Vas-Cog Journal

No.6 April 01. 2020

Official Journal of Vas-Cog Japan Society

Review article

Hirofumi Sakurai.

"Frailty and sarcopenia in patients with dementia"

Yoshiki Hase.

"Exploring Interventional Strategies for Vascular Dementia"

Case report

Yosuke Osakada, et al.

"Delayed Serial Microvascular Injury and Cognitive Decline After Whole Brain Irradiation"

ISSN : 24239372

Table of Contents

Editorial

Shuko Takeda, MD, PhD.
Associate Professor
Department of Clinical Gene Therapy,
School of Medicine, Osaka University

The brand new Vas-Cog Journal

Vas-Cog Journal, initially launched in 2015 as a newsletter of the Vas-Cog Japan Society, underwent a revamp last year. A brand new style was designed, given its rise in status as an international academic journal that accepts peer-reviewed papers in addition to regular articles by the editorial board members. Vas-Cog Journal now welcomes your submissions of high-quality original articles and case reports regarding vascular dementia and related diseases. The current issue of Vas-Cog Journal (No. 6) presents two sophisticated review articles and an intriguing case report, both of which were accepted via the new submission system.

A comprehensive review article, co-written by Drs. Sakurai and Hanyu at Tokyo Medical University, focuses on the interplay among dementia, frailty, and sarcopenia, providing new insights into the mechanisms underlying these age-related diseases. Another review article by Dr. Hase from Dr. Kalaria's Laboratory at Newcastle University, UK, covers a broad range of topics on the pathogenesis of vascular dementia, and proposes novel interventional strategies against vascular cognitive impairment. In a case report from Okayama University, Dr. Osakada describes an intriguing case of delayed microvascular injury and cognitive decline after whole-brain irradiation against a brain tumor. The detailed description of this particular case provides useful information and offers fresh insights regarding the possible pathogenesis of irradiation-induced brain injuries.

Issue No. 6 of Vas-Cog Journal also reports the outlines of the 10th Annual Meeting of Vas-Cog Japan, which was held on August 3rd, 2019, in Tokyo, and hosted by Profs. Akishita (The University of Tokyo) and Ikeda (Gunma University). The main theme of the meeting, "Cross-talk of Vascular Factors and Neurodegeneration," was contributed to by more than 200 participants, who discussed a wide range of popular topics on vascular dementia. The upcoming annual meeting, Vas-Cog Japan 2021, will be held on September 11th and 12th in Tokushima. It will be hosted by Profs. Sata (Tokushima University) and Takizawa (Tokai University). The main theme of this meeting will be "Dementia Practice from Vascular and Neurological Medicine," focusing on the close relationship between vascular diseases and neurodegenerative disorders. Professor Abe at Okayama University reports on the international meeting of Vas-Cog Asia 8, which was held jointly with the Asia-Pacific Stroke Conference 2019 in Manila on October 2nd, 2019. Most of the participants belonged to Asian countries, and discussed and shared the current knowledge and future trends of vascular-related cognitive impairment.

In this issue of Vas-Cog Journal, Prof. Ikeda of Gunma University summarizes reports from the 11th Board and Council Meeting of the Japanese Society for Vascular Cognitive Impairment, which was held on August 3rd, 2019 in Tokyo during the annual meeting of Vas-Cog Japan 2019. Additionally, submission instructions to Vas-Cog Journal are provided in this issue.

Finally, I express my sincere gratitude to the President of Vas-Cog Japan (Prof. Morishita of Osaka University), the Editor-in-Chief of Vas-Cog Journal (Prof. Shoji), the editorial bord members, and secretaries for all their efforts toward publishing this issue of the journal. I hope you enjoy the brand new look of Vas-Cog Journal.

Review article

Frailty and sarcopenia in patients with dementia

Hirofumi Sakurai, MD, PhD.; Haruo Hanyu, MD, PhD.
Department of Geriatric Medicine, Tokyo Medical University

Short Title: Frailty and sarcopenia in dementia

Disclosures: The authors declare no conflict of interest.

Abstract:

Increasing emphasis has been placed on extending healthy life expectancy. Patients with dementia, cerebrovascular disease, and frailty due to old age account for 24.8%, 18.4%, and 12.1%, respectively, of people aged 65 years or more requiring nursing care.

The causes of dementia are numerous, and the most common type is Alzheimer's disease (AD), followed by vascular dementia (VaD), and dementia with Lewy bodies. Lifestyle-related diseases such as diabetes and hypertension are involved in the onset and progression of dementia.

The term "frailty" indicates an intermediate stage between a healthy state and one where an individual will require nursing care. Frailty involves physical, mental, and psychological decline, and possibly also social factors such as solitude and financial distress.

Sarcopenia, which causes muscle loss, and a decrease in muscular strength and physical function, is the key factor in physical decline.

Dementia, sarcopenia, and frailty are closely related. The frequency of frailty is higher in patients with AD than in healthy elderly people. Cerebrovascular disease (CVD), such as lacunes and white matter lesions, is common in elderly patients with AD. Frailty is more closely associated with AD + CVD than with AD alone; and it also shows a stronger association with VaD than with AD.

The close relationship between dementia and frailty/sarcopenia is believed to constitute a vicious cycle.

Key words: Frailty, sarcopenia, Alzheimer's disease, cerebrovascular disease (CVD), vascular dementia

Corresponding Author:
Hirofumi Sakurai
Department of Geriatric Medicine, Tokyo Medical University
6-7-1 Nishishinjuku, Shinjuku-ku, Tokyo 160-0023, Japan
Tel.: +81-(0)3-3342-6111, Fax: +81-(0)3-3342-2305
E-mail: sakurah@tokyo-med.ac.jp

Introduction

Healthy life expectancy refers to the period during which a person is able to live independently without needing care in their daily life. According to a survey conducted in 2016 by the Ministry of Health, Labor and Welfare of Japan, average life expectancy was 80.98 years for males and 87.14 years for females, while healthy life expectancy was 72.14 and 74.79 years, respectively.The difference between average life expectancy and healthy life expectancy was 12.35 years for women and 8.84 years for men. The results of the same survey also revealed the causes for the need for nursing care in people aged 65 years or over, with dementia, cerebrovascular disease (CVD), and frailty due to old age occupying 24.8%, 18.4%, and 12.1% of this particular population, respectively[1].

Recently, increasing emphasis has been placed on extending healthy life expectancy, and achieving this goal will require new efforts to combat dementia, cerebrovascular disorders, and frailty. The causes of dementia are numerous, and the most common type is Alzheimer's disease (AD), followed by vascular dementia (VaD), and dementia with Lewy bodies (DLB). Lifestyle-related diseases such as diabetes and hypertension are involved in the onset and progression of dementia.

Dementia, CVD, and frailty are closely related to each other. In this article, I would like to give an overview of the relationship between frailty and dementia, including findings made at our department related to this issue.

Frailty

Frailty can be reversed, allowing return to healthy state (Figure 1)

Frailty has been shown to be associated with increased physical limitations and disability, and results in generally poorer health in older people[2].

The term "frailty" is used to denote the intermediate stage between a healthy state and one where the individual will require nursing care. This term was first proposed by the Japan Geriatrics Society in 2014. It is characterized by an increased susceptibility to stress due to the decrease that occurs in physiological reserves with advanced age, with likely outcomes including impaired function in daily activities, the need for nursing care, and death.

Before reaching a frail state, a healthy individual will also pass through another distinct stage termed "pre-frailty". Both the pre-fail and frail states are not irreversible, however: appropriate intervention and support, including guidance on exercise and nutrition, can result in a return to a healthy state with improved function in daily activities. Therefore, early intervention is important[3].

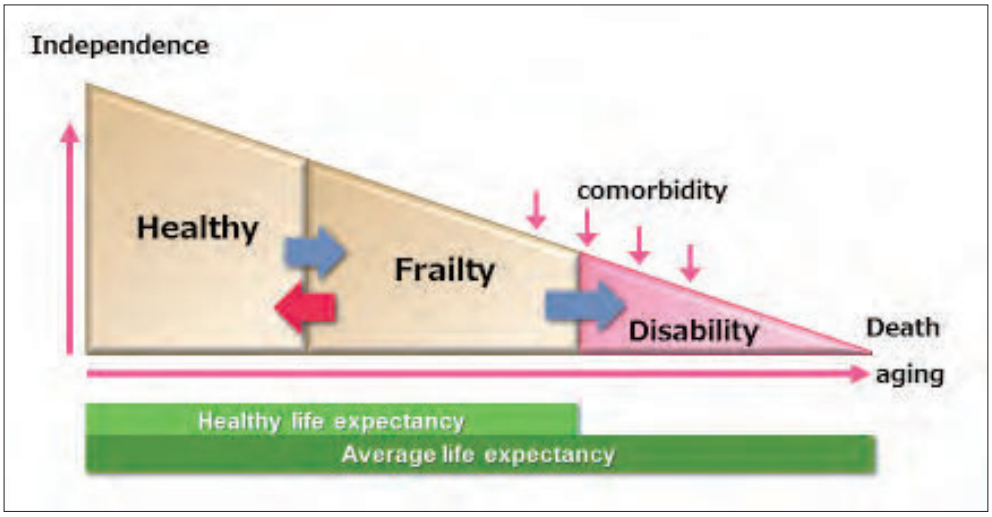


Figure 1　Frailty can be reversed, allowing return to healthy state

Frailty has three elements (Figure 2)

Frailty involves a decline not only in an individual's physical condition, but also in their mental and psychological well-being. This may take the form of a decline in cognitive abilities or depression, for example. Social factors, such as solitude and financial distress, must also be taken into account in its development.

Sarcopenia is considered to be the key factor in physical decline with age, resulting in muscle loss, and a decrease in muscular strength and physical function.

Diagnostic criteria for frailty (Table 1)

Physical frailty was determined according to the revision of the screening test utilized in the Obu Study Health Promotion for the Elderly[4]. The criteria for physical frailty were based on the presence or absence of the following 5 measurable characteristics: weakness (low grip strength: men < 26 kg, women < 18 kg); slowness (walking speed of < 1.0 m/sec over 6m at usual pace); weight loss (2-3kg in 6months); low physical activity; and exhaustion. An individual meeting 3 or more, 2 or 1, and none of these 5 characteristics was deemed to be at the frail, pre-frail, and non-frail stage, respectively.

Comprehensive geriatric assessment (CGA), which is commonly used to assess physical impairment in the elderly, is also useful for assessing frailty.

One study investigated outcomes in individuals scoring frail in more than 8 out of 25 items included in a kihon checklist applied in a survey conducted by the Ministry of Health, Labor and Welfare of Japan in 2010. The results showed that at 1 year later, the number of these individuals requiring support/ nursing care was 5 times greater than that in those who did not, while the number of deaths was 4 times greater[5].

Diagnostic criteria for sarcopenia (Figure 3)

Sarcopenia is defined according to a set of criteria developed by the Asian Working Group for Sarcopenia (AWGS)[6]. These criteria comprise the following 3 components: low handgrip strength (< 26 kg for men and < 18 kg for women); low gait speed (walking speed of < 0.8 m/sec at the usual space); and low muscle mass as assessed according to the skeletal muscle mass index (7.0 kg/m^2 for men and 5.7 kg/m^2 for women as measured by bioelectrical impedance: BIA).

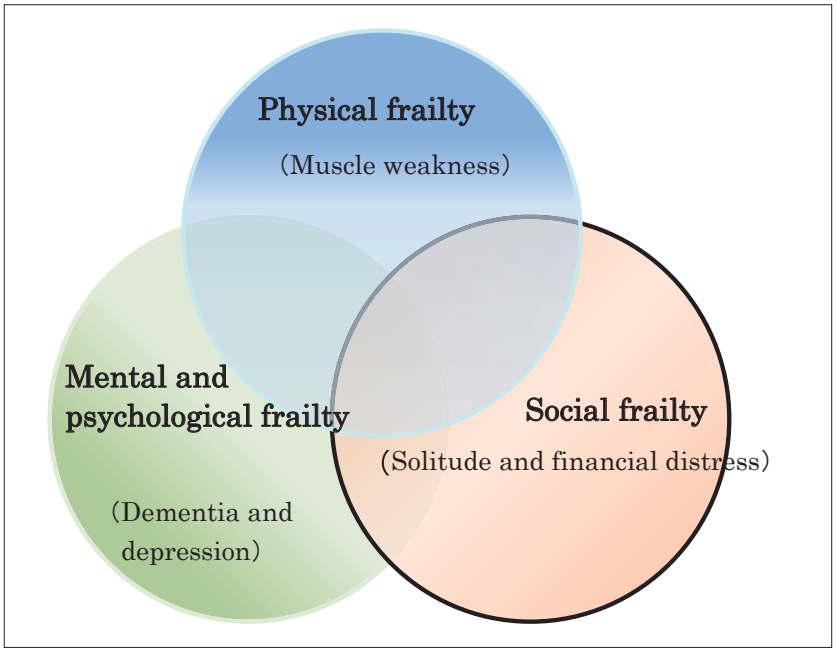


Figure 2 The three elements of frailty

Table 1　Diagnostic criteria for frailty

Evaluation method for frailty: Japanese-Cardiovascular Health Study (J-CHS) criteria

	Evaluation criteria
Weight loss	2~3 kg in 6 months
Muscle weakness	Grip strength：men＜26 kg, women＜18 kg
Exhaustion	(Last two weeks) I feel tired
Gait speed	Gait speed＜1.0 m/ s
Physical activity	① Do you exercise lightly? ② Do you exercise regularly? Answer "No" for both of the above

Number of applicable items
0 : healthy　　1~2：pre-frailty　　3 or more：frailty

Relationship between AD and frailty

A meta-analysis of studies investigating the relationship between AD and frailty revealed that the prevalence of frailty in patients with mild-to-moderate AD was between 11.1% and 50.0% (prevalence, 31.9%; 95% confidence interval; 15.7% to 48.5%)[7]. Moreover, the prevalence of frailty in patients with AD (31.9%) was higher than that in the general elderly (10%)[8].

One earlier study by our group investigating the prevalence of frailty in 140 outpatients with mild-to-moderate AD attending our memory clinic revealed that the ratio of frailty to pre-frailty in this group was 68% (frailty, 24%;pre-frailty, 44%)[9].

Relationship between AD and sarcopenia (Figure 4)

A cohort study of community-dwelling elderly revealed an association between cognitive function and skeletal muscle mass or motor function[10]. Muscle strength has been shown to be associated with mild

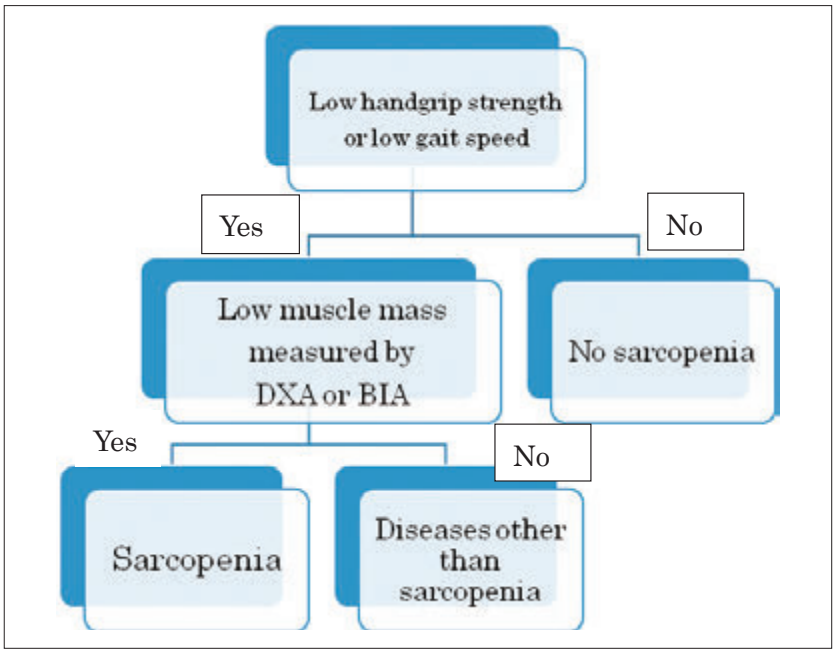


Figure 3　Diagnostic criteria for sarcopenia (AWGS2014)

cognitive impairment and the development of Alzheimer's dementia[11]. It has been reported that brain volume and lean mass are positively correlated in early AD patients[12].

One study by our group investigating the relationship between the severity of AD and the frequency of sarcopenia demonstrated that the frequency of sarcopenia increased with the progression of dementia, with the results showing that it was 12% in the healthy elderly (MMSE, 27 points), 39% in patients with early AD or mild cognitive impairment (MCI) (MMSE, 25 points), 46% in patients with mild AD (MMSE, 22 points), and 56% in patients with moderate AD (MMSE, 17 points)[13].

A decrease in lower extremity muscle strength and walking speed is already observed even in patients with early AD/MCI. One study showed that this decrease in strength was not only observed in the lower extremities, but also in the upper extremities in patients with moderate AD[13], indicating the need for intervention to be commenced from an early stage in the development of AD.

Prevalence of frailty status in patients with AD or AD + CVD

Frailty shows stronger association with AD+CVD than AD alone (Figure 5)

Cerebrovascular disease, such as lacunes and white matter lesions, is common in elderly patients with AD.In one study, our group compared the prevalence of physical frailty in patients with AD alone with that in those with AD accompanied by CVD. A total of 82 outpatients with AD alone (AD group) and 25 with AD accompanied by CVD (AD + CVD group) aged 65 years and older attending our memory clinic were enrolled.

