracting), memory, or speed of processing of information.</td>
</tr>
</tbody>
</table>

The diagnosis is supported by the following features:

1. Depression onset after 50 years of age or change in the course of depression after the onset of vascular disease in patients with onset before 50 years of age.
2. Marked loss of interest or pleasure.
3. Psychomotor retardation.
4. Lack of family history of mood disorders.
5. Marked disability in instrumental or self-maintenance activities of daily living.

with clinically defined vascular depression. These patients were characterized by cognitive dysfunction, disability, retardation, lack of insight and less agitation and limited depressive ideation. Based on these findings, Alexopoulos et al. concluded that vascular depression could be identified through clinical features. From these clinical studies, they considered vascular depression to be a broad category of depression related to vascular lesions, and put forth the concept of vascular depression, including depression accompanied with vascular risk factors alone, without evidence on MRI in addition to depression occurring after evident stroke, i.e., post-stroke depression (PSD), and MRI-defined vascular depression as reported by Krishnan et al.

However, it has been pointed out that the diagnostic criteria of Alexopoulos et al. are not specific to vascular depression, providing no distinction from conventional depression in the elderly. In this connection, Krishnan et al. have insisted on the use of diagnostic criteria that place importance on MRI findings. This has resulted in two definitions of vascular depression being employed, namely, that proposed by Alexopoulos et al. and that given by Krishnan et al. Since controversy exists among researchers as to which definition to use, the concept of vascular depression has yet to be firmly established. This paper presents the diagnostic criteria commonly used in Japan, i.e., those proposed by Steffens and Krishnan, which stress the findings obtained from diagnostic imaging.

In spite of the above-mentioned discrepancy between the definitions of vascular depression proposed by Alexopoulos et al. and Krishnan et al., both include PSD in the category of cerebrovascular disease-related depression. However, PSD should be understood from the viewpoint of depression resulting from vascular lesions in specific brain areas and from the aspect of psychological response to physical disorders derived from stroke; this is still a controversial issue in PSD.

On the other hand, the concept of MRI-defined vascular depression was developed from research on depression in elderly individuals with no clinically distinct cerebrovascular disease, and thus it involves no psychological factors such as response to physical disorders in PSD. Therefore, MRI-defined vascular depression may involve different mechanisms of onset from those operating in PSD, and it seems problematic to discuss these types of depression collectively under the single category of vascular depression.

The two conditions should be distinguished from each other through studies of their pathology. It also seems desirable to investigate MRI-defined vascular depression and PSD separately, to avoid confusion in diagnosis.

Pathological Features of PSD

Depression that occurred in the wake of cerebrovascular disease was regarded as PSD in Europe and North America in the latter half of the 1970s, and data from empirical research have continued to accumulate since then. Although survey methods have varied, the average incidences of PSD as determined by DSM criteria in inpatients in the acute stage of stroke are reported to be as follows: major depression, 22%; minor depression (mild depression), 17%. Since about 40% of patients with stroke become depressive, correct recognition and treatment of the condition are extremely important.

Robinson and his colleagues, who are leaders in PSD research, reported in 1981 that depression was more frequent in patients whose lesions were in the left hemisphere, particularly in the left frontal region, than in those whose lesions were in other regions, and that the closer to the frontal pole the forefront of the lesion, the severer the depression. Many reports have corroborated the left frontal lesion hypothesis, but some have indicated a higher incidence of depression in patients with lesions in the right hemisphere or have found
no difference in the incidence of depression, regardless of whether the lesion is located in the right or left hemisphere. Thus, no consensus currently exists among researchers.

