

# Chapter 14

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## Vascular Dementia

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## What are the diagnostic criteria for vascular dementia (VaD)?

### Answer

Representative diagnostic criteria for VaD include the International Statistical Classification of Diseases and Related Health Problems (ICD-10) published by the World Health Organization (WHO), the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) published by American Psychiatric Association, the diagnostic criteria for ischemic vascular dementia proposed by Alzheimer's Disease Diagnostic and Treatment Center (ADDDTC) in California, and the NINDS-AIREN diagnostic criteria published by the National Institute of Neurological Disorders and Stroke (NINDS) and Association Internationale pour la Recherche et l'Enseignement en Neurosciences (AIREN).

In the statement for healthcare professionals from the American Heart Association/ American Stroke Association (AHA/ASA), the prodromal stage of VaD is termed vascular mild cognitive impairment (VaMCI, or VCI-no dementia), and the term vascular cognitive impairment (VCI) is proposed to include the spectrum of severity from the prodromal stage to VaD.

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### Comments and evidence

VaD is a subtype of dementia caused by cerebrovascular disorder, with heterogeneous underlying pathology. The NINDS-AIREN diagnostic criteria, which was developed for research, have high specificity and are widely used clinically, but the low sensitivity is a drawback<sup>1)</sup>.

In 2011, AHA/ASA proposed an inclusive term “vascular cognitive impairment (VCI)” from the viewpoint of treatment priority<sup>2)</sup>. VCI includes VaD and VCI-no dementia or vascular mild cognitive impairment (VaMCI). Note that although the term VCI in the broad sense includes not only the prodromal stage but also the dementia stage, “VCI-no dementia” is also used to describe the prodromal stage<sup>2, 3)</sup>.

On the other hand, in DSM-5 published in 2013, dementia is positioned as a major neurocognitive disorder. Within this category, VaD is classified as “major vascular neurocognitive disorder”<sup>4)</sup>.

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- 1) Roman GC, Tatemichi TK, Erkinjuntti T, et al. Vascular dementia: diagnostic criteria for research studies. Report of the NINDS. AIREN International Workshop. *Neurology*. 1993; 43(2): 250-260.
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### Search formula

PubMed search: June 18, 2015 (Thursday)

#1 “Dementia, Vascular/diagnosis” [Mesh] OR (“vascular dementia” AND (diagnosis OR diagnostic)) OR (“vascular cognitive impairment” AND (diagnosis OR diagnostic)) OR (“Vascular Diseases/complications” [Mesh] AND “Cognition Disorders/diagnosis” [Mesh])

Ichushi search: June 18, 2015 (Thursday)

#1 (Dementia-vascular/TH OR vascular dementia/TI OR Vascular cognitive impairment/TI) AND ((SH = Diagnostic use, diagnosis, diagnostic imaging, X ray diagnosis, radionuclide diagnosis, ultrasound diagnosis) OR Diagnosis/TH) AND (Diagnostic criteria/AL OR Judgment criteria/AL OR Criteria/TI OR Evaluation criteria/TH OR Classification/TH OR Classification/TI OR ICD classification /TH OR DSM/TH)

## How are the types of vascular dementia (VaD) classified?

### Answer

According to the NINDS-AIREN diagnostic criteria, VaD is classified into the following types: (1) multi-infarct dementia (MID), (2) strategic single infarct dementia, (3) small vessel disease dementia, (4) hypoperfusion vascular dementia, (5) hemorrhagic vascular dementia, and (6) others.



### Comments and evidence

VaD is a type of dementia caused by cerebrovascular disorder, and its underlying pathology is heterogeneous.

The NINDS-AIREN diagnostic criteria which were developed for research classify VaD into the following clinical subtypes<sup>1)</sup>.

- (1) Multi-infarct dementia (MID)
- (2) Strategic single infarct dementia
- (3) Small vessel disease dementia
- (4) Hypoperfusion vascular dementia
- (5) Hemorrhagic vascular dementia
- (6) Others

In small vessel disease dementia, lacunar infarction, white matter lesions (leukoaraiosis), cerebral hemorrhage, and microbleeds are observed in the territory of penetrating arteries as a result of arteriolosclerosis, while cerebral amyloid angiopathy is observed in cortical regions. Small vessel disease dementia that develops as a result of arteriolosclerosis is called subcortical vascular dementia. Subcortical vascular dementia is divided into two types: multiple lacunar infarct dementia when lacunar infarcts are the main cause, and Binswanger disease when white matter lesions are the main cause.