The AD + CVD group showed a significantly higher frequency of frailty (40%) and pre-frailty (52%) than the AD group (frailty, 16%; pre-frailty, 38%).

The study also included an evaluation of sarcopenia in each group based on the above-mentioned criteria of the AWGS. The AD + CVD group showed a significantly higher frequency of sarcopenia (68%) than the AD group (30%)[14].

Further work by our group based on MRI and SPECT imaging suggested an association between frailty and small vessel disease pathology, including periventricular hyper-intensity, deep white matter hyper-intensity, and decreased regional cerebral blood flow (rCBF) in the anterior cingulate in patients with AD[15].

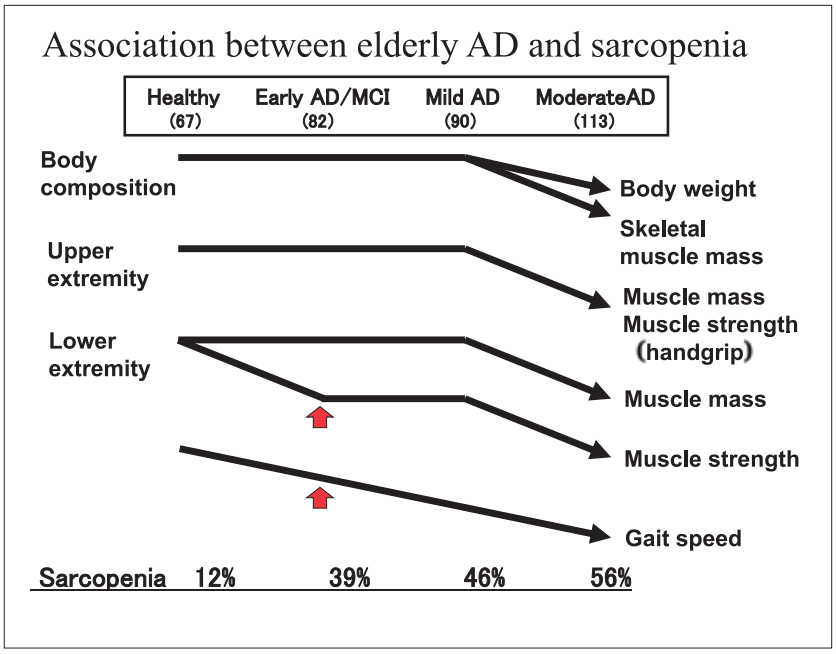


Figure 4 Sarcopenia and muscle function at various stages of Alzheimer's disease

Lower extremity muscle strength and walking speed already show decrease even in patients with early AD/MCI

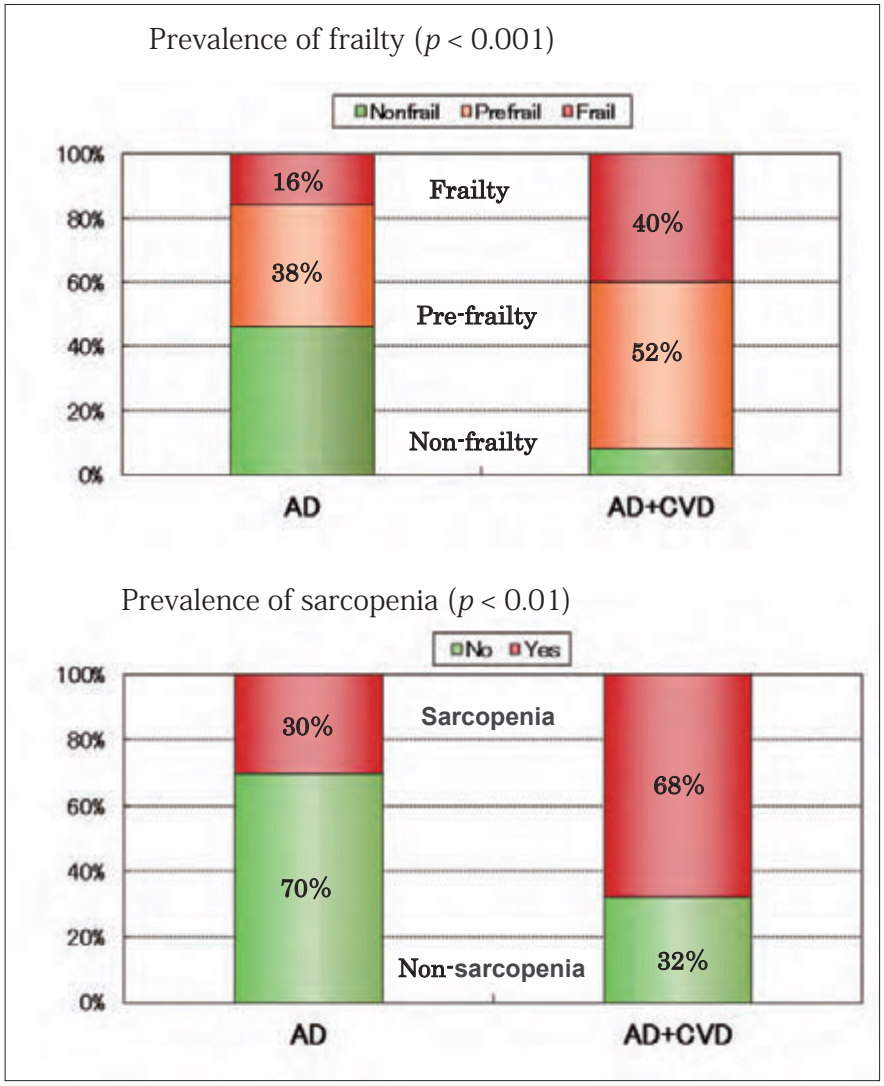


Figure 5 Prevalence of frailty and sarcopenia in AD and AD + CVD

Frailty and sarcopenia show stronger association with VaD or DLB than with AD (Figure 6)

In one study, our group investigated frailty and sarcopenia in patients with AD (24 men and 53 women; mean age, 83.0 ± 5.1 years), VaD (10 men and 12 women; mean age, 80.4 ± 5.0 years), or DLB (28 men and 20 women; mean age, 81.2 ± 5.5 years) using a relatively simple screening test (Dr. SUPERMAN)[16]. Our results showed a correlation between Lewy body dementia or vascular dementia and an increase in dysfunction, such as a reduction in ADL, falls, and upper and lower limb dysfunction compared with in AD[17].

A cross-sectional study of 654 local residents over the age of 75 years revealed that the risk of developing dementia from a state of frailty was 3.2 times the odds ratio (95% CI: 1.7 to 6.2) in patients with AD and 6.7 times the odds ratio (95% CI: 1.6 to 27.4) in those with vascular dementia[18].

Another study monitoring 5,480 people in three French cities over a period of 7 years found that the risk of developing dementia from a status of frailty was 1.22 times the odds ratio in patients with AD (95% CI: 0.80 to 1.86) and 2.50 times the odds ratio in those with VaD (95% CI: 1.01 to 6.19). Frailty thus showed a stronger association with VaD than with AD[19].

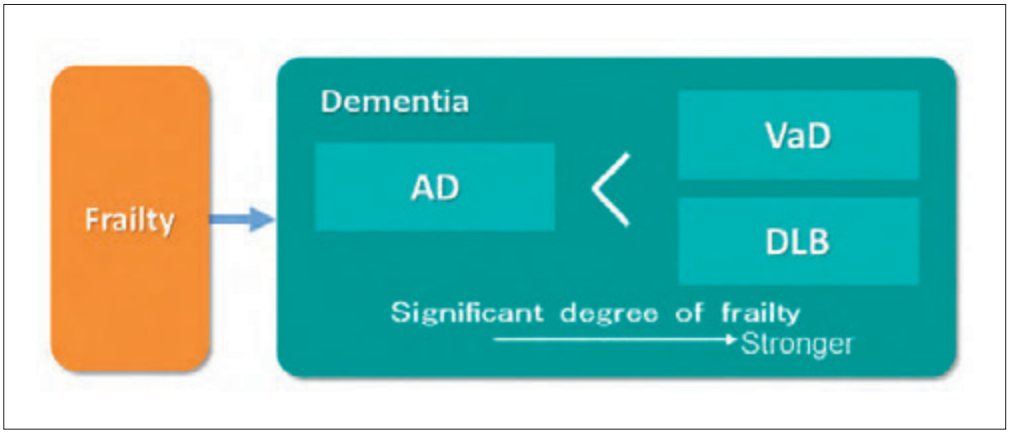


Figure 6 Relationship between frailty and dementia type

Common mechanisms for dementia, sarcopenia, and frailty

A systematic review investigating the relationship between frailty and cognitive impairment identified a number of common factors between them, including the presence of Alzheimer's pathology, reduced testosterone, poor nutrition, chronic inflammation, the risk of cerebrovascular disease, and depression[20].

Our group has shown that a greater degree of oxidative damage was found in AD with CVD than in AD alone[21].

Much work remains to be done on the relationship between frailty/sarcopenia and cognitive impairment, however, and further research is needed.

Conclusion

There is a close correlation between dementia and frailty/sarcopenia, with the combination believed to constitute a vicious cycle. In patients with dementia, the amount of physical activity decreases due to decreased motivation, and ADL decreases due to the appearance of muscle weakness and fatigue. On the other hand, it has been reported that ADL is reduced and the risk of developing dementia is high in frail elderly people.

This close relationship among frailty, sarcopenia, and dementia in the elderly, indicates the importance of preventive measures, including guidance on nutrition and exercise, in the elderly, and more research needs to be done on this issue.

Acknowledgments

The authors would like to thank Professor Jeremy Williams of the Department of International Medical Communications at Tokyo Medical University for editing and reviewing the English of this manuscript.

References

1. 2016 Basic Survey of National Life by Ministry of Health, Labor and Welfare.
2. Fried LP et al. Frailty in older adults: evidence for phenotype. J Gerontol A Biol Sci Med Sci 2001: 56A: M146-M156.
3. Kuzuya M et al. Nihon Rounen Igakukaizassi 2009; 46: 279-285.
4. Shimada H et al. Combined prevalence of frailty and mild cognitive impairment in a population of elderly Japanese people. J Am Med Dir Assoc 2013; 14: 518-524.
5. Satake et al. Validity of the Kihon Checklist for assessing frailty status. Geriatr Gerontol Int 2016; 16: 709-715.
6. Chen LK et al. Sarcopenia in Asia: consensus report of the Asian Working Group for sarcopenia. J Am Med Dir Assoc 2014; 15: 95-101
7. Kojima G, Liljas A, Iliffe S, et al:Prevalence of frailty in mild to moderate Alzheimer's disease: a systematic review and meta-analysis. Curr Alzheimer Res 2017; 14: 1256-1263.
8. Collard RM, Boter H, Schoevers RA, et al: Prevalence of frailty in community-dwelling older

persons: a systematic review. J Am Geriatr Soc 2012: 60: 1487-1492.

9. Namioka N, Hanyu H, Shimizu S, et al: Oxidative stress and inflammation are associated with physical frailty in patients with Alzheimer's disease.Geriatr Gerontol Int 2017; 17:913-918.
10. Bums JM et al. Reduced lean mass in early Alzheimer disease and its association with brain atrophy. Arch Neurol 2010; 67: 428-433.
11. Auyeung TW, Kwok T, Lee J, et al. Functional decline in cognitive impairment-the relationship between physical and cognitive function. Neuroepidemiology 2008; 31 :167-173
12. Boyle PA, Buchman AS, Wilson RS, et al. Association of muscle strength with the risk of Alzheimer's disease and the rate of cognitive decline in community-dwelling older persons. Arch Neurol 2009; 66:1339-1344.
13. Ogawa Y, Kaneko Y, Hanyu H, et al. Sarcopenia and muscle functions at various stages of Alzheimer's disease. Front Neurol 2018 Aug 28; 9: 710. doi:10, 3389/ fneur.2018.00710
14. Hirose D, Hanyu H, Sakurai H, et al.: Frailty and sarcopenia in subjects with Alzheimer's disease with or without cerebrovascular disease. Geriatr Gerontol Int 2016; 16: 653-654.
15. Hirose D, Shiizu S, Hanyu H, et al. Neuroimaging Characteristics of frailty status in patients with Alzheimer's disease.
J Alzheimers Dis 2019; 67:1201-1208
16. Iwamoto T, Hnyu H, Umahara T et al.: Newly developed comprehensive geriatric assessment initiative "Dr. SUPERMAN" as a convenient screening test. Geriatr Gerontol Int 2013; 13:811-812.
17. Namioka N, Hanyu H, Hatanaka H, et al.: Comprehensive geriatric assessment in elderly patients with dementia. Geriatr Gerontol Int 2015; 15:27-33.
18. Kulmala J et al: Association between Frailty and Dementia: a population-based study. Gerontology 2014; 60: 16-21.
19. Avila-Funes JA et al: Is frailty a prodromal stage of vascular dementia? Results from the Three-City Study. J Am Geriatr Soc 2012; 60: 1708-1712.
20. Robertson DA, Savva GM, Kenny RA: Frailty and cognitive impairment-a review of the evidence and causal mechanisms. Ageing Res Rev 2013; 12: 840-851.
21. Hatanaka H, Hanyu H, Hirose D et al. Peripheral oxidative stress markers in individuals with Alzheimer's disease with or without cerebrovascular disease. J Am Geriatr Soc 2015; 63: 1472-1474.

Review article

Exploring Interventional Strategies for Vascular Dementia

Yoshiki Hase, MD, PhD ; Raj N Kalaria, FRCP, PhD

Neurovascular Research Group, Translational and Clinical Research Institute, Newcastle University, Newcastle upon Tyne, United Kingdom

Short title :

Novel Therapeutic target for Vascular Dementia

Disclosures:

YH and RNK declare no conflict of interests concerning this study. Our work is supported by grants from the Medical Research Council (MRC, G0500247), Newcastle Centre for Brain Ageing and Vitality (BBSRC, EPSRC, ESRC and MRC, LLHW), and Alzheimer's Research UK (ARUK, PG2013–022). Tissue for this study was collected by the Newcastle Brain Tissue Resource, which is funded in part by a grant from the UK MRC (G0400074), by the Newcastle NIHR Biomedical Research Centre in Ageing and Age Related Diseases award to the Newcastle upon Tyne Hospitals NHS Foundation Trust, and by a grant from the Alzheimer's Society and ART as part of the Brains for Dementia Research Project. YH was supported by SENSHIN Medical Research Foundation, Osaka, Japan and The Great Britain Sasakawa Foundation, London, United Kingdom.

Abstract:

Vascular dementia (VaD) is regarded as the second most common type of dementia but recent surveys suggest vascular cognitive impairment (VCI) is even more frequent in most populations worldwide. White matter hyperintensities (WMHs) detected on brain MRI are the radiological signature of cerebral small vessel disease (SVD), which is highly characteristic in subcortical ischaemic vascular dementia (SIVD), the most prevalent subtype of VaD. Vascular risk factors are strongly associated with WMHs and development of post-stroke VaD or dementia. The gliovascular unit (GVU) has a critical role in SIVD. Therefore, any component of the GVU could be a therapeutic target for VaD. When considering pharmacological approaches, more attentions ought to be paid onto pleiotropic effects of existing drugs. Autonomic dysfunction is highly prevalent in VaD patients and is a treatable factor to protect GVU from VaD pathologies. As non-pharmacological approaches for VaD, environmental enrichment (EE) and physical exercise training, particularly limited EE rather than full-time EE, have been proved to preserve GVU integrity in VaD. Glial responses, especially clasmatodendrosis, would be a novel therapeutic target for VaD. Animal models of VaD are useful to demonstrate pathophysiology, explore and establish safe and effective treatments. Nevertheless, pathophysiological substrate of VaD is heterogeneous. Multimodal combination treatments targeting GVU, implementing both pharmacological and non-pharmacological interventions, would be a promising interventional strategy to counter vascular dementia.

Key Words:

Animal model, Chronic cerebral hypoperfusion, Environmental enrichment, Gliovascular unit, Vascular dementia,

Corresponding Author:

Name: Dr. Yoshiki Hase, MD, PhD

Address: Translational and Clinical Research Institute, Newcastle University, Campus for Ageing and Vitality, Newcastle upon Tyne, NE4 5PL, United Kingdom

TEL: +44(0)1912081218

Email: yoshiki.hase@newcastle.ac.uk

Introduction

Current trends suggest a high burden of cerebrovascular disorders worldwide that is concomitant with increased frequency of vascular cognitive impairment (VCI). There is no cure for VCI or for vascular dementia (VaD), the second most common type of dementia among the ageing population (1). It is therefore timely that safe and effective interventional strategies, which delay onset, slow down cognitive decline in patients with cerebrovascular disorders, or reduce the burden of VaD are implemented urgently. Subcortical ischaemic vascular dementia (SIVD) is the most prevalent subtype of VaD, where elderly exhibit disability and deficits in cognitive function over long periods of their remaining lives (2)(3). SIVD is primarily characterised by cerebral small vessel disease (SVD), which is described by a variety of pathologies including lacunar infarcts, microinfarcts, microbleeds and white matter (WM) lesions (4)(5)(6). It is thought that diffuse WM changes linked to SIVD largely result from a chronic hypoperfusive state or cerebrovascular insufficiency during ageing (7)(8). While the pathological mechanisms that lead to the progression of VCI because of SIVD or post-stroke patients who develop dementia remain unclear, it is urgent to target strategies, which restore or maintain brain perfusion. In this article, we will review the latest findings regarding pathogenesis and potential novel interventional strategies for VCI and VaD.