To clarify this discrepancy, Robinson’s group recently carried out a long-term follow-up study that extended to two years after stroke and focused on the time of observation, i.e., the length of time after stroke, among different studies. According to their report, depression in the acute post-stroke stage was associated with left frontal lesions. In a short-term follow-up of 3–6 months post-stroke, depression was associated with closeness of the lesion to the frontal pole both in patients with right and left hemisphere lesions. A long-term follow-up of 1–2 years post-stroke showed that depression was associated with the size of the lesion and closeness to the occipital pole in patients with right hemisphere lesions. In addition, biological factors were more prominent in the acute stage, whereas socio-psychological factors became involved in the onset of depression in the chronic stage, indicating more complicated determinants of the onset of PSD over the course of time. They reported that the discrepancies among previous reports could be explained by differences in the time after stroke that examinations were conducted in the studies. However, their findings have been challenged, necessitating further investigation.

Mechanisms of Occurrence of Vascular Depression

As mentioned previously, vascular depression is considered to be a heterogeneous entity, including PSD and MRI-defined vascular depression and, according to the diagnostic criteria of Alexopoulos et al., cases that show vascular risk factors. The mechanisms of occurrence of vascular depression are complicated: currently available hypotheses are the local lesion hypothesis attributing onset to left frontal lesions on the basis of PSD studies and the threshold hypothesis obtained from studies of MRI-defined vascular depression. The latter assumes that accumulation of cerebrovascular lesions, rather than the location of cerebral lesions, causes depression by lowering the threshold of disease onset. It is also speculated from previous data that impairment of cortico-striato-pallido-thalamo-cortical circuits, a neuronal network that controls affect, plays an important role in the development of vascular depression.

Treatment of Vascular Depression

As mentioned above, objection has been voiced to the definition of vascular depression proposed by Alexopoulos et al., which includes cases that have vascular risk factors alone. However, their definition may have great value in that it has drawn attention to the importance of prevention and treatment of vascular disease in elderly patients with depression and has contributed to the prevention or improved prognosis of depression in the elderly. The treatment of vascular disease and use of antidepressants or other psychotropic drugs are indispensable for the treatment of vascular depression.

1. Treatment of vascular disease

Although the details are best left to monographs, the control and treatment of hypertension, hyperlipidemia, and diabetes mellitus, all of which are risk factors for cerebrovascular disease, are extremely important. Antiplatelet therapy and anticoagulant therapy are useful for the prevention of recurrent stroke and are therefore necessary for patients with PSD. Their usefulness for the treatment of patients with MRI-defined vascular depression remains to be clarified in future studies. It is of interest that a calcium-channel blocker, nimodipine, has recently been shown to increase the rate of remission and decrease the rate of recurrence of depression when combined with standard antidepressant therapy in patients with vascular depression.
2. Treatment with psychotropic drugs

Reports on psychotropic drug therapy for vascular depression focus mainly on patients with PSD. Drugs effective for PSD, in which cerebral organic involvement is prominent, are generally considered to be effective for vascular depression as a whole. Table 2 shows major overseas studies on the psychotropic drug therapy reported to date.9) The usefulness of the secondary amine nortriptyline, a tricyclic antidepressant, has often been reported. The efficacy of trazodone, which is associated with fewer anticholinergic side effects, has also been reported. However, it has been pointed out that delirium and over-sedation are not unusual as adverse reactions to these drugs.

Selective serotonin reuptake inhibitors (SSRIs) are reported to be associated with fewer adverse reactions of this kind than conventional antidepressant drugs, and the usefulness of citalopram and fluoxetine (both unavailable in Japan), two drugs of this class, has been documented through several studies. The usefulness of sertraline, another SSRI, in the treatment of vascular depression has also been reported, suggesting that SSRIs are promising therapeutic options. However, it has been noted that SSRIs may cause gastrointestinal symptoms such as nausea and diarrhea in the early phase of therapy. Since adverse reactions are more likely to be induced in patients with vascular depression who have vulnerability in the brain, it is important that medication with any antidepressant drug be initiated at a low

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### Table 2 Major Reports of Antidepressant Therapy for PSD