MID is mainly caused by multiple large and small cerebral infarcts in the cortical region. The clinical course is characterized by acute onset or step-wise deterioration, and the symptoms include aphasia, apraxia, agnosia, visuospatial deficit, constitutional impairment and executive dysfunction, together with motor paralysis. Strategic single infarct dementia is caused by cerebral infarcts in areas important for higher brain function. These include the cortical region in the dominant hemisphere such as the angular gyrus and territories of the anterior cerebral artery, the middle cerebral artery, and the posterior cerebral artery, and the subcortical region in the thalamus or basal forebrain.

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- 1) Roman GC, Tatemichi TK, Erkinjuntti T, et al. Vascular dementia: diagnostic criteria for research studies. Report of the NINDS-AIREN International Workshop. *Neurology*. 1993; 43(2): 250-260.

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#1 "Dementia, Vascular/diagnosis" [Mesh] OR ("vascular dementia" AND (diagnosis OR diagnostic)) OR ("vascular cognitive impairment" AND (diagnosis OR diagnostic)) OR ("Vascular Diseases/complications" [Mesh] AND "Cognition Disorders/diagnosis" [Mesh])

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#1 (Dementia-vascular/TH OR vascular dementia/TI OR Vascular cognitive impairment/TI) AND ((SH = Diagnostic use, diagnosis, diagnostic imaging, X ray diagnosis, radionuclide diagnosis, ultrasound diagnosis) OR Diagnosis/TH) AND Diagnostic criteria/AL OR Judgment criteria/AL OR Criteria/TI OR Evaluation criteria/TH OR Classification/TH OR Classification/TI OR ICD classification/TH OR DSM/TH)

## What are the imaging features of vascular dementia (VaD)?

### Answer

Small vessel disease dementia, the most common type of VaD, is characterized by lacunar infarcts and white matter lesions. If the extent and distribution of a lesion adequately explain the neurological symptoms, it is considered to be the culprit lesion of dementia. On the other hand, the temporal relationship between stroke and onset of dementia may support the culprit lesion in some cases, including multi-infarct dementia and strategic single infarct dementia. Hereditary vascular dementia includes cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) and cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL). They show extensive white matter lesions, lacunar infarcts, microbleeds, and brain atrophy, and are characterized by white matter lesion in the temporal pole.

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### Comments and evidence

The most common type of VaD is cerebral small vessel disease dementia. Although lacunar infarcts and white matter lesions are characteristic of this disease, patients may remain asymptomatic even after lacunar infarcts have occurred, and do not necessarily show a course of cognitive impairment characterized by stepwise deterioration of dementia after stroke. In such cases, if the extent, distribution, and location of the small blood vessel lesion adequately explain the neurological symptoms (neuroimaging-supported), the lesion is considered to be the culprit lesion of dementia. On the other hand, the temporal relationship between stroke and dementia may provide support for a culprit lesion of dementia (temporally supported) as evidence for diagnosis, and multi-infarct dementia and strategic single infarct dementia belong to this type<sup>1,2</sup>.

The MRI features of VaD include lacunar infarct, white matter lesion, cerebral hemorrhage (deep type, subcortical type), multiple cortical infarcts, microbleeds, cortical micro-infarct, localized brain surface hemosiderin deposition, perivascular space enlargement, watershed infarct, and cortical laminar necrosis. Lacunar infarct is an infarct with a diameter of 3 to 13 mm occurring in the territory of penetrating arteries, and is observed as hypointensity on T1-weighted MRI, hyperintensity on T2-weighted image, and hypointensity with a rim of hyperintensity on FLAIR image<sup>3</sup>. White matter lesion is observed as normal to hypointensity on T1-weighted image, and hyperintensity on T2-weighted and FLAIR images. White matter lesions are relatively infrequent in the occipital lobe and temporal lobe, although CADASIL and CARASIL are characterized by lesions in the temporal pole<sup>4,5</sup>.