Vascular risk factors (VRFs) and dementia

It is now abundantly clear that reducing risk of vascular disease reduces risk of cognitive impairment or dementia. Several longitudinal studies suggest that the strongest predictors for development of dementia after stroke was the presence of cardiovascular risk factors. In our large longitudinal prospective cohort of the Cognitive Function After Stroke (CogFAST) study (9) in elderly stroke survivors, who predominantly had small infarcts or SVD type of changes, we found that during the mean follow-up period of ~4 years, up to 25% of subjects developed dementia after their first episode of stroke. At baseline, none of them had confirmed to have dementia. Neuroimaging and post-mortem investigations revealed that more than 75% who developed dementia could be diagnosed to have VaD, lacking significant Alzheimer type of pathology. The study remarkably revealed that the strongest predictors of dementia after stroke was multiple (two or more) cardiovascular risk factors including hypertension, hyperlipidemia and diabetes mellitus. This fact implies that risk to developing dementia after stroke is strongly related to the presence of vascular risk factors and VaD type of pathology. We also found that cognitive processing speed and performance on measures of attention were significantly associated with greater white matter hyperintensities (WMH) volumes, particularly in the frontal lobe regions and were worse in those with hypertension (10). We further found that the presence of an APOE epsilon4 allele was associated with greater progression of cognitive decline in stroke survivors. This also has implications for interventions aimed at the secondary prevention of dementia in stroke patients (11). However, in clinical settings, extensive treatment or control of vascular risk factors in old age is essential to prevent or slow down the progression of VCI and prevent VaD (3).

Small vessel disease (SVD) as an important target

We note that cerebral SVD manifests in several cortical and subcortical insults. However, microvascular abnormalities are key to SVD. Microvascular changes including arteriolosclerosis, intimal thickening, fibroid necrosis, hyalinization, and enlarged perivascular spacing occurring during ageing but these lesions are at their peak or most severe in VaD. These changes are also prominent in post-stroke survivors, who develop dementia (PSD) and those who do not (PSND). While it is difficult to differentiate the burden of these lesions between PSD and PSND, it is noteworthy that they both exhibit higher total vascular pathology scores (12) compared to normal ageing control subjects (13). With the microvascular network, even capillaries are affected particularly in the rarefied white matter (WM) in both

PSD and VaD (14). Collapsed and string microvessels, microaneurysm-like structures and tortuous vessels were frequently observed in patients with PSD and VaD. In terms of tissues changes, greater frontal WM volumes separate post-stroke survivors who develop dementia or PSD versus those who remain stable (PSND). Among post-stroke patients, we also noted that the prevalence of microinfarcts was greater in PSD compared to PSND subjects, suggesting the presence of cerebral microinfarcts is one of the predictors of dementia after stroke (9).

There is evidence that SVD pathology may also be exacerbated by autonomic dysfunction. Our recent study also revealed detrimental effects of autonomic dysfunction on severity of VaD and other dementias (13). At least 40% of dementia patients, including VaD patients, exhibit some form of autonomic dysfunction in life (15). The proposed mechanism of autonomic dysfunction on vascular pathology is that recurrent episodic hypotension promotes chronic cerebral hypoperfusion. This then causes ischaemic damage or rarefaction of the WM, and eventually leads to disconnection of the WM and impaired cognitive function (16). In our study, autonomic dysfunction was associated with higher burden of SVD changes, particularly in the deep frontal WM in patients with age-related dementia including VaD (13). We emphasize the importance of screening autonomic function for elderly dementia, especially VaD patients in clinics. The most critical finding was that in some cases, autonomic dysfunction is likely 'asymptomatic' (17). Thus, there are dementia patients who have no apparent clinical symptoms of autonomic dysfunction e.g. repeated falls and syncope. These individuals could be only proved to have dysautonomia by clinical examination. However, 'asymptomatic' autonomic dysfunction also has the same adverse effects on cerebrovascular pathology as symptomatic dysautonomia. Therefore, 'asymptomatic' autonomic dysfunction is also a risk to develop SVD and WM damage, similar to symptomatic dysautonomia. Treatments to improve autonomic dysfunction, even for preciously detected 'asymptomatic autonomic dysfunction' cases, implementing lifestyle intervention or pharmacological approaches or combination of both would ameliorate SVD pathology and contribute to prevent or slow down cognitive decline in patients diagnosed with VaD and have features of autonomic dysfunction. Collectively, these findings strongly implicate that ischemic insults or chronic cerebral hypoperfusion cause or worsen ageing associated SVD and VaD.

Loss of white matter integrity in VaD

White matter hyperintensities (WMH), detected on brain magnetic resonance imaging (MRI) of T2-weighted imaging (T2WI) and fluid-attenuation inversion recovery (FLAIR) imaging, are associated with cognitive dysfunction in patients with SVD, stroke and VaD (18), most probably due to loss of white matter integrity. In our longitudinal CogFAST cohort, volume of WMHs were associated with higher mortality rate, shorter time to dementia onset, and were also an independent predictor of survival to dementia (19). These findings indicate that severity of WMHs is related to loss of white matter integrity and impairment in functional connectivity within cortical-subcortical circuits to instigate dementia and reduced life expectancy after stroke.

The pathophysiological substrates of WMH are heterogeneous (20). One of the key features of WMH is loss of myelin rather than axonal degeneration. We have previously reported severe myelin loss in the frontal white matter of VaD patients compared to other types of age-related dementias (5), suggesting disruptions of frontal-subcortical circuits are more profound in VaD compared to other dementias (21). This observation is consistent with finding from a study showing decreased myelin proteins in the WM in SVD and VaD (22). Loss of oligodendrocytes as another substrate of WMH (20) is frequently observed in SVD and VaD patients (23).

Other substrates of WMH are inflammatory changes, evident in form of gliosis including astrogliosis, causing gliovascular unit (GVU) dysfunction and blood brain barrier (BBB) disruption (20). The GVU (Figure 1) controls and maintains the functions of the BBB. The cellular components of the

GVU in the white matter (WM), consists of endothelial cell, pericyte, astrocyte, microglia and oligodendrocyte (23). In physiological conditions, these cells are interacting each other to maintain brain homeostasis through BBB. Loss or damage of microvascular, mural and glial cells caused by ischemic injury or chronic cerebral hypoperfusion results in dysfunction of GVU (24) and increased BBB permeability, which may promote diffuse WM changes and cognitive decline (25). Cilostazol, a phosphodiesterase type Ⅲ inhibitor, restored BBB damage in an experimental stroke model in mice (26). EE also showed protective effect on BBB in a rat model of chronic cerebral hypoperfusion (27). Therefore, protection of GVU or its cellular components, especially in the WM, would be a key strategy to preserve BBB and WM integrity, as well as to prevent subsequent strokes and cognitive decline.

Astrogliosis, clasmatodendrosis and disruption of GVU

Astrocytes, one of the major cellular components of the GVU, maintain brain homeostasis by interacting with blood vessels via astrocytic end-feet. Perivascular end-feet of astrocytes have a critical role to regulate e.g. electrolytes, amino acids and water homeostasis in brain (28). The water homeostasis in brain is regulated by water channel family aquaporins (29). Aquaporin-4 (AQP4) is present on astrocytic end-feet surrounding small vessels in brain and exchanging water between vascular lumen and brain parenchyma. AQP4 also play a role in pathologic conditions, e.g. reduce oedema formation after cerebral ischemia (30).

Astrocytes are sensitive to various stimuli and transform to reactive cells as activated astrogliosis, often observed in response to ischaemic insults (31). Previous reports suggest that reactive astrocytes caused elevated reactive oxygen species (ROS) and induced cellular inflammation (32), which progresses to more widespread brain injury (33). Therefore, targeting of astrocytes which may return reactive astrocytes to a quiescent phenotype (31) would represent a therapeutic target for VaD. Recent report showed that the opioid analgesic oxycodone suppressed detrimental reactive astrogliosis by inhibiting nuclear factor kappa-B (NF- κ B) signaling in reactive astrocytes (34).

A phenomenal morphological change in astrocytes is described as clasmatodendrosis, a cluster of damaged astrocytes (clasmatodendrocytes) with hypertrophic cell bodies and loss of or retracted processes (35). We previously found the presence of severe clasmatodendrosis in the deep WM of post-stroke survivors who developed dementia, and also had greater WM hyperintensity (WMH) volumes (19). Similar astrocytopathy was observed in patients with hereditary cerebrovascular disease, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) (36). CADASIL is also characterized by strategic WMH detected on brain MRI. Therefore, clasmatodendrosis is one of the key pathophysiological markers of progressing WM lesions. In addition to clasmatodendrosis, abnormal distribution of AQP4, characterised by aggregation of AQP4 at the periphery of GFAP-positive astrocytes/clasmatodendrocytes, was evident in post-stroke survivors who developed dementia with greater WMH compared with age-matched normal control subjects (19). These observations strongly implicate that clasmatodendrosis and AQP4 dislocation in VaD patients is caused by vascular changes, pathological alterations in GVU and BBB disruption.

Animal model of small vessel disease (SVD) and vascular dementia (VaD)

For the past decades, experimental animal models of cerebral hypoperfusion (37), which restrict cerebral blood flow by occluding or narrowing cervical and cerebral arteries, have been extensively analysed in mice (38), (39), (40), rats (41), (42), (43), (44), (45), (46), gerbils (47), as well as non-human primates (19), aiming to elucidate the pathological mechanisms of developing SVD and VaD. In addition to these models, bilateral common carotid artery stenosis (BCAS) in mice, as a mouse model of chronic cerebral

hypoperfusion, has been established (48), (49). BCAS mouse model exhibited BBB dysfunction (50), changes in glial cells such as: loss of oligodendrocytes, astrogliosis and microglial proliferation, particularly in the WM, as well as hippocampal pathology (51). As BCAS model characterises similar cerebrovascular pathologies to human VaD patients, it has been widely used and has been accepted as one of the most useful rodent models of VaD (52), (53), (54).

Bilateral common carotid artery stenosis (BCAS) mouse model to explore potential treatments and interventions

The BCAS mouse model has been very useful to uncover pleiotropic effects of pharmacological agents, role of genes and cell therapy against SVD and VaD. For example, BCAS has been utilised to evaluate efficacies of an anti-platelet agent cilostazol, phosphodiesterase type 3 (PDE3) inhibitor (55), (56); anti-hypertensive drug: telmisartan, an angiotensin Ⅱ type 1 receptor blocker (57); an antibiotic agent: minocycline, tetracycline (58); an angiogenic peptide: adrenomedullin (59); a gene silencer: silent information regulator 2 homolog 1 (SIRT1) (60), (61) and bone marrow derived mononuclear cells (62). All of these compounds and agents showed protective effects on cerebrovascular pathologies, WM changes and cognitive decline induced by BCAS, suggesting these are promising interventional strategies to ameliorate VaD pathologies. Notably, a recent study proved that cilostazol, a phosphodiesterase type 3 (PDE3) inhibitor, slowed down cognitive decline in patients with mild cognitive impairment (63), and has been successfully applied for a prospective multi-center clinical trial (64).

Our past studies have also successfully reproduced WM changes similar to VCI and VaD patients in the long-term version of the BCAS model (65). We explored the effects of differing degrees of environmental enrichment (EE) on WM pathological changes. Long-term BCAS in mice caused WM damage characterised by WM atrophy, WM disintegration and loss of oligodendrocytes, resulted in cognitive dysfunction. These unfavourable changes were attenuated by EE more effectively by limited exposure to EE (only 3 hours a day) rather than full-time (24 hours a day) exposure to EE. Thus EE, especially limited amount of EE and physical exercise training, appears a safe and effective interventional strategy for VaD patients with extensive WM pathology.

Physical activity or exercise has been shown as a strategy to slow down cognitive impairment in humans with VCI (66). Previous experimental evidence a rat model of chronic cerebral hypoperfusion showed that environment-induced physical exercise and cognitive stimulation as well as social interactions, which are incorporated in EE and physical exercise training, exhibit beneficial effects on cognitive dysfunction (27), (67), (68). These studies reported that EE preserved BBB integrity, increased brain plasticity, enhanced neurogenesis, and increased synaptogenesis. Furthermore, combination of EE and physical exercise enhanced neurogenesis (69) and upregulation of genetic expressions associated with neurogenesis, synaptic plasticity, neuroprotection and intact memory function (70), resulted in preserved cognitive function (71). EE also has been reported to have favourable effects on motor function recovery after experimental stroke (72), (73). Thus, EE and even moderate physical exercise training could be safely and consistently encouraged in man and therefore an effective interventional strategy for patients with SVD, VaD and stroke.

Our research group has also successfully replicated astrocytopathy, including reactive astrocytes and clasmatodendrosis with aberrant distribution of AQP4, similar to VaD patients in the BCAS model (74) as well as in a non-human primate model of cerebral hypoperfusion (19). Long-term BCAS in mice caused astrogliosis, clasmatodendrosis with AQP4 dysfunction in the WM. AQP4 dislocation and clasmatodendrosis may enhance WM pathology due to the disturbance of water homeostasis. We found that limited regime of EE not only reduced astrocytopathy but ameliorated other aspects of GVU functions (74). Thus, glial responses, especially clasmatodendrosis, would be a new aspect to explore

pathogenesis and establish novel treatment for VaD. This suggests limited exposure to EE preserves BBB function via maintenance of GVU integrity. We surmise that long-term BCAS is a relatively reliable model of VaD, which accurately replicates several features of the pathophysiology of WM changes as evident in VaD patients. EE, especially limited amount of EE and physical exercise training, appears a safe and effective interventional strategy to attenuate unfavourable effects of cerebral hypoperfusion and slow down subsequent cognitive decline in VaD.

Conclusions

We have reviewed pertinent findings regarding the pathogenesis of VaD and its potential therapeutic targets. Gliovascular disruption caused by ischemic insults or chronic cerebral hypoperfusion has been suggested to play critical role to develop VaD pathology in brain. Therefore, each component of GVU would be a therapeutic target for VaD. Firstly, strict control of VRFs is essential to protect GVU from VaD pathology. It is also important to explore and establish safe and effective strategies. Pharmacological approaches, which value more for pleiotropic effects of existing drugs e.g. antiplatelet agents such as cilostazol, or antihypertensive drugs such as angiotensin Ⅱ receptor antagonists, would be ideal in terms of safety point of view and cost effectiveness. Secondary, autonomic dysfunction, even asymptomatic dysautonomia, should be highly considered as a treatable factor to ameliorate small vessel disease (SVD) pathology in patients with VaD. Finally, non-pharmacological approaches comprising EE, physical exercise training, social interactions and mental activity would be effective interventional strategies for VaD. Nonetheless, we ought to be aware that the pathophysiology of VaD is heterogeneous and therefore, just one intervention may not be sufficiently efficacious. Large-scale prospective clinical trials in well-characterised cohorts would be required, a combination of multimodal interventions implementing pharmacological and non-pharmacological interventions (Figure 2) would be promising interventional strategies to prevent VaD, and likely to impact on processes involved in other ageing-related dementias.

Conflict of interest

The authors declare no conflict of interest

Acknowledgement

We are grateful to the patients, families, and clinical house staff for their cooperation in the investigation of this study. We also appreciate the cooperation of the Newcastle Brain Tissue Resource (NBTR) directors and staff in assisting us with this study. We are thankful to Janet Slade and Arthur Oakley for the expert technical assistance and for assisting us in managing and screening the cohort. We specially thank Neil Hamilton and Sandra Hogg for excellent technical assistance with respect to the daily care of mice and animal husbandry.