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Rating scale</th>
<th>Design</th>
<th>Medication</th>
<th>Duration</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipsy et al. (1984)</td>
<td>34</td>
<td>HAM-D Zung’s SDS</td>
<td>DB/PC</td>
<td>NOR (20–100mg) PL</td>
<td>4–6w</td>
<td>NOR&gt;PL</td>
</tr>
<tr>
<td>Reding et al. (1986)</td>
<td>27</td>
<td>Zung’s SDS Barthel ADL</td>
<td>DB/PC</td>
<td>TRZ (50–200mg) PL</td>
<td>32±6d (TRZ) 25±4d (PL)</td>
<td>TRZ&gt;PL</td>
</tr>
<tr>
<td>Lauritzen et al. (1994)</td>
<td>20</td>
<td>HAM-D MES</td>
<td>DB</td>
<td>IMP + MIA (mean 75+25mg) DMI + MIA (mean 66+27mg)</td>
<td>6w</td>
<td>IMP&gt;DMI</td>
</tr>
<tr>
<td>Andersen et al. (1994)</td>
<td>66</td>
<td>HAM-D MES</td>
<td>DB/PC</td>
<td>CPM (10–40mg) PL</td>
<td>6w</td>
<td>CPM&gt;PL</td>
</tr>
<tr>
<td>Gonzalez-Torrecillas et al. (1995)</td>
<td>48</td>
<td>HAM-D Barthel ADL</td>
<td>Open</td>
<td>FLX (20mg), NOR (25–75mg) Untreated</td>
<td>6w</td>
<td>FLX, NOR&gt;untreated</td>
</tr>
<tr>
<td>Dam et al. (1996)</td>
<td>52</td>
<td>HAM-D Barthel ADL</td>
<td>DB/PC</td>
<td>MAP (150mg), FLX (20mg) PL</td>
<td>3m</td>
<td>FLX&gt;MAP&gt;PL</td>
</tr>
<tr>
<td>Wiart et al. (2000)</td>
<td>31</td>
<td>MADRS</td>
<td>DB/PC</td>
<td>FLX (20mg) PL</td>
<td>45d</td>
<td>FLX&gt;PL</td>
</tr>
<tr>
<td>Robinson et al. (2000)</td>
<td>104*</td>
<td>HAM-D</td>
<td>DB/PC</td>
<td>FLX (10–40mg), NOR (25–100mg), PL</td>
<td>12w</td>
<td>NOR&gt;PL~FLX</td>
</tr>
<tr>
<td>Kimura et al. (2002)</td>
<td>12</td>
<td>HAM-D</td>
<td>Open</td>
<td>MIL (30–75mg)</td>
<td>6w</td>
<td>Remission rates 70% (continuing cases) 58% (all cases)</td>
</tr>
</tbody>
</table>


dose and increased gradually, while exercising caution as to possible adverse reactions.

Methylphenidate, a psycho-stimulant, is also reported to be effective and fast acting, but careful examination is required in regard to its efficacy and safety, including the issue of dependence.

We recently carried out a study to investigate the therapeutic effects of milnacipran, a serotonin and noradrenaline reuptake inhibitor (SNRI), on post-stroke depression, and observed high therapeutic efficacy at doses as low as 30–75 mg/day. Concomitant use of antihypertensive drugs or other cardiovascular drugs is particularly common in patients with vascular depression. In this regard, milnacipran, which is known to have fewer interactions with other drugs, is advantageous for this condition.10)

Therefore, physicians treating vascular depression should first use the SNRI milnacipran or an SSRI, and consider the use of nortriptyline if the response to these therapies is inadequate.

**Conclusion**

Depression in which cerebrovascular disease is involved as a factor is known as vascular depression. However, the diagnostic criteria for this entity remain controversial. The concept of vascular depression includes PSD involving clinically evident cerebrovascular disease and depression involving silent cerebral infarction. These two conditions, however, may differ in pathological features, including mechanisms of onset, and thus need to be dealt with separately. From the therapeutic aspect, this concept is of value in that it has drawn attention to the prevention and treatment of vascular disease in elderly patients with depression. SNRIs and SSRIs are thought to be promising therapeutic options in antidepressant therapy.

**REFERENCES**