Iadecola<sup>2</sup> described the correlation of image abnormalities with clinical subtypes. Changes in cerebral small blood vessels caused by arteriosclerosis and amyloid angiopathy are difficult to visualize by conventional MRI. However, since detailed brain imaging has accurately detected vascular lesions caused by cerebral small vessel disease, clinical and imaging findings together have provided insight on the concept of cerebral small vessel disease<sup>6,7</sup>.

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- 1) Roman GC, Tatemichi TK, Erkinjuntti T, et al. Vascular dementia: diagnostic criteria for research studies. Report of the NINDS-AIREN International Workshop. *Neurology*. 1993; 43(2): 250-260.
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#1 ("Dementia, Vascular/diagnosis" [Mesh] OR ("vascular dementia" AND (diagnosis OR diagnostic)) OR ("vascular cognitive impairment" AND (diagnosis OR diagnostic)) OR ("Vascular Diseases/complications" [Mesh] AND "Cognition Disorders/diagnosis" [Mesh])) AND ("Diagnostic Imaging" [Mesh] OR CT [TIAB] OR "computed tomography" OR MRI OR "magnetic resonance imaging" OR SPECT OR "single-photon emission computed tomography" OR PET OR "positron emission tomography")

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#1 (Dementia-vascular/TH OR vascular dementia/TI OR Vascular cognitive impairment/TI) AND ((SH = Diagnostic use, diagnosis, diagnostic imaging, X ray diagnosis, radionuclide diagnosis, ultrasound diagnosis) OR Diagnosis/TH) AND (Diagnostic imaging/TH OR CT/TI OR Computer tomography OR Computer tomography OR MRI/TI OR magnetic resonance imaging OR magnetic resonance tomography OR Magnetic resonance imaging OR Nuclear magnetic resonance imaging OR SPECT/TI OR Single photon emission computed tomography OR Single photon emission computed tomography OR Single photon computed tomography OR Single photon emission computed tomography OR Single photon emission computed tomography OR PET/TI OR Positron emission tomography OR Positron emission tomography)

## What is the condition when vascular dementia (VaD) coexists with Alzheimer's disease dementia?

### Answer

Alzheimer's disease dementia and cerebrovascular disorders have common risk factors, and they tend to coexist. There is a disease concept of Alzheimer's disease with cerebrovascular disorder (CVD) (AD with CVD), or mixed dementia. In the advanced stage of Alzheimer's disease dementia, CVD has little effect on cognitive function. In the early stage of Alzheimer's disease dementia, however, CVD is a factor that promotes cognitive impairment. B

### Comments and evidence

The proportion of patients with mixed dementia; Alzheimer's disease dementia coexisting with VaD, increases with aging. The percentage of mixed dementia among all dementia cases varies widely from 0 to 55% even in pathological reports<sup>1)</sup>. In general, when cerebrovascular disorder and Alzheimer pathology coexist with either one of them capable of causing dementia, the condition is called mixed dementia. However, there is also opinion that mixed dementia should be defined as the coexistence of both diseases (Alzheimer's disease with CVD). This difference in definition may be a reason for the widely variable frequency reported<sup>1)</sup>.

Patients with mixed brain pathologies such as Alzheimer's disease dementia, CVD, and dementia with Lewy body are 2.8 times more likely to manifest dementia compared to those with only one disease<sup>2)</sup>. CVD has little effect on cognitive function in the advanced stage of Alzheimer's disease dementia, but CVD is a factor that promotes cognitive impairment in the early stage of Alzheimer's disease dementia<sup>3)</sup>.

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#1 ("Dementia, Vascular" [Mesh] OR "vascular dementia" OR "vascular cognitive impairment" OR ("Vascular Diseases/ complications" [Mesh] AND "Cognition Disorders" [Mesh])) AND ("Alzheimer Disease" [Mesh] OR alzheimer*) OR ("Alzheimer Disease" [Majr] AND "Cerebrovascular Disorders" [Majr]) OR ("mixed dementia" [TI] AND "Dementia" [Mesh])
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Ichushi search: June 18, 2015 (Thursday)

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## What are the clinical course and prognosis of vascular dementia (VaD)?

### Answer

The typical clinical course of VaD starts with post-stroke dementia in which dementia develops after a stroke, followed by stepwise deterioration of cognitive function after each stroke episode. However, cerebral small vessel disease has a slowly progressive course and may be difficult to differentiate from degenerative dementia.

Patients with VaD has significantly shorter survival than persons without dementia. Although survival has been reported to be shorter in VaD patients than in those with Alzheimer's disease dementia, there is no sufficient scientific evidence.