References

1. Kalaria RN. Neuropathological diagnosis of vascular cognitive impairment and vascular dementia with implications for Alzheimer's disease. Vol. 131, Acta Neuropathologica. Springer Verlag; 2016. p. 659–85.
2. Román GC, Erkinjuntti T, Wallin A, et al. Subcortical ischaemic vascular dementia. Vol. 1, Lancet Neurology. Lancet Publishing Group; 2002. p. 426–36.
3. Hachinski V, Iadecola C, Petersen RC, et al. National Institute of Neurological Disorders and Stroke-Canadian Stroke Network vascular cognitive impairment harmonization standards. Stroke. 2006 Sep;37(9):2220–41.
4. Wardlaw JM, Smith EE, Biessels GJ, et al. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. Vol. 12, The Lancet Neurology. 2013. p. 822–38.
5. Ihara M, Polvikoski TM, Hall R, et al. Quantification of myelin loss in frontal lobe white matter in vascular dementia, Alzheimer's disease, and dementia with Lewy bodies. Acta Neuropathol [Internet]. 2010 May [cited 2019

Dec 2];119(5):579–89. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20091409

6. Pantoni L. Cerebral small vessel disease: from pathogenesis and clinical characteristics to therapeutic challenges. Vol. 9, The Lancet Neurology. 2010. p. 689–701.
7. Pantoni L. 2001-2011: A decade of the LADIS (leukoaraiosis and DISability) study: What have We learned about white matter changes and small-vessel disease? Vol. 32, Cerebrovascular Diseases. 2011. p. 577–88.
8. Longstreth WT, Manolio TA, Arnold A, et al. Clinical correlates of white matter findings on cranial magnetic resonance imaging of 3301 elderly people: The cardiovascular health study. Stroke. 1996;27(8):1274–82.
9. Allan LM, Rowan EN, Firbank MJ, et al. Long term incidence of dementia, predictors of mortality and pathological diagnosis in older stroke survivors. In: Brain. Oxford University Press; 2011. p. 3713–24.
10. Burton EJ, Kenny RA, O'Brien J, et al. White matter hyperintensities are associated with impairment of memory, attention, and global cognitive performance in older stroke patients. Stroke. 2004 Jun;35(6):1270–5.
11. Ballard CG, Morris CM, Rao H, et al. APOE ε4 and cognitive decline in older stroke patients with early cognitive impairment. Neurology. 2004 Oct 26;63(8):1399–402.
12. Deramecourt V, Slade JY, Oakley AE, et al. Staging and natural history of cerebrovascular pathology in dementia. Neurology. 2012 Apr 3;78(14):1043–50.
13. Hase Y, Polvikoski TM, Firbank MJ, et al. Small vessel disease pathological changes in neurodegenerative and vascular dementias concomitant with autonomic dysfunction. Brain Pathol. 2019;doi: 10.11.
14. Hase Y, Ding R, Harrison G, et al. White matter capillaries in vascular and neurodegenerative dementias. Acta Neuropathol Commun. 2019 Feb 7;7(1):16.
15. Allan L, McKeith I, Ballard C, et al. The prevalence of autonomic symptoms in dementia and their association with physical activity, activities of daily living and quality of life. Dement Geriatr Cogn Disord. 2006 Aug;22(3):230–7.
16. Sambati L, Calandra-Buonaura G, Poda R, et al. Orthostatic hypotension and cognitive impairment: A dangerous association? Neurol Sci. 2014;35(6):951–7.
17. Merola A, Romagnolo A, Rosso M, et al. Orthostatic hypotension in Parkinson's disease: Does it matter if asymptomatic? Park Relat Disord. 2016 Dec 1;33:65–71.
18. Debette S, Markus HS. The clinical importance of white matter hyperintensities on brain magnetic resonance imaging: Systematic review and meta-analysis. Vol. 341, BMJ (Online). 2010. p. c3666.
19. Chen A, Akinyemi RO, Hase Y, et al. Frontal White matter hyperintensities, clasmatodendrosis and gliovascular abnormalities in ageing and post-stroke dementia. Brain. 2016 Jan 1;139(1):242–58.
20. Gouw AA, Seewann A, Van Der Flier WM, et al. Heterogeneity of small vessel disease: A systematic review of MRI and histopathology correlations. Vol. 82, Journal of Neurology, Neurosurgery and Psychiatry. BMJ Publishing Group; 2011. p. 126–35.
21. Swartz RH, Stuss DT, Gao F, et al. Independent cognitive effects of atrophy and diffuse subcortical and thalamico-cortical cerebrovascular disease in dementia. Stroke. 2008 Mar;39(3):822–30.
22. Barker R, Wellington D, Esiri MM, et al. Assessing white matter ischemic damage in dementia patients by measurement of myelin proteins. J Cereb Blood Flow Metab. 2013 Jul;33(7):1050–7.
23. Hase Y, Horsburgh K, Ihara M, et al. White matter degeneration in vascular and other ageing-related dementias. Vol. 144, Journal of Neurochemistry. Blackwell Publishing Ltd; 2018. p. 617–33.

24. Holland PR, Searcy JL, Salvadores N, et al. Gliovascular disruption and cognitive deficits in a mouse model with features of small vessel disease. J Cereb Blood Flow Metab [Internet]. 2015 Jun [cited 2019 Dec 2];35(6):1005–14. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25669904
25. Nation DA, Sweeney MD, Montagne A, et al. Blood–brain barrier breakdown is an early biomarker of human cognitive dysfunction. Vol. 25, Nature Medicine. Nature Publishing Group; 2019. p. 270–6.
26. Hase Y, Okamoto Y, Fujita Y, et al. Cilostazol, a phosphodiesterase inhibitor, prevents no-reflow and hemorrhage in mice with focal cerebral ischemia. Exp Neurol. 2012 Jan;233(1):523–33.
27. Qu C, Xu L, Shen J, et al. Protection of blood-brain barrier as a potential mechanism for enriched environments to improve cognitive impairment caused by chronic cerebral hypoperfusion. Behav Brain Res. 2019 Nov;379(DOI: 10.1016/j.bbr.2019.112385): 112385.
28. Abbott NJ, Rönnbäck L, Hansson E. Astrocyte-endothelial interactions at the blood-brain barrier. Vol. 7, Nature Reviews Neuroscience. 2006. p. 41–53.
29. Badaut J, Lasbennes F, Magistretti PJ, et al. Aquaporins in brain: Distribution, physiology, and pathophysiology. Vol. 22, Journal of Cerebral Blood Flow and Metabolism. Lippincott Williams and Wilkins; 2002. p. 367–78.
30. Taniguchi M, Yamashita T, Kumura E, et al. Induction of aquaporin-4 water channel mRNA after focal cerebral ischemia in rat. Mol Brain Res. 2000 May 31;78(1–2):131–7.
31. Choudhury GR, Ding S. Reactive astrocytes and therapeutic potential in focal ischemic stroke. Vol. 85, Neurobiology of Disease. Academic Press Inc.; 2016. p. 234–44.
32. Nahirnyj A, Livne-Bar I, Guo X, et al. ROS detoxification and proinflammatory cytokines are linked by p38 MAPK signaling in a model of mature astrocyte activation. PLoS One. 2013 Dec 23;8(12).
33. Sofroniew M V., Vinters H V. Astrocytes: Biology and pathology. Vol. 119, Acta Neuropathologica. 2010. p. 7–35.
34. Zhou L, Fan L, Kong C, et al. Oxycodone suppresses the lipopolysaccharide-induced neuroinflammation by downregulating nuclear factor- κ B in hippocampal astrocytes of Sprague-Dawley rats. Neuroreport. 2020 Jan 27;31(2):99–108.
35. Tomimoto H, Akiguchi I, Suenaga T, et al. Alterations of the blood-brain barrier and glial cells in white-matter lesions in cerebrovascular and Alzheimer's disease patients. Stroke. 1996;27(11):2069–74.
36. Hase Y, Chen A, Bates LL, et al. Severe white matter astrocytopathy in CADASIL. Brain Pathol. 2018 Nov 1;28(6):832–43.
37. Washida K, Hattori Y, Ihara M. Animal Models of Chronic Cerebral Hypoperfusion: From Mouse to Primate. Int J Mol Sci [Internet]. 2019 Dec 7 [cited 2019 Dec 10];20(24):6176. Available from: https://www.mdpi.com/1422-0067/20/24/6176
38. Hattori Y, Kitamura A, Nagatsuka K, et al. A novel mouse model of ischemic carotid artery disease. PLoS One. 2014 Jun 18;9(6).
39. Hattori Y, Kitamura A, Tsuji M, et al. Motor and cognitive impairment in a mouse model of ischemic carotid artery disease. Neurosci Lett. 2014 Oct 3;581:1–6.
40. Hattori Y, Enmi JI, Kitamura A, et al. A novel mouse model of subcortical infarcts with dementia. J Neurosci. 2015;35(9):3915–28.
41. Kalaria RN, Bhatti SU, Palatinsky EA, et al. Accumulation of the β amyloid precursor protein at sites of ischemic injury in rat brain. Neuroreport. 1993;4(2):211–4.
42. Wakita H, Tomimoto H, Akiguchi I, et al. Glial activation and white matter changes in the rat brain induced by chronic cerebral hypoperfusion: an immunohistochemical study. Acta Neuropathol. 1994 May;87(5):484–92.
43. Wakita H, Tomimoto H, Akiguchi I, et al.

Protective effect of cyclosporin a on white matter changes in the rat brain after chronic cerebral hypoperfusion. Stroke. 1995;26(8):1415–22.

44. Farkas E, Donka G, de Vos RAI, et al. Experimental cerebral hypoperfusion induces white matter injury and microglial activation in the rat brain. Acta Neuropathol. 2004 Jul;108(1):57–64.
45. Kitamura A, Fujita Y, Oishi N, et al. Selective white matter abnormalities in a novel rat model of vascular dementia. Neurobiol Aging. 2012;33(5):1012.e25-1012.e35.
46. Kitamura A, Saito S, Maki T, et al. Gradual cerebral hypoperfusion in spontaneously hypertensive rats induces slowly evolving white matter abnormalities and impairs working memory. J Cereb Blood Flow Metab. 2016 Sep 1;36(9):1592–602.
47. Kudo T, Tada K, Takeda M, et al. Learning impairment and microtubule-associated protein 2 decrease in gerbils under chronic cerebral hypoperfusion. Stroke. 1990;21(8):1205–9.
48. Shibata M, Ohtani R, Ihara M, et al. White matter lesions and glial activation in a novel mouse model of chronic cerebral hypoperfusion. In: Stroke. 2004. p. 2598–603.
49. Shibata M, Yamasaki N, Miyakawa T, et al. Selective impairment of working memory in a mouse model of chronic cerebral hypoperfusion. Stroke. 2007 Oct;38(10):2826–32.
50. Nakaji K, Ihara M, Takahashi C, et al. Matrix metalloproteinase-2 plays a critical role in the pathogenesis of white matter lesions after chronic cerebral hypoperfusion in rodents. Stroke. 2006 Nov;37(11):2816–23.
51. Nishio K, Ihara M, Yamasaki N, et al. A mouse model characterizing features of vascular dementia with hippocampal atrophy. Stroke. 2010 Jun;41(6):1278–84.
52. Ihara M, Tomimoto H. Lessons from a mouse model characterizing features of vascular cognitive impairment with white matter changes. Vol. 2011, Journal of Aging Research. 2011. p. doi; 10.4061/2011/9878761.
53. Ihara M, Taguchi A, Maki T, et al. A Mouse Model of Chronic Cerebral Hypoperfusion Characterizing Features of Vascular Cognitive Impairment. Methods Mol Biol. 2014;1135:95–102.
54. Madigan JB, Wilcock DM, Hainsworth AH. Vascular contributions to cognitive impairment and dementia: Topical review of animal models. Vol. 47, Stroke. Lippincott Williams and Wilkins; 2016. p. 1953–9.
55. Kitamura A, Manso Y, Duncombe J, et al. Long-term cilostazol treatment reduces gliovascular damage and memory impairment in a mouse model of chronic cerebral hypoperfusion. Sci Rep. 2017 Dec 1;7(1).
56. Ohtomo R, Bannai T, Ohtomo G, et al. Cilostazol alleviates white matter degeneration caused by chronic cerebral hypoperfusion in mice: Implication of its mechanism from gene expression analysis. Neurosci Lett. 2018 Jan 1;662:247–52.
57. Washida K, Ihara M, Nishio K, et al. Nonhypotensive dose of telmisartan attenuates cognitive impairment partially due to peroxisome proliferator-activated receptor-γ activation in mice with chronic cerebral hypoperfusion. Stroke. 2010 Aug;41(8):1798–806.
58. Manso Y, Holland PR, Kitamura A, et al. Minocycline reduces microgliosis and improves subcortical white matter function in a model of cerebral vascular disease. Glia. 2018 Jan 1;66(1):34–46.
59. Maki T, Ihara M, Fujita Y, et al. Angiogenic and vasoprotective effects of adrenomedullin on prevention of cognitive decline after chronic cerebral hypoperfusion in mice. Stroke. 2011 Apr;42(4):1122–8.
60. Hattori Y, Okamoto Y, Maki T, et al. Silent information regulator 2 homolog 1 counters cerebral hypoperfusion injury by deacetylating endothelial nitric oxide synthase. Stroke. 2014;45(11):3403–11.

61. Hattori Y, Okamoto Y, Nagatsuka K, et al. SIRT1 attenuates severe ischemic damage by preserving cerebral blood flow. Neuroreport. 2015;26(3):113–7.
62. Fujita Y, Ihara M, Ushiki T, et al. Early protective effect of bone marrow mononuclear cells against ischemic white matter damage through augmentation of cerebral blood flow. Stroke. 2010 Dec;41(12):2938–43.
63. Ihara M, Nishino M, Taguchi A, et al. Cilostazol add-on therapy in patients with mild dementia receiving donepezil: A retrospective study. PLoS One. 2014 Feb 26;9(2).
64. Saito S, Kojima S, Oishi N, et al. A multicenter, randomized, placebo-controlled trial for cilostazol in patients with mild cognitive impairment: The COMCID study protocol. Alzheimer's Dement Transl Res Clin Interv. 2016 Nov 1;2(4):250–7.
65. Hase Y, Craggs L, Hase M, et al. The effects of environmental enrichment on white matter pathology in a mouse model of chronic cerebral hypoperfusion. J Cereb Blood Flow Metab. 2018 Jan 1;38(1):151–65.
66. Ihara M, Okamoto Y, Hase Y, et al. Association of physical activity with the visuospatial/executive functions of the montreal cognitive assessment in patients with vascular cognitive impairment. J Stroke Cerebrovasc Dis. 2013 Oct;22(7): e146-51.
67. Sun H, Zhang J, Zhang L, et al. Environmental Enrichment Influences BDNF and NR1 Levels in the Hippocampus and Restores Cognitive Impairment in Chronic Cerebral Hypoperfused Rats. Curr Neurovasc Res. 2012 Nov 11;7(4):268–80.
68. Bayat M, Sharifi MD, Haghani M, et al. Enriched environment improves synaptic plasticity and cognitive deficiency in chronic cerebral hypoperfused rats. Brain Res Bull. 2015 Oct 1;119:34–40.
69. Sakalem ME, Seidenbecher T, Zhang M, et al. Environmental enrichment and physical exercise revert behavioral and electrophysiological impairments caused by reduced adult neurogenesis. Hippocampus. 2017 Jan 1;27(1):36–51.
70. Rampon C, Jiang CH, Dong H, et al. Effects of environmental enrichment on gene expression in the brain. Proc Natl Acad Sci U S A. 2000 Nov 7;97(23):12880–4.
71. Fischer A. Environmental enrichment as a method to improve cognitive function. What can we learn from animal models? Neuroimage. 2016 May 1;131:42–7.
72. de Boer A, Storm A, Soler MG, et al. Environmental enrichment during the chronic phase after experimental stroke promotes functional recovery without synergistic effects of EphA4 targeted therapy. Hum Mol Genet [Internet]. 2019 Dec 9 [cited 2019 Dec 18];10.1093/hmg/ddz288. Available from: https://academic.oup.com/hmg/advance-article/doi/10.1093/hmg/ddz288/5669993
73. Quattromani MJ, Cordeau P, Ruscher K, et al. Enriched housing down-regulates the Toll-like receptor 2 response in the mouse brain after experimental stroke. Neurobiol Dis. 2014;66:66–73.
74. Hase Y, Craggs L, Hase M, et al. Effects of environmental enrichment on white matter glial responses in a mouse model of chronic cerebral hypoperfusion. J Neuroinflammation. 2017 Apr 11;14(1).

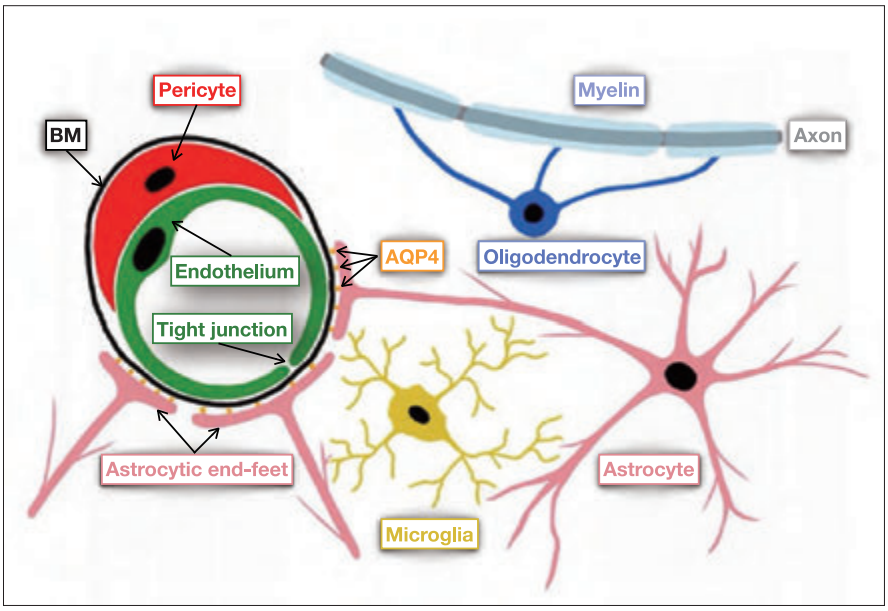


Figure 1. Schematic diagram of major cellular components of the gliovascular unit (GVU).

The GVU comprised of various cellular components, plays a critical role to control and maintain functions of the blood brain barrier (BBB). Abbreviations; AQP4, Aquaporin-4; BM, basement membrane.

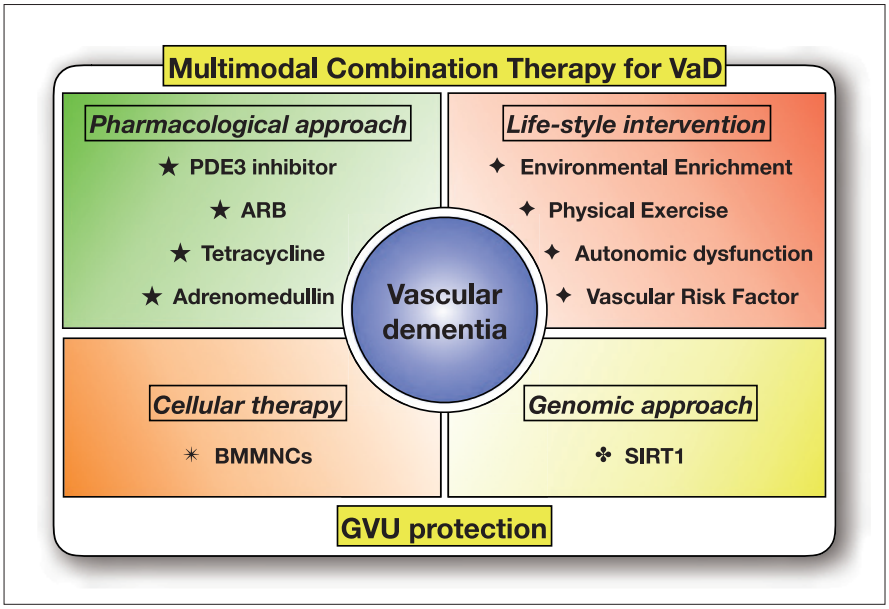


Figure 2. Outline of multimodal combination therapy for vascular dementia (VaD).

Each component in both pharmacological and non-pharmacological approaches has been proposed to have protective effects on gliovascular unit (GVU) and eventually counter VaD. Abbreviations; ARB, angiotensin Ⅱ receptor blocker; BMMNCs, bone marrow derived mononuclear cells; GVU, gliovascular unit; PDE3 inhibitor, phosphodiesterase type Ⅲ inhibitor; SIRT1, silent information regulator 2 homolog 1; VaD, vascular dementia.

Case report

Delayed Serial Microvascular Injury and Cognitive Decline After Whole Brain Irradiation

Yosuke Osakada, MD ; Toru Yamashita, MD, PhD ; Ken Ikegami, MD ; Yuko Kawahara, MD, PhD ; Yoshio Omote, MD, PhD ; Nozomi Hishikawa, MD, PhD ; Mami Takemoto, MD, PhD ; Yasuyuki Ohta, MD, PhD ; Koji Abe, MD, PhD

Department of Neurology, Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama University

Short title: Microvascular injury after whole brain irradiation

Conflict of interest: The authors state that they have no conflicts of interest.

Abstract

An 11-year-old girl underwent craniotomy for suprasellar germinoma. Thereafter, whole brain irradiation (50 Gy) was performed. Her cognitive decline progressed from the age of 35. Brain computed tomography indicated that calcification began in the basal ganglia (at the age of 25), followed by the cerebellar dentate nucleus (at the age of 34) and the cerebral cortex (at the age of 43). A late delayed complication of whole brain irradiation against a brain tumor induced microvascular injury and cognitive decline. The present case showed serial brain calcification, which may be related to the progress of microvascular injury after whole brain irradiation.

Corresponding author: Prof. Koji Abe
Department of Neurology, Okayama University Graduate School of Medicine, Dentistry and Pharmacy, 2-5-1 Shikata-cho, Okayama 700-8558, Japan.
Tel: +81-86-235-7365; Fax: +81-86-235-7368; E-mail: p5ag1b09@okayama-u.ac.jp

Introduction

Recent advances in brain surgery and drug therapy have improved life prognosis of brain tumor patients[1]. However, surviving patients sometimes show delayed irradiation-induced brain injury, and its pathology is still unknown and there are few long-term follow-up case reports. Late delayed complication of irradiation therapy against brain tumor induces intracranial calcification, cerebral infarction, microbleeds and cognitive decline[2]. Here we report a brain tumor case with delayed brain injury after whole brain irradiation that was followed up with a computed tomography (CT) scan over 18 years.

Case

An 11-year-old girl was diagnosed as having a suprasellar germinoma. After undergoing partial craniotomy, whole brain irradiation (50 Gy) was performed. After these therapies, the tumor shrank, and hormonal supplement therapy was administered to her as an outpatient. Since her intellectual performance and learning ability were lower than normal, her last level of education was at the junior high school level. Later, she started working at the age of 28. At the age of 30, she obtained her driver's license. However, disabilities in daily life appeared through memory loss and reduced attention, and therefore she stopped working at the age of 35. At the

age of 39, she caused a car accident, and subsequently gave up her driver's license at the age of 41. At the age of 43, she was referred to our hospital because of abnormal brain imaging (Fig. 1).

Upon admission to our hospital, she showed hypopituitarism, diabetes, hypertension and a non-alcoholic fatty liver. Her cognitive function declined to 23/30 in the total score of the mini-mental state examination (MMSE), but she showed no other neurological abnormalities. Brain CT revealed bilateral and symmetrical calcification of the basal ganglia and infarction of the left frontal lobe, at the age of 25 (14 years after irradiation). Calcification appeared in the dentate nucleus at the age of 34 (23 years after irradiation) and in the right frontal lobe at the age of 40 (29 years after irradiation) (Fig. 2A, arrows). From the age of 40, progressive cerebral atrophy became evident (Fig. 2A).

At the age of 43 (32 years after irradiation) a whole-body CT scan did not show any calcified lesions, except for the brain (Fig. 2B). Brain magnetic resonance angiography (MRA) showed a narrowing and irregularity of the middle cerebral artery (Fig. 2C, arrows), fluid attenuated inversion recovery (FLAIR) showed an old infarction and white matter lesion (Fig. 2D, arrows), and T2* showed micro bleeds in the left frontal lobe and cerebellar dentate nucleus (Fig. 2D, arrowheads). An electroencephalogram (EEG) had already showed slowing of background activity at the age of 37 (Fig. 2E).

Discussion

The present case showed characteristic imaging findings such as intracranial calcification, cerebral infarction, microbleeds and cerebral atrophy (Fig. A, D). Compared to previous reports (Table 1)[3-6], these pathological findings were followed up with a CT scan over a longer period of time (18 years). As the present case had no systemic diseases or vascular risk factors that caused calcification except for well-controlled hypertension and diabetes, the present imaging findings (Fig. A, C, D) may have been caused by whole brain irradiation.

In the present case, calcification began in the basal ganglia, followed by the cerebellar dentate nucleus and the cerebral cortex. Radiation therapy sometimes causes necrosis of small vessels such as arterioles, veins, and capillaries[7], leading to microscopic vasculitis, fibrosis, hyalinization, and calcification[8]. Thus, the serial calcification found in the present case may be related to the progress of microvascular injury after whole brain irradiation over time.

Irradiation-induced brain injury was described in acute (days to weeks), early delayed (1-6 months), and late delayed (＞6 months) phase[9]. Acute and early delayed injuries such as cerebral edema or transient demyelination are basically reversible. On the other hand, late delayed brain injury characterized by vascular abnormalities, demyelination, and ultimately white matter necrosis is essentially irreversible and progressive, eventually causing cognitive decline[2]. Although a previous report showed cognitive decline 12 years after whole brain irradiation (average age of 45)1, the present case showed cognitive decline 24 years after irradiation (35 years of age).

In summary, the present case showed serial brain calcification, which may be related to the progress of microvascular injury after whole brain irradiation. Cognitive decline was caused by cerebrovascular disorder in the late stage of radiation-induced late delayed injury.

Acknowledgments

We appreciate the cooperation of the patient. This work was partly supported by the Okayama Prefecture Intractable Disease Medical Council, a Grant-in-Aid for Scientific Research (B) 17H0419619, (C) 15K0931607, 17H0419619 and 17K1082709, and Grants-in-Aid from the Research Committees (Kaji R, Toba K, and Tsuji S) from the Japan Agency for Medical Research and Development (AMED) 7211700176, 7211700180 and 7211700095.

Reference

1. Douw L, Klein M, Fagel S, et al. Cognitive and radiological effects of radiotherapy in patients with low-grade glioma: long-term follow-up. The Lancet Neurology 2009; 8: 810-818.

2. Greene-Schloesser D, Robbins M, Peiffer A, et al. Radiation-induced brain injury: A review. Front Oncol 2012; 2: 73.
3. Suzuki S, Nishio S, Takata K, et al. Radiation-induced brain calcification: paradoxical high signal intensity in T1 weighted MR images. Acta Neurochir (Wien) 2000; 142: 801-804.
4. Shobha N, Smith E, Demchuk A, et al. Small vessel infarcts and microbleeds associated with radiation exposure. Can J Neurol Sci 2009; 36: 376-378.
5. Miura M, Nakajima M, Fujimoto A, et al. Small vessel disease associated with cranial irradiation. Rinsho Shinkeigaku 2015; 55: 743-747.
6. Andrea C, Fuchsia H, Alan N, et al. A Cross-Sectional Cohort Study of Cerebrovascular Disease and Late Effects After Radiation Therapy for Craniopharyngioma. Pediatr Blood Cancer 2016; 63: 786-793.
7. Nonoguchi N, Miyatake S, Fukumoto M, et al. The distribution of vascular endothelial growth factor-producing cells in clinical radiation necrosis of the brain: pathological consideration of their potential roles. J Neurooncol 2011; 105: 423-431.
8. Pantoni. Cerebral small vessel disease: From pathogenesis and clinical characteristics to therapeutic challenges. The Lancet Neurology 2010; 9: 689-701.
9. Tofilon, Philip J, John R, et al. The Radioresponse of the Central Nervous System: A Dynamic Process. Radiation Research 2000; 153(4): 357-370.

Table 1: clinical characteristics of patients with radiation-related brain injury

	Brain tumor	n	Age of irradiation (y.o.)	Age of image evaluation (y.o.)	Irradiation dose	Clinical symptom	Image abnormality	Lesion
Suzuki et al. [2]	suprasellar germinoma	3	11 avg.	21 avg.	63 Gy avg.	mental retardation	calcification	basal ganglia, brain stem
Nandavar et al. [3]	glioma (pons)	1	37	51	50 Gy	right facial weakness, dysarthria, right hemiparesis, headache	infarction, thalamic hemorrhage, microbleeds	basal ganglia, brain stem, temporal lobe, periventricular
Andrea et al. [4]	craniopharyngioma	20	10 avg.	36 avg.	50 Gy avg.	cognitive dysfunction	infarction, hemorrhage	basal ganglia, brain stem
Miura et al. [5]	suprasellar germinoma	2	17 avg.	36 avg.	50 Gy avg.	hemiparesis, dysarthria	infarction, microbleeds	basal ganglia
Present case	suprasellar germinoma	1	11	25, 34, 37, 40, 43	50 Gy	mental retardation, cognitive dysfunction	calcification, infarction, microbleeds, brain atrophy	basal ganglia, dentate nucleus, deep white matter

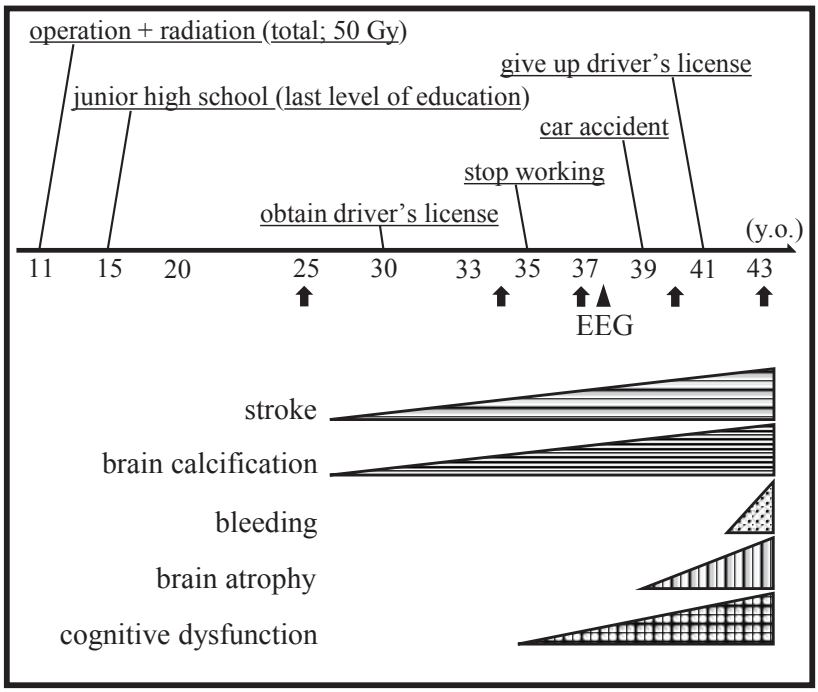


Figure 1: Life history and clinical features

Chronology shows the patient's life history after irradiation therapy. A brain CT was performed at the ages of 25, 34, 37, 40 and 43 (arrows), and EEG was performed at the age of 37 (arrowhead).

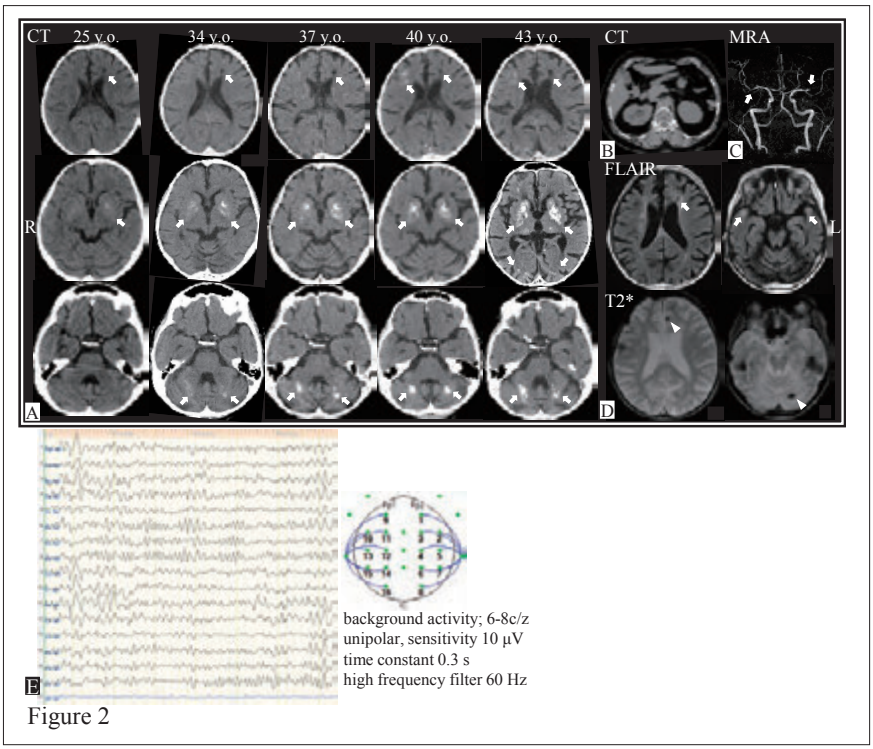


Figure 2:

A) A brain CT revealed calcification of basal ganglia and infarction of the left frontal lobe at the age of 25, cerebellar dentate nucleus at the age of 34, and of the right frontal lobe at the age of 40.
B) No calcification was observed in a whole-body CT.
C) MRA showed narrowing and irregularity of bilateral MCA.
D) FLAIR showed an old infarction and white matter lesion (arrows), and T2* showed micro bleeds (arrowheads) in the left frontal lobe and cerebellar dentate nucleus. E) An EEG showed slowing of background activity.

10th Year Anniversary Greetings from Vas-Cog Japan, the Japanese Society for Vascular Cognitive Impairment

Ryuichi Morishita, MD, PhD

President: The Japanese Society for Vascular Cognitive Impairment

Vas-Cog Japan, in its 10th year after being launched in 2010, has been developing quite considerably. The society was first established under the strong leadership of former Presidents Prof. Ken Nagata and Pro. Koji Abe, aiming to promote both basic and clinical research on vascular cognitive impairment and other related diseases. I took over the society last year as the third president from 2018. I would like to express my sincere gratitude to all members of VasCog Japan for your kind cooperation, assistance, and friendship.

The Vas-Cog Japan society has been steadily growing, thanks to the efforts of the Chairman for Increasing Membership and Public Relations, Prof. Haruo Hanyu. As of March 2020, we have 174 active members from 143 in last year, including 26 directors and 59 councilors, and the membership is expected to increase in the future. Furthermore, the financial structure has been going very well year by year. I sincerely thank the members, councilors, and directors who have supported this society for all these achievements. As our society has already met the requirements to be registered as an academic organization in the Science Council of Japan with regard to the number of members, membership management, and publication of journals, the Chairman for the Promotion of Becoming a Society, Prof. Katsuya Urakami, has been working on our application for registration. Under the guidance of Prof. Yoshio Ikeda, the Chairman of Financial Affairs, we have been continuing to strengthen the financial structure. Regarding conflicts of interest, we set up a COI committee and prepare provisions under the direction of the Chairman, Prof. Masahiko Suzuki.

We have been publishing an annual newsletter since 2014. The newsletter has been widely distributed to related academic societies in various countries and is well accepted, thanks to the hard work of former President Prof. Koji Abe. Due to the efforts of the Chief Editor of the academic magazine, Prof. Mikio Shoji, it has developed into Vas-Cog Journal, a joint publication with Vas-Cog Asia. We will continuously improve the journal's style and strengthen its content.