### Comments and evidence

In VaD, cognitive impairment typically deteriorates in a stepwise manner after or associated with each stroke episode. Dementia that develops after the first stroke is called post-stroke dementia. In community epidemiological studies, post-stroke dementia occurs in 30% of stroke patients, and the prevalence increases from 7% after 1 year to 48% after 25 years<sup>1)</sup>. Some cases of post-stroke dementia are caused by Alzheimer's disease dementia, accounting for 19-61% of post-stroke dementia.

The survival of patients with VaD is worse than control subjects without dementia<sup>2-4)</sup>. Compared to Alzheimer's disease dementia, survival of VaD is significantly poorer in some reports<sup>5-8)</sup>, but not significantly different in others<sup>4, 9)</sup>, with inconsistent results. The average survival time after onset of VaD was 5.1 years for males and 6.7 years for females, and survival after onset of Alzheimer's disease dementia patients was 5.0 years for males and 7.8 years for females, showing a tendency of shorter overall survival in VaD patients<sup>5)</sup>. In the Hisayama study that followed 828 older people for over 17 years, 275 persons developed dementia and 164 were autopsied. The results showed that the 10-year survival rate was lower in dementia with Lewy bodies (2.2%), while there was no significant difference between Alzheimer's disease dementia (18.9%) and VaD (13.2%)<sup>4)</sup>.

Many reports have shown age and severity of stroke to be predictors of cognitive impairment after stroke. In the Efficacy of Nitric Oxide in Stroke (ENOS) trial that analyzed 1,572 stroke patients, 38% showed cognitive decline within 3 months, and was associated with not only age and stroke severity, but also hypertension, atrial fibrillation, and brain atrophy<sup>10)</sup>.

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### Search formula

PubMed search: June 18, 2015 (Thursday)

#1 ("Dementia, Vascular" [Majr] OR "vascular dementia" [TI] OR "vascular cognitive impairment" [TI] OR ("Vascular Diseases/complications" [Majr] AND "Cognition Disorders" [Majr])) AND ("Prognosis" [Mesh] OR "Disease Progression" [Mesh] OR prognosis [TI] OR prole [TI] OR course[TI] OR outcome[TI] OR "natural history" [TI])

Ichushi search: June 18, 2015 (Thursday)

#1 (Dementia-vascular/TH OR vascular dementia/TI OR Vascular cognitive impairment/TI) AND (Prognosis/TH OR Prognosis/TI OR Natural course/TI)

## What are the systemic complications and associated symptoms of vascular dementia (VaD)?

### Answer

(1) VaD is often accompanied by gait disturbance, falls, urinary disorder, pseudobulbar paralysis, and mood disorders such as depression. In addition to stroke, VaD may be complicated by systemic vascular disorders such as ischemic heart disease and peripheral artery disease.

(2) Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is associated with migraine with aura, mood disorder (depression), and arteriosclerotic changes in the fundus.

(3) Cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL) is associated with not only dementia but also alopecia (baldness) and low back pain associated with spondylosis deformans.

### Comments and evidence

The most widely used diagnostic criteria for VaD are the diagnostic criteria of the National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN)<sup>1)</sup>. The NINDS-AIREN diagnostic criteria describe specific systemic complications and associated symptoms including early presence of gait disturbance, unstable gait and frequent falls, early presence of urinary disorder, pseudobulbar palsy, personality disorder, abulia, depression, and emotional incontinence. On the other hand, “features that make the diagnosis of VaD unlikely” include (1) early onset of memory deficit or cognitive impairments including aphasia, apraxia, and agnosia, in the absence of corresponding focal lesions on brain imaging; (2) absence of neurological signs; and absence of cerebrovascular lesions on brain CT or MRI. Compared to Alzheimer's disease dementia, VaD is often accompanied by impaired physical functions such as neurologic deficit symptoms.

Depression is significantly more common in VaD than in Alzheimer's disease dementia, suggesting that VaD may worsen depression<sup>2-4)</sup>. The manifestation of depression after onset of stroke is attracting attention as post-stroke depression.

CADASIL, which is a hereditary VaD, is known to be accompanied by migraine with aura, mood disorder (depression), and arteriosclerotic changes in the fundus<sup>5)</sup>.