The 10th Annual Meeting of Vas-Cog Japan was successfully held August 3, 2019, at "Sola City Conference Center" in Tokyo, organized by chairpersons Prof. Yoshio Ikeda and Prof. Masahiro Akishita. I express our sincere gratitude, on behalf of all members of Vas-Cog Japan, to the chairpersons for their strong commitment to the success of the meeting. The 11th annual meeting Vas-Cog Japan 2021 will be held on September 11th and 12th, 2021 at Awa Kanko Hotel, Tokushima, with Prof. Masataka Sata, Department of Cardiovascular Medicine, Institute of Biomedical Sciences, Tokushima University Graduate School and Prof. Shunya Takizawa, Department of Neurology, Tokai University School of Medicine, as the chairpersons. Our affiliate VasCog Asia plays an increasingly significant role in the field of vascular dementia research. Vas-Cog Asia 8 was held in Manila on October 2, 2019, jointing with Asia-Pacific Stroke Conference (APSC). Next Vas-Cog Asia 9 is going to be held in Seoul on September 11 (2020) under direction of our President Tsong-Hai Lee (Taipei) and Secretary General Toru Yamashita (Okayama). Next Vas-Cog World will be held in Newcastle upon Tyne on September 9-12.

We are also pleased to announce that Osaka was selected to hold the World Expo in 2025, under the theme "Designing Future Society for Our Lives". As the government has set the era of a lifetime at 100 years, the prevention and treatment of dementia is becoming a top-priority task. Our engagement on vascular dementia research and other related diseases will be increasingly important in the aging society.

Vas-Cog Japan, a unique academic society covering a wide variety of interdisciplinary fields, such as cardiology, neurology, and brain surgery, will continue to work on basic and clinical research to elucidate the pathogenesis of vascular dementia and its role in other types of dementia and look for more effective treatment and prevention. We look forward to the participation of many of you in our exciting academic society.

March 10, 2020

Reports of the Vas-Cog Japan 2019

Masahiro Akishita MD, PhD
Department of Geriatric Medicine, Faculty of Medicine,
The University of Tokyo

VAS-Cog Japan2019 was held on August 3, 2019 at the Ochanomizu Sola City Conference Center (Tokyo). The main theme of the meeting was "Crosstalk of vascular factors and neurodegeneration". The new research results on AMPA receptors were given by Prof. Takuya Takahashi from Yokohama City University. Two educational lectures were held; "Differential diagnosis of Alzheimer's disease and Depression" by Prof. Masasru Mimura, Keio University School of Medicine, and "Basic and Clinical Topics of Cerebrovascular Disorders" by Prof. Toshiki Mizuno, Kyoto Prefectural University of Medicine.

The joint symposium with the Japanese Society of Geriatric Pharmacy (JSGP), "For the Collaboration between Physicians and Pharmacists in Dementia Treatment" was held. I, Akishita talked about polypharmacy and drug-based dementia, Prof. Naomi Kurata (Showa University) gave a lecture on medication support and Prof. Yusuke Suzuki (Nagoya University) talked about inter-occupational collaboration in dementia care. About 18 pharmacists participated in the symposium.

Industrial physician qualification renewal training (two credits of specialized training) certified by The Japan Medical Association was held to provide training for juvenile dementia and returning to work after a stroke. After more than two months, the training course was approved for the credit for the first time in Vas-Cog meetings. Despite the limited time for announcement, many of both members and non-members of the Society participated in the session.

We were pleased with many submissions for The Young Investors Awards (YIA). Dr. Naoki Saji (National Center for Geriatrics and Gerontology), Dr. Naoto Takenoshita (Tokyo Medical University), and Dr. Yorito Hattori (Weill Cornell Medicine) were nominated. All presentations of the three nominees were excellent, therefore all three of them were awarded at the banquet.

Our compact meeting held in one day, provided many participants with opportunities for discussion. The enthusiasm lasted till the banquet, where participants enjoyed food and rice wine from Gumma Prefecture and a view of Ochanomizu Nikolai-do Cathedral. We would like to thank Prof. Yoshio Ikeda and members of Gumma University for the cooperation for the meeting. Thanks to all of you, I would like to express my gratitude for the success of Vas-Cog 2019 and looking forward to seeing you again in the next Vas-Cog Japan meeting in Tokushima.

Reports of the Vas-Cog Japan 2019

Yoshio Ikeda, MD, PhD
Department of Neurology, Gunma University
Graduate School of Medicine

The 10th annual meeting of the Japanese society for vascular cognitive impairment (Vas-Cog Japan 2019) was held on August 3rd, 2019 (Saturday) at the Ochanomizu Sola City Conference Center, Tokyo. We would like to express our deep appreciation for your participation and support. This year's meeting could have a big success with a total of 201 participants.

Our society is characterized by academic activities to investigate various vascular factors that are closely related to the pathogenesis of dementia. With the aim of establishing treatments to suppress or improve the onset and progression of dementia, we prepared various scientific evens that will be useful for participants' future clinical/academic activities.

The main theme of the meeting is "Crosstalk between vascular factors and neurodegeneration", in which we are focusing on the close relationship between the vascular factors and the pathogenesis leading to neuronal degeneration causing dementia. The special lecture was given by Prof. Takuya Takahashi from Yokohama City University, regarding synaptic plasticity and the AMPA receptor imaging. In addition, general presentations (15 platform and 24 poster), special symposiums and seminars, and a joint symposium with the Japanese society of geriatric pharmacy, which aims to promote cooperation among healthcare professionals, were organized with a lot of discussions. As a new event introduced into this year's meeting, the workshops for the occupational health physicians were also conducted.

Finally, we thank all participants for your great contributions, and hope to meet you again in the Vas-Cog Japan 2021 meeting.

Welcome to Vas-Cog Japan 2021

Department of Cardiovascular Medicine
Institute of Biomedical Sciences
Tokushima University Graduate School

Masataka Sata

Department of Neurology
Tokai University School of Medicine,

Shunya Takizawa

It is our great honor to welcome you to the 11th annual meeting of the Japanese Society for Vascular Cognitive Impairment (Vas-Cog Japan 2021). This year's meeting will be held on September 11th and 12th, 2021 at Awa Kanko Hotel, Tokushima. This scientific meeting has been held in August annually. Because we will have Tokyo Olympic and Paralympic 2021 in the summer of next year, we decided to organize this meeting in September in Tokushima to secure transportations and accommodations of the attendees.

Accumulating evidence suggests that life-style related diseases, such as hypertension, diabetes, and dyslipidemia, are risk factors not only for cardiovascular diseases but also for dementia. Thus, it would be fascinating opportunity for the expert researchers in atherosclerosis and dementia to communicate each other to understand recent advances in both areas. The main theme of the meeting is "Dementia practice from vascular and neurological medicine". We are focusing on the close relationship between the vascular diseases and the pathogenesis of neuronal degeneration causing dementia. The special lectures will be given by Prof. Takayoshi Shimohata from Gifu University and Prof. Tomoya Yamashita from Kobe University. Educational lectures will be given by Prof. Koji Abe from Okayama University and Prof. Yuishin Izumi from Tokushima University. We are organizing three symposia "Frontiers in researches in cerebrovascular blood flow and metabolism related to vascular dementia," "Dementia and cardiovascular diseases" and "Protective and exacerbating factors in vascular dementia." We are planning two special symposia organized by young investigators from vascular and neurological medicine.

The venue is very convenient locating near Tokushima station. We are expecting many doctors and researchers on neurology, geriatric medicine, cardiology, metabolic diseases and pharmacology to attend the meeting. Especially, we encourage young researchers to present at the meeting. At Sept 11th (Saturday) night, we are planning a reception party, where you can experience the traditional dance, Awa dancing. After the meeting, you can enjoy various delicious foods of Tokushima, such as Awa-beef, Awa-chicken (Awa-O-Dori), Naruto-red snapper (Naruto-Dai) and Tokushima-ramen. We are looking forward to seeing you at Vas-Cog Japan 2021 in Tokushima!

Meeting report of Vas-Cog Asia 8 from Manila

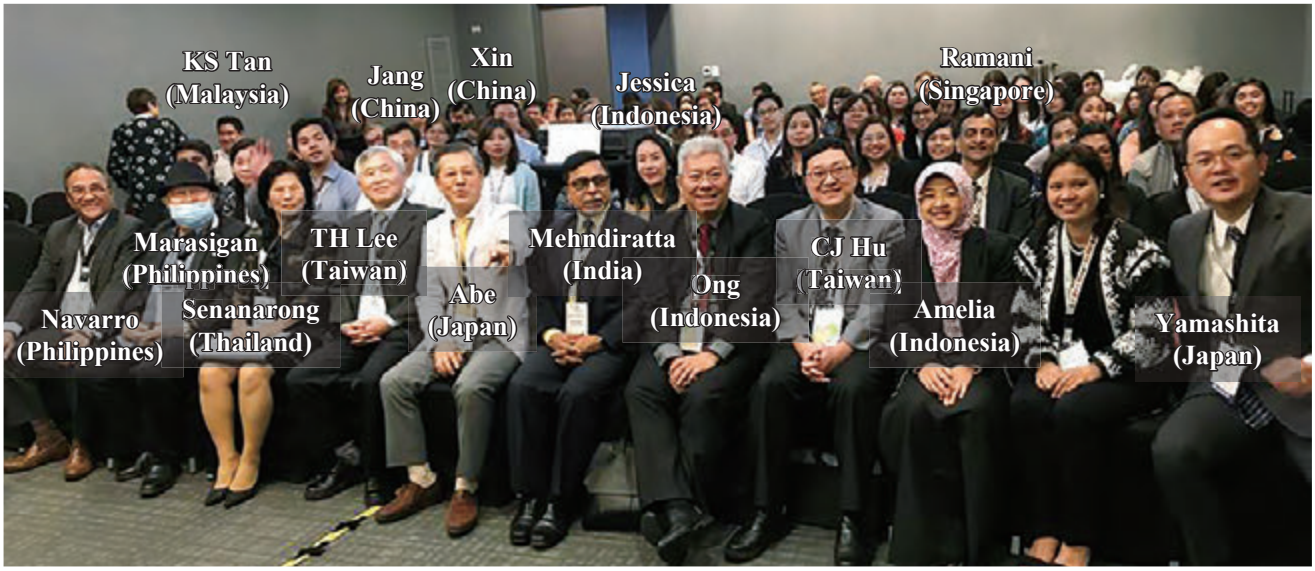
Koji Abe, MD, PhD
former Vas-Cog Asia President

I would like to celebrate the great success of Vas-Cog Asia 8, which was held in Manila on October 2 afternoon (2019) always jointing with Asia-Pacific Stroke Conference (APSC) based on the great supports by Professor Maria Cristina San Jose (APSC2019 chair) and Professors Jose Navarro and Simeon Marasigan (Host of Vas-Cog Asia 8, Manila). Based on the strong support of Vas-Cog Philippines which just launched this February, we welcomed 88 participants from Manila, Japan, Taiwan, Indonesia, China, Hong Kong, Malaysia, Singapore and India. There were variety of important presentations in the present conference. Many basic science, translational research, clinical trials and evidence were discussed especially on the aspects of Alzheimer's disease (AD), vascular dementia (VD), behavioral and psychiatric symptoms of dementia (BPSD), and their important vascular involvement.

Vas-Cog Asia society is an independent society with 24 directors from most Asian countries and many active members, which is dedicated to elucidate the mechanism of vascular factors in Alzheimer's disease and related dementia, and to contribute potential therapy for dementia people in Asia. Many vascular risk factors (VRFs) are related to cognitive decline and affective-emotional changes in dementia patients especially in elder or eldering countries in Asia.

Next Vas-Cog Asia 9 is going to be held in Seoul on September 11 (2020) under direction of our President Tsong-Hai Lee (Taipei) and Secretary General Toru Yamashita (Okayama). Next Vas-Cg World will be held in Newcastle upon Tyne on September 9-12. All of you are welcome to actively join these forthcoming Vas-Cog meetings to present and discuss on vascular factors of all type dementia.

December 5, 2019



Reports of Vas-Cog Japan Council Meeting

Yoshio Ikeda, MD, PhD
Department of Neurology, Gunma University
Graduate School of Medicine

The 11th board and council meeting of the Japanese Society for Vascular Cognitive Impairment was held together with 21 board members, 2 auditors and 27 councilors at the Hall WEST of the Ochanomizu Sola City Conference Center, Tokyo, on the 3rd of August, 2019. The representative director and committee members reported the topics shown below and all proceedings were approved by members.

[Membership]

169 regular members (As of July 30, 2019)

[Report from each committee leader]

* The leader of board for academic organization promotion, Dr. Katsuya Urakami, discussed the necessity to increase the members who paid the annual membership fee, and to increase a chance to publish an original paper written by Japanese in the Vas-Cog Journal. It is also discussed that an offer to give a credit for certificate renewal of other societies would be desired to increase the number of participants at the annual meeting.
* The leader of board for increasing membership and public relations, Dr. Haruo Hanyu, discussed the necessity to increase the number of supporting members and sponsored companies for banner advertisement on the homepage of the Vas-Cog Japan website. Board members were requested to cooperate to distribute a letter of intent to the potential sponsored companies.
* The chief editor of the academic magazine, Dr. Mikio Shoji, reported that "Submission Instructions for authors" was published on the homepage of the Vas-Cog Japan website, and all content will be published in English from the Vas-Cog Journal No. 5. It is also reported that submission of more original papers and advertising recruitment should be promoted.
* The leader of board for COI, Dr. Masahiko Suzuki, reported that the detailed regulations of the Common Guidelines for Conflicts of Interest in Clinical Research were established on the 4th of August, 2018, and administered on the 1st of April, 2020. Requirement of the registration number of ethics committee approval was considered for submission of general presentations at the annual meeting.
* The leader of board for finance, Dr. Yoshio Ikeda, reported the necessity to increase the members who paid the annual membership fee. Analysis of the financial balance found that last year's balance had a deficit if there is no donation from the last annual meeting office. Both auditors, Drs. Shimamura and Matsumura reported in the audit report that the accounting was properly conducted.

[Plans for future meetings]

1. The 11th Meeting (11th and 12th of September, 2021)
   Awa Kanko Hotel in Tokushima
   Chairmen: Dr. Shunya Takizawa and Dr. Masataka Sata
2. Refer to the last page for subsequent schedules.

[Retirement rule for board members and councilors]

In order to activate the society, the rule that all board members and councilors have to retire at the age of 65 has been established.

[Report of new board members / councilors]

* indicates board member or councilor.

[Name list]

● Executive Advisor

Hiroshi Mori
(Nagaoka Sutoku University)

● President

Ryuichi Morishita (Osaka University)

● Executive Directors (General Affairs)

Yoshio Ikeda (Gunma University)

● Executive Directors

Masahiro Akishita (The University of Tokyo)
Koji Abe (Okayama University)
Masafumi Ihara*
(National Cerebral and Cardiovascular Center)
Atsushi Iwata* (The University of Tokyo)
Katsuya Urakami (Tottori University)
Kenjiro Ono*
(Showa University School of Medicine)
Kazuo Kitagawa
(Tokyo Women's Medical University)
Koichi Kozaki (Kyorin University)
Issei Komuro (The University of Tokyo)
Masataka Sata (Tokushima University)
Munehisa Shimamura (Osaka University)
Takayoshi Shimohata*
(Gifu University Graduate School of Medicine)
Ken Shinmura* (Hyogo College of Medicine)
Kazuma Sugie*
(Nara Medical University School of Medicine)
Masahiko Suzuki
(The Jikei University School of Medicine)
Shunya Takizawa (Tokai University)
Hidekazu Tomimoto (Mie University)
Yukihito Higashi* (Hiroshima University)
Etsuro Matsubara (Oita University)
Miyuki Matsumura
(Institute of Geriatrics
Tokyo Women's Medical University)
Toshiki Mizuno
(Kyoto Prefectural University of Medicine)
Shokei Mitsuyama (Kumamoto University)
Masaru Mimura (Keio University)
Masaki Mogi* (Ehime University)
Masahito Yamada (Kanazawa University)

● Auditors

Yumi Kameyama* (The University of Tokyo)
Shuko Takeda* (Osaka University)

● Councilors

Hitoshi Aizawa (Tokyo Medical University)
Yasuhiro Aso (Oita University Hospital)
Satoshi Abe (Shimane University Hospital)
Masaki Ikeda (Gunma University Hospital)
Nobuyoshi Ishii (Oita University)
Hiroo Ichikawa (Fujigaoka Rehabilitation Hospital)
Ryoko Imazeki (Tokai University)
Jun Iwanami (Ehime University)
Shinichiro Uchiyama (International University of Health and Welfare)
Yumiko Uchiyama (Tokyo Women's Medical University)
Takahiko Umahara (Mizuno Memorial Rehabilitation Hospital)
Takao Urabe (Juntendo University Urayasu Hospital)
Yasuyuki Ohta (Okayama University)
Sumito Ogawa (The University of Tokyo)
Haruhisa Kato (Tokyo Medical University)
Tatsushi Kamiya (Kamiya Clinic)
Nobuya Kawabata (Yachiyo Hospital)
Noriyuki Kimura (Oita University)
Hitomi Kurinami (Osaka University)
Minoru Kouzuki (Tottori University)
Taro Kojima (The University of Tokyo)
Hisatomo Kowa (Kobe University)
Masaki Kondo (Kyoto Prefectural University of Medicine)
Kenji Sakai (Kanazawa University Hospital)
Hirofumi Sakurai (Tokyo Medical University)
Naoyuki Sato (Center for Development of Advanced Medicine for Dementia)
Masayuki Satoh (Mie University)
Soichiro Shimizu* (Tokyo Medical University)
Mikio Shoji (Geriatrics Research Institute Hospital)
Yoshiki Takao (Kurashiki Heisei Hospital)
Daiki Takano (Yokohama General Hospital)
Ayumi Takamura (Tottori University)
Yasushi Takeya (Osaka University)
Kentarou Deguchi (Okayama City Hospital)
Hiroo Terashi (Tokyo Medical University)
Yasuo Terayama (Shonan Keiiku Hospital)
Takashi Tokashiki (Okinawa National Hospital)
Takahiko Tokuda (Kyoto Prefectural University of Medicine)
Kazuaki Nagashima (Gunma University)
Ken Nagata (Yokohama General Hospital)
Masao Nagayama (IUHW Atami Hospital)
Yu Hasegawa (School of Health Sciences at Fukuoka)
Haruo Hanyu (Tokyo Medical University)
Yasuto Higashi (Himeji Central Hospital)
Nozomi Hishikawa (Okayama University)
Toshiya Fukui (Kawasaki Memorial Hospital)
Yukio Fujita (Gunma University)
Masatsugu Horiuchi (Hanwa Daini Senboku Hospital)
Kouki Makioka (Gunma University Hospital)
Yasuhiro Manabe (National Hospital Organization Okayama Medical Center)
Tohru Minamino (Niigata University)
Takafumi Miyachi (Yanai Medical Center)
Li-Juan Min (Ehime University)
Kazuhiro Muramatsu (Saiseikai Yokohamashi Tobu Hospital)
Kenichi Meguro (Tohoku University)
Hideki Mochizuki (Osaka University)
Shuhei Yamaguchi (Shimane Prefecture Hospital Bureau)
Takashi Yamazaki (Yokohama General Hospital)
Toru Yamashita (Okayama University Hospital)
Hiroshi Yoshizawa (Tokyo Women's Medical University)
Koji Wakayama (The University of Tokyo)
Yosuke Wakutani (Kurashiki Heisei Hospital)

A report from the Public Relations Committee

Haruo Hanyu
Department of Geriatric Medicine,
Tokyo Medical University

The Increasing Members and Public Relations Committee of the Japanese Society for Vascular Cognitive Impairment (Vas-Cog Japan) has been working to increase the number of general and supporting members and to announce activities of the Society, such as annual meetings and the like.