Furthermore, CARASIL, also a hereditary VaD, is known to be associated with not only dementia but also alopecia and lower back pain associated with spondylosis deformans<sup>6)</sup>.

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### Search formula

PubMed search: June 27, 2015 (Saturday)

#1 “Dementia, Vascular/complications” [Majr] OR (“vascular dementia” [TI] AND complication\* [TI]) OR (“vascular cognitive impairment\*” [TI] AND complication\* [TI])

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#1 (Dementia-vascular/TH OR vascular dementia/TI OR Vascular cognitive impairment/TI) AND (Complication/TI OR Associated symptom/TI)



## What are the risk factors for vascular dementia (VaD) and how are they controlled?

### Recommendation

- (1) VaD risk factors include aging, lack of exercise, a history of stroke (especially recurrent), hypertension, diabetes, dyslipidemia, obesity, atrial fibrillation, and smoking.
- (2) For prevention of VaD, antihypertensive therapy for midlife hypertension is recommended. **1B** However, no consensus has been reached regarding the target blood pressure reduction.
- (3) Smoking cessation is recommended for VaD prevention. **1B**
- (4) Physical exercise is recommended for VaD prevention. **2C**
- (5) Continuous weight control from midlife (prevention of obesity) is recommended for VaD prevention. **2C**

### Comments and evidence

The Hisayama Study in Japan identified aging, low score in Hasegawa Dementia Scale, a history of stroke, and high systolic blood pressure as significant risk factors for VaD, while high hematocrit also tended to be a risk. In particular, midlife hypertension has been shown to be a strong risk factor for VaD<sup>1,2</sup>, and midlife hypertension should be treated actively from the viewpoint of dementia prevention.

On the other hand, among the large-scale randomized trials of antihypertensive drugs conducted mainly in older people, 6 trials also assessed cognitive function as an outcome measure. Among these 6 trials, 4 trials found no definitive effects of antihypertensives on the risk of dementia and on cognitive function<sup>3</sup>, while the remaining 2 trials showed usefulness of these agents in reducing the risk of dementia in one trial (Syst-Eur trial)<sup>4</sup> and demonstrated efficacy for post-stroke dementia in the other trial (PROGRESS trial)<sup>5,6</sup>.

As described above, there is inadequate scientific evidence for antihypertensive treatment and the optimal target of blood pressure reduction in older people. Therefore, no conclusions have been reached regarding the effect of antihypertensive treatment for late-life hypertension on the prevention of dementia. However, antihypertensives are prescribed because there is no evidence that they deteriorate cognitive function.

Diabetes is a risk factor for stroke, but glycemic control alone does not prevent the recurrence of stroke, and control of other risk factors including hypertension is important. There is insufficient scientific evidence that using insulin therapy for glycemic control improves cognitive function<sup>7</sup>. Statin use reduces stroke by 17%<sup>98</sup>, but the effects on cognitive function are inconsistent among reports<sup>9</sup>. In one study, use of strong statins for more than 1 year reduced new-onset dementia (hazard ratio 0.71, 95% confidence interval 0.61 to 0.82)<sup>10</sup>, but dementia was not classified into subtypes in that study. In addition, a cohort study in residents aged over 60 years in Taiwan showed that the use of strong statins reduced the incidence of new-onset dementia [hazard ratio 0.73 (95% confidence interval 0.65 to 0.81)]. The effect was not significant when analysis was focused only on VaD [hazard ratio: 0.92 (95% confidence interval 0.72-1.18)].

A meta-analysis (19 prospective studies with follow-up periods of 2 to 30 years) has revealed that smoking is a risk factor of VaD, as is for Alzheimer's disease dementia<sup>11</sup>. The relative risk of VaD in current smokers is 1.78-fold compared with those who have never smoked, and this result is almost the same as that for Alzheimer's disease dementia (1.79-fold)<sup>11</sup>. Although further studies are needed to determine the extent of VaD risk reduction by smoking cessation, smoking cessation is desirable for VaD prevention.

In terms of physical activity, a prospective study of 749 older people observed for an average of 3.9 years evaluated the effects of exercise in 54 persons who developed Alzheimer's disease dementia and 27 people who developed VaD. In this analysis, exercise and walking reduced the risk of developing VaD<sup>12</sup>. Therefore, moderate physical activity is desirable.

In relation to eating habits, antioxidants (vitamins E and C) and fish-derived lipids (consumption of fatty fish) protect against VaD, while fried fish, elevated homocysteine, and low levels of folic acid and vitamins B<sub>12</sub> increase the risk of VaD<sup>13</sup>. However, for older people with high blood levels of homocysteine, the risk of dementia cannot be reduced by supplementation with vitamin B complex<sup>14</sup>.

It has been shown that both underweight and obesity correlate with dementia (U-shape phenomenon)<sup>15</sup>. In particular, obesity (BMI  $\geq$  30) increases the risk of developing VaD by a factor of 5.01 in a prospective study of 10,136 persons aged 40

to 45 years with a mean follow-up period of 36 years. However, in a short-term (3-5 years) study in older people, the correlation between obesity and VaD is poor<sup>15</sup>. Therefore, continuous weight control (prevention of obesity) from midlife is desirable for VaD prevention.

Atrial fibrillation increases the risk of dementia through various mechanisms<sup>16</sup>. Although there are few studies that classify and analyze VaD and Alzheimer's disease dementia separately, many reports have shown that the risk of dementia is increased 2 to 3 times in patients with atrial fibrillation associated with stroke.

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PubMed search: June 27, 2015 (Saturday)

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#1 ("Dementia, Vascular/prevention and control" [Majr] OR ("vascular dementia" [TI] AND prevent* [TI]) OR (vascular cognitive impairment* [TI] AND prevent* [TI])) OR (("Dementia, Vascular/etiology" [Majr] AND Risk [Mesh]) OR ("vascular dementia" [TI] AND risk [TI]) OR (vascular cognitive impairment* [TI] AND risk [TI]))
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Ichushi search: June 27, 2015 (Saturday)

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#1 ((Dementia-vascular/TH OR vascular dementia/TI OR Vascular cognitive impairment/TI) AND ((SH = PREVENTION) or Prevention/TI or Control/TI)) OR ((Dementia-vascular/TH OR vascular dementia/TI OR Vascular cognitive impairment/TI) AND (Risk factor/TH OR Risk factor /TI OR Risk/TI))
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## What is antithrombotic therapy for vascular dementia (VaD)?

### Recommendation

There is little evidence for the use of antithrombotic drugs for primary prevention of dementia. However, appropriate anticoagulant therapy is desirable for dementia prevention only in patients with atrial fibrillation.

To prevent dementia after noncardiogenic cerebral infarction, consider using antiplatelet drugs.

2C

### Comments and evidence

The effectiveness of antiplatelet drugs for dementia is not consistent across several observational studies. In the Aspirin for Asymptomatic Atherosclerosis (AAA) trial, 3,350 subjects were given aspirin 100 mg or placebo for over 5 years, but no significant difference in cognitive function was demonstrated between two groups<sup>1)</sup>. In another cohort study of 3,809 community-dwelling persons, the odds ratio for cognitive decline after 6 years of aspirin use was 0.97 (95% confidence interval 0.82-1.15)<sup>2)</sup>. Therefore, previous studies have not confirmed the usefulness of prescribing antiplatelet drugs at least for a period of 6 years for primary prevention of dementia. On the other hand, in a study in which 70 patients with multi-infarct dementia were randomized into an aspirin group and a no-aspirin group and followed every year for 3 years, cognitive function was preserved in the aspirin group. However, study limitations such as lack of placebo control and small sample size have been pointed out<sup>3)</sup>. In the South London Stroke Register that analyzed 4,413 patients with ischemic stroke but no atrial fibrillation, aspirin and dipyridamole combination therapy showed a tendency of protection against cognitive impairment [relative risk, 0.8 (95% confidence interval 0.68 to 1.01)]<sup>4)</sup>. Thus, although antiplatelet therapy may not be useful for primary prevention of dementia, this therapy may be considered for prevention of dementia after ischemic stroke.

In the PRoFESS trial, a study was performed in patients with ischemic stroke comparing treatment using aspirin and dipyridamole combination therapy and clopidogrel monotherapy. After a mean follow-up period of 2.4 years, there was no difference in cognitive decline between two treatment groups<sup>5)</sup>. Therefore, the effect of combination therapy with antiplatelet drugs and the class effect (difference in dementia prevention effect by antiplatelet drugs with different mechanisms of action) for dementia prevention remain unclear.