The members of this Committee consist of the Chairman (Prof. Haruo Hanyu, Tokyo Medical University) and four other members (Dr. Yumiko Uchiyama, Tokyo Women's Medical University Yachiyo Medical Center; Dr. Masaki Kondo, Kyoto Prefectural University of Medicine; Dr. Takashi Yamazaki, Yokohama General Hospital; and Dr. Hiroshi Yoshizawa, Tokyo Women's Medical University).

The members increase steadily, and there are at present 174 active members, including 26 directors and 59 councilors. Recently, several young investigators have joined Vas-Cog Japan. Members are expected to increase in the near future.

In addition, we have three supporting companies, including Eisai, Nippon Chemiphar, and Japan Mediphysics. These supporters provide web pages publishing advertisement banners. We hope that many pharmaceutical and related companies will join our Society.

As the new leader of board for increasing membership and public relations

Kazuo Kitagawa
Department of Neurology.
Tokyo Women's Medical University

It is my honor to work for advertisement of Japan Vas-Cog Society. Main topics of this society is involvement of vascular component on cognitive decline and dementia. This aspect is very important because the number of cognitive impairment increases as the aging society progresses. People can communicate not only with the same experts but researchers in other scientific field. Former president Prof. Abe and current president Prof Morishita have activated the level of this society for several years. Next May, Professor Abe organized the joint meeting of Japan Neurology Society and Japan Vas-Cog Society as the conference president of the 61st annual meeting of Japan Neurology Society at Okayama. Japan Vas-Cog society is expected to be widely known to all members of Japan Neurology Society and participants, over 7000 people, to the conference. The annual meeting of this society always focus on attractive topics related to vascular involvement on cognitive disease. The society publishes a newsletter and puts information or poster of our annual meeting in both domestic and international other conference every year. It is important to let many people who are interested in our topics join the society and attend the meeting of this society. I would like all society executives and members to join the activity of our society.

As an editor of journal of VASCOG-J

Toshiki Mizuno
Department of Neurology,
Kyoto Prefectural University of Medicine

It is my honor to work as an editor for VASCOG-J journal. Vascular dementia (VaD) is a difficult clinical entity to classify because many processes contribute to cognitive decline. In 2003, Hachinski proposed a new clinical concept called vascular cognitive impairment (VCI). I agreed with this concept when I heard his lecture at VASCOG2003, but I wondered whether this new concept would be accepted in Japan because a corresponding concept, mild cognitive impairment (MCI), had already been accepted, so the new concept of VCI might be thought of as a prodromal stage of VaD.

Hachinski explained his concept in detail and proposed a future direction in an article entitled "Vascular cognitive impairment harmonization standards" (*Stroke* 2006;37:2220–2241). Considering the progress of imaging, genetics, biochemistry, and pathology, this knowledge should be applied to provide a better understanding of VCI as proposed by Hachinski.

About 10 years later, new diagnostic criteria for VCI were proposed by the Vascular Impairment of Cognition Classification Consensus Study (VICCCS) group, which is composed of international participants (*Alzheimers Dement* 2017;13(6):624–633). These criteria are divided into mild or major type according to the level of cognitive impairment. While ordinal VaD is classified as major VCI, predementia stage is classified as mild VCI. Stroke episode is an important event in the previous criteria for VaD. Cases directly related to a stroke event are classified as post-stroke dementia according to the VICCCS. While subcortical ischemic VaD and multi-infarct (cortical) dementia subtype are categorized independently, these pathological changes can exist with other neurodegenerative pathologies and are categorized as mixed dementia. While small vessel disease contributes to clinical cognitive impairment as subcortical ischemic VaD, small vessel disease also exaggerates the progress of other neurodegenerative diseases, including Alzheimer's disease.

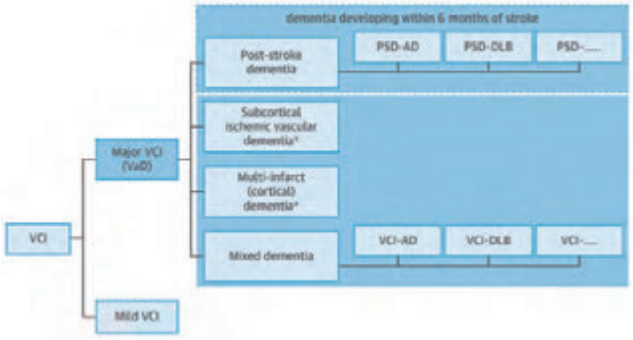


Figure 1.
Progress toward standardized VCI diagnostic guidelines in the Vascular Impairment of Cognition Classification Consensus Study.

Actually, much evidence accumulated about neurodegenerative diseases is accelerated by ischemic events in the brains of elderly patients. Particularly, studies on emission systems that excrete abnormal proteins from the brain have recently been gaining attention. The lymphatic and glymphatic drainage pathways can be visualized by improving dyes and imaging in vivo, but the main pathway of emission systems remains controversial. However, previous studies have revealed that vessel pulsation is important to eliminate abnormal proteins through the lymphocytic or venous system.

In addition, more genetic, biomarker, inflammation, and imaging studies are needed to solve the problems associated with dementia among the aged in Japan. It is my hope that this journal will continue contributing to the progress of dementia studies from a wide range of aspects in the future.

New submission system for Vas-Cog Journal

Vas-Cog Journal is an official journal of the Japanese Society of Vascular Cognitive Impairment. It was initially launched in 2015 as a newsletter. Vas-Cog Journal changed its style in 2019 and started accepting submissions from a wide range of scientists and clinicians in addition to the regular articles by the editorial board members. High-quality academic papers on vascular dementia and related disorders are welcome, and expected to enhance the scientific value of the journal.

Details regarding the new submission system are provided in "**Vas-Cog Journal Submission Instructions for Authors**" in this issue. Please note that at least the first author and corresponding author should be members of the Japanese Society of Vascular Cognitive Impairment. All manuscripts must be submitted electronically through the online submission system on the official web site of the Japanese Society of Vascular Cognitive Impairment (http://www.jtbw-mice.com/vas-cogj/). The submitting author should upload the manuscript files in appropriate word and PDF file formats according to the instructions provided. After submission via the online submission system, the contact/submitting author should complete the "Authorship Agreement" form with all coauthors' signatures, and email it to the Editorial Office (vas-cogj@jtb.com).

Vas-Cog Journal is currently accepting the following manuscript types: original article, review article (invited), editorial (invited), and case report. All original manuscripts will be evaluated by two independent reviewers assigned by the Editors. The members of the Editorial Board are listed in "Vas-Cog Journal Submission Instructions for Authors" in this issue as well as on the official web site.

Articles of Association of the Japanese Society for Vascular Cognitive Impairment

Chapter 1.Name

(Name)
Article1
The society shall be named Nihon Nokekkan Ninchisho Gakkai Sokai and shall be written as "the Japanese Society for Vascular Cognitive Impairment" (abbreviated as VAS-COG J) in English.

(Offices)
Article2
The Society's head office shall be in 2-2 Yamadagaoka, Suita-city, Osaka 565-0871

Chapter 2.Purpose and Business Activities

(Purpose)
Article3
The society is established for development of a new field of study of cognitive impairment. To this end, the society shall study clinical basic research with a wide field of vision about related matters of vascular lesion and cognitive impairment in Japan; also shall exchange information with international researchers; shall uncover causes of cognitive impairment and participation of vascular lesions, then shall research the possibilities for drug development.

(Business Activities)
Article4
The society shall engage in the following business activities to achieve the purpose provided in the preceding article:
(1) Business activities such as publication of academic journals
(2) Business activities such as holding annual meetings (Annual meetings shall be financed by the participants' entry fees but other organizations may co-host the meetings.)
(3) Business activities such as supporting and awarding study relating to the medical treatment of vascular cognitive impairment.
(4) Any other business activities for achieving the purpose provided in the preceding article.

Chapter3.Members

Article5
The society shall be comprised of the following types of members:
1. Regular members
2. Student members
3. Supporting members
4. Advisers

Article6
Any member shall be distributed academic journals and may present his/her study in annual meetings, symposiums and lectures.

Article7
Regular members and student members who agree with the purpose of the society, are individuals, who shall pay the annual membership fees separately designated by the General Assembly. Any applicant who joins the society shall fill in the designated application form, with the annual membership fee, and shall apply to the secretariat's office.

Article8
Supporting members are individuals or organizations who agree with the purpose of the society and pay the supporting membership fees to support activities of the society.

Article9
Advisers have an achievements in development related to vascular lesions and cognitive impairment especially and shall be determined by the Board of Directors with Board Member's recommendation. Advisers shall be exempt from the annual membership fee.

Article10
Members shall disqualify his/her membership if he /she falls under any of the following cases:
1. Cases in which he/she submits a withdrawal application to the society.
2. Cases in which he/she has not paid the annual membership fee for three years, and refuses demands of payment.
3. Any other case in which he/she violates the articles of incorporation and other regulations or has damaged the reputation of the society, and Board of Councilors shall determine his/her dismissal from the society.

Article11
Regular members and student members shall be accepted an adjournment with notification by the Representative Director, if they separately establish fixed conditions.

Chapter4.Officers and Councilors

Article12
The society shall have the following officers.
Board Members :twenty six members
Auditors :two members

Article13
The society shall have Councilors.

Article14
Auditors and additional Board Members outside the Board Members specified above, shall be determined according to a separate process. Councilors shall also be determined according to a separate process. The Chairman shall be selected by a recommendation of the Board of Directors. Each committee leader shall be chosen by the Representative Director, then approved by the Board of Directors. The Representative Director, the Chairman, the Leader of Society Promotion, the Leader of Finance, and the Chief Editor shall be members of the Board of Directors.

Article15
The Representative Director shall represent the society, control the performance of the society work and

convene the Board of Councilors.
The Representative Director and Board Members shall organize the Board of Directors, and manage the work of the society.
The Representative Director shall report budget statements, account settlement, human resources of Board Members and any of the other main work of the society to the Board of Councilors and the General Assembly.

Article16
The society shall have a Board for Society Promotion, a Board of Finance and an Editorial Board.
The Representative Director may establish other boards with the approval of the Board of Directors. Except in cases discussed in Article14, each leader of each committee shall be nominated by the Representative Director from among the Board Members, then be approved by the Board of Directors. Members of committees shall be approved by the Board of Directors, and then the Representative Director shall commission him/her. Terms for committee members last four years and maybe renewed indefinitely.

Article17
Auditors shall audit accounting, and shall give advice to the Board of Directors about managing the society. Auditors shall not hold any other offices and committee assignments.

Article18
Officers and Councilors shall serve a term of one fiscal year. The Representative Director, Executive Director, Board Members, Auditors and Councilors' terms are two years, and they may serve a maximum of two terms in a row.
Officers shall reach the mandatory retirement age on March 31st of the year in which they become 65 years old.

Article19
If a vacancy occurs, the Board of Directors shall appoint new Board Members if necessary, but those newly appointed members' terms are bound by the remaining period of their predecessors.

Article20
Councilors shall organize the Board of Councilors, and discuss issues necessary to the management of the society.

Article21
The Chairman shall represent the society in the fiscal year, and shall carry out their mission as a representative of the society.
1. The Chairman shall be nominated and then confirmed by the Board of Directors.
2. The Chairman's term is one year, from the day following the end of the previous Annual Meeting to the day the current Annual Meeting finishes.

Chapter5.Council

Article22
Annual Meeting, Board of Councilors and General Assembly shall be held once a year.

Article23
The Representative Director shall hold a Board of Councilor's Meeting temporarily if requested by more than one-third of the councilors.

Articles24
Meetings of the Board of Directors shall be called by the Representative Director if necessary. Meetings of the Board of Directors require attendance of over two-thirds of members, and shall be decided by over half of the Board Members in attendance. In case a vote is a tie, the Representative Director shall determine how to proceed. Individuals nominated by the Representative Director may attend a Board of Directors Meeting.

Chapter6.Accounts

Articles25
The fiscal year of the society shall commence on Apr 1st of every year and shall end on Mar 31st of the following year.

Articles26
The society shall be financed by annual dues, supporting members' fees, various subsides and donations.

Articles27
Expenses of the society shall be processed by the general fund account and special fund account.

Articles28
The general fund account shall record all income and expenditures excluding the special fund account.

Articles29
The special fund account shall record income and expenditures to assure a stable financial basis for the society. There shall also be provision to record income and expenditure of funds established for special purposes.

Article30
Establishment of each kind of fund, transfer of funds, and use of funds shall be approved by the Representative Director.

【Additional rules】

1. Any revision of the society's articles shall be approved by the Board of Directors.
2. The Board Members shall not be paid for their duties.
3. The articles of the society shall take effect from the day following approval by the Board of Directors.
4. The annual member fee shall be ￥5,000.
5. The date of foundation shall be October 01,2014.

Established on October 01, 2014
Revised on September 18, 2015
Revised on August 06, 2016
Revised on May 01, 2017
Revised on April 01, 2018
Revised on August 03, 2019

Vas-Cog Journal　Submission Instructions for authors

Vas-Cog Journal is an official journal of the Japanese Society of Vascular cognitive impairment. Original Articles deal with either clinical or experimental investigation of the vascular cognitive impairment. The journal will also consider the publication of review articles. Manuscripts must conform to Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals (ICMJE Recommendations) (http:// www.icmje.org/ recommendations/).

Submission of a manuscript to **Vas-Cog Journal** implies that the article is original and that no portion (including figures or tables) is under consideration elsewhere or has been previously published in any form other than as an abstract. Previous publication includes publishing as a component of symposia, proceedings, transactions, books (or chapters), articles published by invitations or reports of any kind, as well as in electronic databases of a public nature.

Submission of a manuscript implies that, when accepted for publication, the authors agree to automatic transfer of the copyright to the Japanese Society of Vascular Cognitive Impairment. Every reproduced figure or table must have permission from the copyright holder. Authors should obtain permission in advance of manuscript submission, and clearly state that in the figure/table legend. Examples:(1) Adapted from reference no. xx with permission. (2) Reproduced with permission from xxxx, et al. Neurology 2018; 91: xx – xx.

When reporting experiments on human subjects, indicate whether the procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional or regional). The participants' informed consent should be obtained and should be indicated in the text. When reporting experiments on animals, indicate whether institutional or national guidelines for the care and use of laboratory animals were followed.

In accordance with the Clinical Trial Registration Statement from the International Committee of Medical Journal Editors (http://www.icmje.org/), all clinical trials published in **Vas-Cog Journal** should be registered in a public trials registry at or before the participant recruitment. Refer to CONSORT 2010 guidelines (http://www.consort-statement.org/) for randomized clinical trials, and the STROBE statement (http://www.strobe-statement.org/) for observational studies (cohort, case-control, or cross-sectional designs).

Submission of Manuscripts:

At least the first author and corresponding author should be members of Japanese Society of Vascular Cognitive Impairment. All manuscripts must be submitted electronically through online submission system in the official web site of Japanese Society of Vascular Cognitive Impairment (http://www.jtbw-mice.com/vas-cogj/). The submitting author should upload the manuscript files in appropriate word and PDF file formats according to the instructions provided. Before completing submission, the submitting author is required to thoroughly check the PDF file.