In the SPS3 trial, patients with symptomatic lacunar infarction were followed for an average of 3 years, and cognitive function was compared between aspirin monotherapy and combination therapy with two antiplatelet drugs. No dementia prevention effect was observed for dual antiplatelet therapy<sup>6)</sup>.

In cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), which is a hereditary vascular dementia, cerebral hemorrhage may develop during the course of disease, and administration of antiplatelet drugs may increase the risk of cerebral hemorrhage<sup>7)</sup>. Even in sporadic vascular dementia, it is necessary to pay attention to bleeding complications when using antiplatelet drugs.

In a 3000-day observational study of 2,693 patients with no history of stroke or dementia who received warfarin for atrial fibrillation, the groups with poor warfarin control [time in therapeutic range (TTR) <25%, 26-50%, and 51-75%] had dementia hazard ratios of 5.34, 4.10, and 2.57, respectively, compared to the good warfarin control group (TTR >75%)<sup>8)</sup>. In patients with atrial fibrillation, appropriate anticoagulant therapy for dementia prevention is desirable.

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## ■ Search formula

PubMed search: June 28, 2015 (Sunday)

#1 ("Dementia, Vascular" [Mesh] OR "vascular dementia" [TI] OR vascular cognitive impairment\* [TI]) AND ("Fibrinolytic Agents" [Mesh] OR "Fibrinolytic Agents" [Pharmacological Action] OR "Anticoagulants" [Mesh] OR "Anticoagulants" [Pharmacological Action] OR "Platelet Aggregation Inhibitors" [Mesh] OR Platelet Aggregation Inhibitors [Pharmacological Action] OR "clopidogrel" [Supplementary Concept] OR aspirin\* [TI] OR clopidogrel [TI] OR cilostazol [TI] OR antiplatelet\* [TI] OR warfarin [TI] OR novel oral anticoagulant\* [TI] OR NOAC [TI] OR anticoagulation\* [TI])

Ichushi search: June 28, 2015 (Sunday)

#1 (Dementia-vascular/TH OR Vascular dementia/TI OR Vascular cognitive impairment/TI) AND (Anti-platelet agent/TH OR Anti-platelet agent/TI OR Anti-platelet drug/TI OR Aspirin/TI OR Aspirin/TI OR Clopidogrel/TI OR Clopidogrel/TI OR Warfarin/TI OR Warfarin/TI OR "novel oral anticoagulant"/TI OR NOAC/TI OR Platelet aggregation inhibition/TI)

## Are there effective drugs for cognitive impairment in vascular dementia (VaD)?

### Recommendation

For the treatment of core symptoms of VaD, the cholinesterase inhibitors; namely, donepezil **2B**, galantamine **2B** and rivastigmine **2C**; as well as the N-methyl-D-aspartate (NMDA) receptor antagonist memantine **2B** are recommended (off-label).

### Comments and evidence

In a double-blind randomized clinical trial conducted in patients with VaD, the donepezil group showed significant improvement in cognitive function compared to the placebo group. In particular, strong evidence was obtained for short-term treatment of approximately 24 weeks for mild to moderate VaD. In the future, establishment of evidence for the usefulness of long-term administration is awaited<sup>1)</sup>. For cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), a hereditary VaD, although administration of donepezil was not effective to improve cognition overall, usefulness was noted for executive function only<sup>2)</sup>.

Treatment with galantamine achieved significant improvement in cognitive function compared to the placebo group in a double-blind randomized clinical trials conducted in VaD patients<sup>3)</sup> and in Alzheimer's disease dementia patients with cerebrovascular disorders<sup>4)</sup>.

In a double-blind randomized clinical trial in VaD patients, rivastigmine significantly improved some cognitive function assessment items compared to the placebo group<sup>5)</sup>.

Treatment with memantine, an NMDA receptor antagonist, resulted in significant improvement in cognitive function compared to the placebo group in double-blind randomized clinical trials in patients with VaD and in patients with Alzheimer's disease dementia and cerebrovascular disease<sup>6,7)</sup>.

The above four drugs may be effective to certain extent for VaD, but one cannot exclude the possibility that the observed effectiveness may be mediated by the effect on coexisting Alzheimer's dementia.