Authorship Agreement:

After submission through the online submission system, the contact/submitting author should complete the "Authorship Agreement" form (**http://www.jtbw-mice.com/vas-cogj/kaishi.html**) with all co-authors' signatures, and email it to the Editorial Office (**vas-cogj@jtb.com**). Because any additional co-authors cannot be approved after the manuscript has been accepted, ensure that all co-authors have been properly listed during the submission process. If additional authors are included in a revised manuscript, the contact author of the manuscript is required to provide another "Authorship Agreement" form signed by the added authors as well as detailed reasons for their addition.

Manuscript Format:

All manuscripts should be written in English (US spelling) and prepared according to the following specifications.

1. The main document should be typewritten by word with double spacing and include the following in general: (1) Title page, (2) Abstract, (3) Key words, (4) Text, (5) Acknowledgements, (6) References and (7) Legends for Tables and/or Figures. This word file should be sent to the office with **attached converted PDF file of final published style.**
2. Pages should be numbered consecutively in this sequence, beginning with the title page.
3. The title page must have the following content:
   (1) Complete title of the paper; Abbreviations are not acceptable in the title.
   (2) Name(s) of author(s) with highest academic degree(s); Only MD, PhD, or BSc could be included.
   (3) Affiliations of all authors at the time of the study; i.e., department and institution
   (4) Short title; Up to 50 characters including spaces can be used.
   (5) Disclosures; Information of all COI, grants, sources of funding related to the manuscript should be declared.
   (6) Name and address of the author responsible for correspondence
   (7) Total word count of the manuscript
   (8) Total numbers of Tables, Figures and Supplementary files
4. Abstracts in manuscript types "Original Article of Clinical or Experimental Research" should be structured, and consist of the following 3 headings: 1: Background: Rationale for study; 2. Method and Results: Brief presentation of methods and presentation of significant results; Note that both categories should be included under the one heading. 3. Conclusions: Succinct statement of data interpretation
5. Units of measurement should be SI units, except for blood pressure, which should be expressed in mmHg. Do not spell out numbers and standard units of measurement except at the beginning of sentences. Use Arabic numerals and standard

abbreviations to indicate numbers and units.

6. References must be numbered consecutively as they appear in the text and be listed in the same numerical order at the end of the article. They should accord with the system used in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals. Only published manuscripts are accepted as references. If a reference is from a yet-to-be-published book, include 'In Press' as well as the anticipated year of publication. If a reference is published online only, the "D.O.I" or "URL as well as the last available date accessed" should be provided. The titles of referenced journals should be abbreviated to the style used in Index Medicus (http://www.nlm.nih.gov/tsd/serials/lji.html). All author names should be listed when referenced material has 3 or less authors; when it has 4 or more, only the first 3 authors' names should be listed, with "et al." at the end.
   Examples:
   (1) Yamashita T, Kamiya T, Deguchi K, et al. Dissociation and protection of the neurovascular unit after thrombolysis and reperfusion in ischemic rat brain.J Cereb Blood Flow Metab. 2009 (4):715-25.
   (2) Takeda S and Morishita R. Diabetes and Alzheimer's Disease. In: Yamagishi S, editor. Diabetes and Aging-related Complications. Springer, 2018; 101-111
   (3) Takeda S, Wegmann S, Cho H, et al. Neuronal uptake and propagation of a rare phosphorylated high-molecular-weight tau derived from Alzheimer's disease brain.Nat Commun. 2015 Oct 13;6:8490. doi: 10.1038/ncomms9490.
7. All figures in a manuscript are recommended to be in full color; **publication in color requires page charge of JPY65,000 for one color page** (see also "VI. Publication Charges"). **For invited articles, publication in color is cost-free for one page and requires JPY65,000/one exceeding color page.** Letters and symbols in figures should be clear and of sufficient size to be legible after reduction to the width of one column. Specify the size to be printed, if necessary.
8. Content of supplementary files will only be published in the online journal. Therefore, if a supplementary file contains References, they should be separate from those in the Main Document, and only refer to the content in the supplementary file(s). There is a size limit of 5 MB for uploaded supplementary file(s) per manuscript.

II. Manuscript Types:

1. Original article

Total word count is less than 6,000 words and less than 220 words for Abstract. Number of Table and Figures are less than 8 and less than 3 supplementary figures. No limitation of numbers of references. Three to 5 Keywords and structured abstract with 3 headings are other requirements.

2. Images in Vascular Cognitive Impairment

Images in "**Vascular Cognitive Impairment**" should contain a novel color image with scientific impact. Note that we do not accept any case reports. The manuscript consisted of less than 400 words, 1 figure and 2 supplementary files, normally occupies 1 journal page.

3. Review Article (Invited)

"Review Article" is usually invited one upon request from the Editor-in-Chief, but we will also consider limited number of non-invited submissions. Total word count is less than 6,000 words and less than 220 words for Unstructured Abstract. Number of Table and Figures are less than 8 and less than 3 supplementary figures. No limitation of numbers of references.

4. Editorial (Invited)

"Editorial" normally occupies no more than 2 journal pages about subject manuscript should be cited Upon request from the Editor-in-Chief. Total word count is less than 1,500 words and no abstract, less than 2 Table or figures and less than 15 references.

5. Case Report

Total word count is less than 3,000 words and less than 100 words for Unstructured Abstract. Number of Table and Figures are less than 4 and 20 references. Vas-Cog Journal encourage submission by young researches in this section.

6. Letter to the Editor and Author's Reply

This is an opinion-letter to a manuscript which has been published in Vas-Cog Journal. The manuscripts must not exceed 1,000 words in length and have no more than 5 co-authors.

Authors who submit or resubmit manuscripts to the journal are required to have all of their manuscript files strictly reflect the requirements outlined here. When any part does not, we cannot start either the initial or revision review process. "Total word count" is the total number of all words appearing in the manuscript files, except for the text in Table(s) and Figure(s). Note that legends for these are included in the "Total word count".

III. Conflict of Interest Disclosure Policy:

The submitting author should complete the online form in the submission system and have the same information included in "Disclosures" in the main document in order to disclose all authors' relationships that could be perceived as real or apparent conflict(s) of interest. When submitting a manuscript for publication, all authors are required to disclose any financial relationship (within the past 12 months) with a biotechnology manufacturer, a pharmaceutical company, or other commercial entity that has been involved in the subject matter or materials discussed in the manuscript. When a manuscript has been accepted for publication, all disclosed COI will appear in the article.

Example:

Disclosures：A (author name) serves as a consultant to Z (entity name); B's spouse is chairman of Y; C received a research grant from X; Deceived lecture fees from V; E holds a patent on U; F has been reimbursed by T for attending several conferences; G received honoraria for writing promotional material for S; H has no conflict of interest.

IV. Review of Manuscripts:

All original manuscripts are usually evaluated by 2 reviewers assigned by the Editors.

V. Proofs:

Galley proofs of accepted manuscripts will be sent to the authors for their correction. Changes should be limited to typographical errors or errors in the presentation of data. Excessive corrections may be rejected by editors and/or be charged to the authors.

VI. Publication Charges:

Free for publication charge in manuscript submission rules within total word count, Tables, Figures and References. JPY8,000/one exceeding page charge (JPY65,000 for one color page).

VII. Reprints:

Reprints are available in a multiple of 100 copies when ordered with the return of the proofs. The approximate cost per 100 copies is JPY10,000, including color pages. Free PDF publication.

Vas-Cog Journal
Authorship Agreement

Each author must read and sign the statements on
1. Authorship Responsibility, **2. Copyright**, and **3. Disclosure Declaration**.

1. Authorship Responsibility.
Author(s) certify that the manuscript is original and that neither the manuscript nor one with substantially similar content has been previously published or being considered for publication elsewhere in any form other than an abstract. Author(s) have read the manuscript and approved its submission to Vas-Cog Journal.

2. Copyright.
In consideration of the acceptance of the work for publication, the authors agree to transfer all copyright ownership to the Japanese Society for Vascular Cognitive Impairment (Vas-Cog Japan).

3. Disclosure Declaration.
All relevant financial, personal or professional relationships with other people or organizations must be disclosed in the online form and main document. Otherwise, the signature indicates author(s) have no relationships or conflicts to disclose. Authors' disclosures will appear after the "Acknowledgments" section in the accepted article.

*Multiple pages may also be accepted. Please copy and use this form if it is necessary.
<CAUTION> We do not accept any additional co-authors after the manuscript has been accepted. Please make sure that you add all co-authors in the revision process.

Manuscript title:

_____

1) Author's Print Name:_____

Signature:_____ Date:_____

2) Author's Print Name:_____

Signature:_____ Date:_____

3) Author's Print Name:_____

Signature:_____ Date:_____

4) Author's Print Name:_____

Signature:_____ Date:_____

5) Author's Print Name:_____

Signature:_____ Date:_____

6) Author's Print Name:_____

Signature:_____ Date:_____

7) Author's Print Name:_____

Signature:_____ Date:_____

8) Author's Print Name:_____

Signature:_____ Date:_____

9) Author's Print Name:_____

Signature:_____ Date:_____

10) Author's Print Name:_____

Signature:_____ Date:_____

Sponsers

Eisai Co., Ltd.

Novartis Pharma K.K.

ONO PHARMACEUTICAL CO., LTD.

Osaka Yakken Co.,Ltd.

Otsuka Pharmaceutical Co., Ltd.

Sumitomo Dainippon Pharma Co., Ltd.

Takeda Pharmaceutical Company Limited

(in alphabetical order)

Editor's Note

Mikio Shoji, MD., PhD
Director, Dementia Center,
Geriatrics Research Institute and Hospital

The 6th issue of Vas-Cog Journal reports the outline of the 10th annual meeting, VAS-COG Japan 2019, hosted by Professor Masahiro Akishita and Professor Yoshio Ikeda on August 3, 2019 in Tokyo, joining about 200 participants. Year by year, participants in Vas-Cog J annual have been increasing. Besides clinical doctors and researches, paramedical stuff, students and companies are joining and boosting up this meeting successfully. I would like to appreciate every effort by Vas-Cog J members and be delighted so much.

In this issue, 2 outstanding review articles, case reports and information of related meetings have been carried. Council meeting reports and description about new submission systems were published.

Last 5 years, I have been editing the Vas-Cog journal. Vas-Cog Journal has developed from simple meeting reports into the one of fully equipped international journals with open contribution rules and advertisements. From the next issue, editor in chief will be transferred to Dr. Toshiki Mizuno, the professor, Division of Neurology and Gerontology, Kyoto Prefecture University of Medicine.

I deeply appreciated for every support by president, editorial board members and secretariat, and hope these great efforts contribute further advances in this field with the new editor in Chief.

God bless us every one! (Charles Dickens 1843)

The past and future annual meeting of Vas-Cog Japan

The 1st Meeting : August, 2010 (Tokyo) Chairman : Ken Nagata and Toshiya Fukui
The 2nd Meeting : August, 2011 (Tokyo) Chairman : Koji Abe and Shokei Mitsuyama
The 3rd Meeting : August, 2012 (Tokyo) Chairman : Ryuichi Morishita, Yasuo Terayama, and Koji Abe
The 4th Meeting : August, 2013 (Tokyo) Chairman : Mikio Shoji and Haruo Hanyu
The 5th Meeting : August, 2014 (Kyoto) Chairman : Toshiki Mizuno and Hidekazu Tomimoto
The 6th Meeting : August, 2015 (Tokyo) Chairman : Nobuya Kawabata and Shuhei Yamaguchi
The 7th Meeting : August, 2016 (Kanazawa) Chairman : Masatsugu Horiuchi and Masahito Yamada
The 8th Meeting : August, 2017 (Tokyo) Chairman :Shinichiro Uchiyama and Issei Komuro
The 9th Meeting : August, 2018 (Beppu) Chairman : Katsuya Urakami and Etsuro Matsubara
The 10th Meeting : August, 2019 (Tokyo) Chairman : Masahiro Akishita and Yoshio Ikeda
The 11th Meeting : September, 2021 (Tokushima) Chairman : Shunya Takizawa and Masataka Sata
The 12th Meeting : August, 2022 (planned) Chairman : Kazuo Kitagawa and Koichi Kozaki
The 13th Meeting : August, 2023 (planned) Chairman : Masahiko Suzuki
The 14th Meeting : August, 2024 (planned) Chairman : Takayoshi Shimohata
The 15th Meeting : August, 2025 (planned) Chairman : Kazuma Sugie

- to be continued -

11th Annual Meeting of the Japanese Society for Vascular Cognitive Impairment

第11回 日本脳血管・認知症学会総会

VAS-COG Japan 2021

「血管と神経から診る認知症」

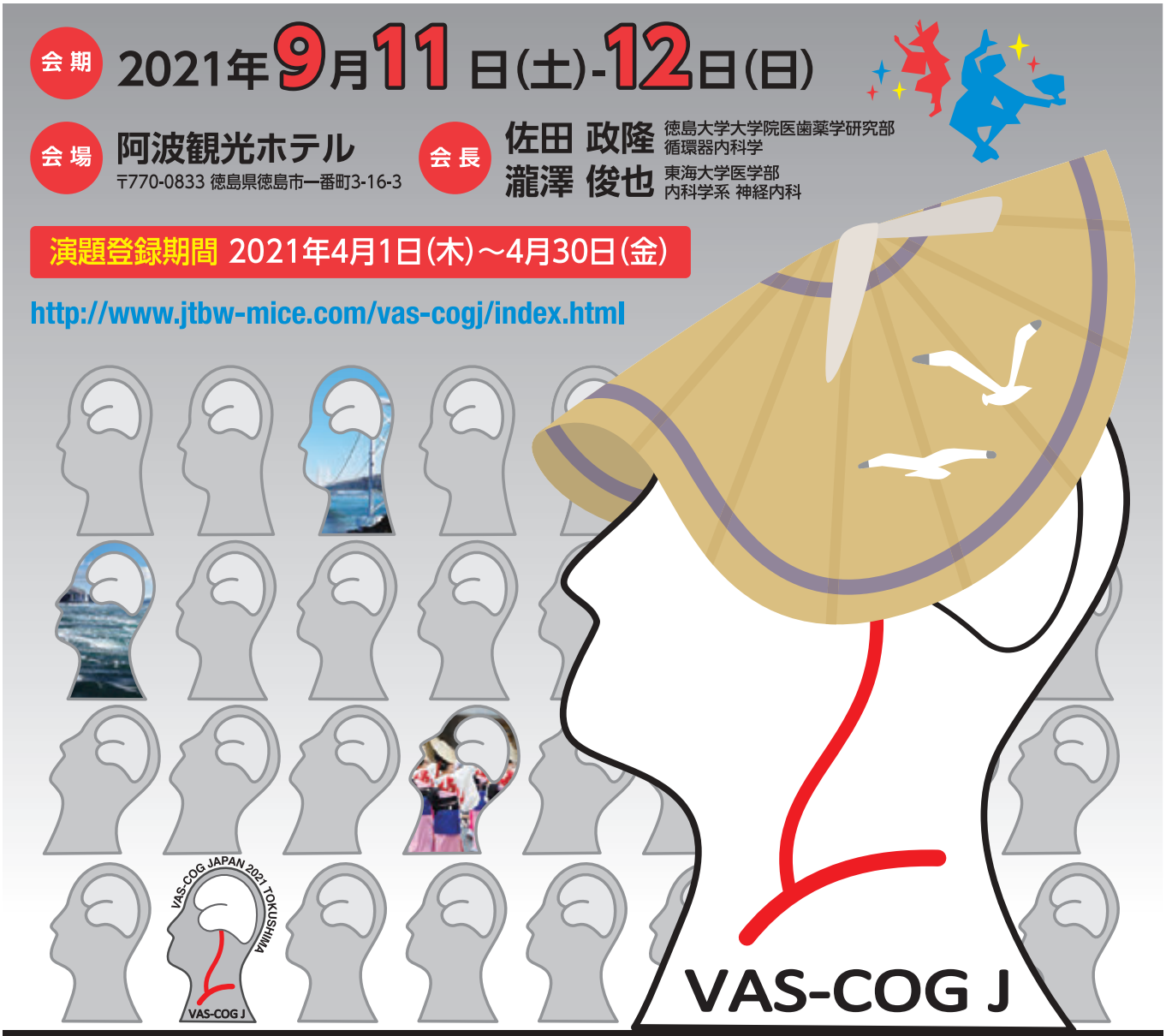
会期 2021年9月11日(土)-12日(日)

会場 阿波観光ホテル
〒770-0833 徳島県徳島市一番町3-16-3

会長 佐田 政隆 徳島大学大学院医歯薬学研究部 循環器内科学
瀧澤 俊也 東海大学医学部 内科学系 神経内科

演題登録期間 2021年4月1日(木)～4月30日(金)

http://www.jtbw-mice.com/vas-cogj/index.html



総会事務局 今関 良子(東海大学医学部 内科学系 神経内科)
八木 秀介(徳島大学大学院医歯薬学研究部 循環器内科学)

運営事務局 株式会社JTB 西日本MICE事業部
〒541-0058 大阪市中央区南久宝寺町3丁目1番8号MPR 本町ビル9階
TEL 06-6252-2830 FAX 06-6252-4015 E-mail mice-vas-cogj@jtb.com