As for other therapeutic agents, several clinical trials have shown that nicergoline improves cognitive function in VaD. In Japan, nicergoline is covered by health insurance for "improvement of decreased motivation due to chronic cerebrovascular disorder associated with sequelae of cerebral infarction". Amantadine is covered by insurance for sequelae of cerebral infarction, and may be considered for use to improve motivation and initiative in VaD. *Ginkgo biloba* has been reported to be effective for the treatment of dementia including VaD in several clinical trials<sup>8)</sup>. Moreover, risperidone at low doses (mean 0.95 mg/day) reduces aggression, agitation and psychiatric symptoms associated with VaD<sup>9)</sup>. Tiapride is covered by health insurance for "improvement of aggressive behaviors, mental agitation, wandering, and delirium associated with sequelae of stroke".

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## ■ Search formula

PubMed search: June 28, 2015 (Sunday)

#1 ("Dementia, Vascular/therapy" [Mesh] OR ("vascular dementia" [TI] AND (therapy OR therapeutic\* OR treatment\*)) OR (vascular cognitive impairment\* [TI] AND (therapy OR therapeutic\* OR treatment\*))) AND ("Hematologic Agents" [Mesh] OR "Hematologic Agents" [Pharmacological Action])

Ichushi search: June 28, 2015 (Sunday)

#1 (Dementia-vascular/TH OR Vascular dementia/TI OR Vascular cognitive impairment/TI) AND Therapeutic use/TH

## What is the clinical position of cerebral amyloid angiopathy (CAA)?

### Answer

- (1) Cerebral amyloid angiopathy is related to the development of dementia.
- (2) There is no known effective treatment for cerebral amyloid angiopathy, but if hypertension coexists, antihypertensive therapy is recommended to prevent cerebral hemorrhage.

### Comments and evidence

Cerebral amyloid angiopathy is a pathological vascular change, which almost always occurs in Alzheimer's disease dementia. However, apart from being a direct cause of bleeding in the brain lobes, symptoms are rarely observed and hence the condition did not attract much attention. However, image and pathological analyses have clearly demonstrated that cerebral amyloid angiopathy is associated with various cerebrovascular disorders such as cortical micro-infarcts and cortical microbleeds<sup>1,2</sup>. Furthermore, report has indicated that it is an independent factor of not only stroke but also dementia<sup>3</sup>. In a systematic review that analyzed the findings of four population-based studies; the Cambridge City over-75s Cohort (CC75C) study, the MRC Cognitive Function and Aging Study (MRC-CFAS), the Honolulu-Asia Aging study, and the Vantaa 85+ study, CAA was observed in 55% to 59% of patients with dementia but in only 28% to 38% of non-dementia patients. Severe CAA was observed in 37% to 43% of patients with dementia but only 7 to 24% of non-dementia patients, with clear differences between the two groups.<sup>3</sup>

In a multicenter randomized study conducted in 6,105 patients with cerebrovascular disease comparing cerebrovascular events during treatment with antihypertensive medications versus placebo for a mean period of 3.9 years, intracerebral hemorrhage associated with CAA was observed in a total of 16 patients. Cerebral hemorrhage was reduced by 77% in patients receiving antihypertensives compared with patients receiving placebo (3 patients in the antihypertensive group, 13 patients in the placebo group)<sup>4</sup>. There is no known effective treatment for CAA, but if patients also have hypertension, antihypertensive therapy is recommended for prevention of intracerebral hemorrhage.

In patients with CAA, acute inflammatory reaction mediated by autoimmune reaction against vascular wall amyloid  $\beta$  may occur concomitantly, causing acute impairment of consciousness and cognitive deterioration. This condition is called CAA-related inflammation (CAA-ri)<sup>5</sup>. As suggested from the pathological mechanism of CAA-ri, administration of immunosuppressive drugs such as corticosteroids and cyclophosphamide is effective in the acute phase<sup>6</sup>.

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### Search formula

PubMed search: June 28, 2015 (Sunday)

#1 ("Dementia" [Mesh]OR dementia[TI]) AND ("Cerebral Amyloid Angiopathy" [Mesh] OR "cerebral amyloid angiopathy")

Ichushi search: June 28, 2015 (Sunday)

#1 (Dementia/TH OR Dementia/TI OR Cognitive impairment/TI) AND (Cerebral amyloid angiopathy/TH OR Cerebral amyloid angiopathy/TI)