< Review article >

Masafumi Ihara.

"Neurovascular approach for Alzheimer's disease."

Shuko Takeda.

"Lifestyle-related diseases and dementia."

< Case report >

Toru Yamashita, *et al.*

"Heterozygous HTRA1 mutation cases showing SAH."

ISSN : 24239372

Table of Contents

Editorial

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

Bon Voyage!

In 2009, Japanese clinical doctors and researchers in the field of vascular dementia have gathered into the Japanese association of Vascular Cognitive Impairment (Vas-Cog Japan). Then, we hold annual meeting every summer for developing researches in this fields. Vas-cog Japan keeps activity and is expanding into the established international society with about 200 members including basic scientist and industrial members. Since 2015, we published Vas-Cog Journal as the News letters. In 2017, Vas-Cog Japan decided to be the academic association and to launch the international official journal. Based on the details, 5th issue of Vas-Cog journal is apparently renewed and publishes articles.

In this issue, Dr. Ihara, Dr. Takeda and Dr. Yamashita published wonderful works in the initial issue of this journal and greatly contributed to advance researches of Vascular cognitive dementia. Dr. Ihara outlined the mechanisms behind Aβ clearance. When vascular degeneration occurs with aging and/or cerebral amyloid angiopathy, Aβ clearance is impaired and accumulation accelerated. Therefore, prevention of vascular degeneration is also important for AD treatment. UpToDate review article by Dr. Takeda showed that lifestyle-related diseases induce arteriosclerosis in cerebrovasculature, which leads to vascular dementia, and also affect AD pathology. AD-related Aβ peptides have a direct impact on cerebrovasculature, causing functional and structural damage. Lifestyle-related diseases and AD synergistically exacerbate the pathogenesis of vascular dementia. Dr. Yamashita presented an interesting case of the Japanese family of autosomal dominant cerebral small vessel disease with heterozygous HTRA1 mutation showing dementia, gait disturbance and subarachnoid hemorrhage.
These articles are all elaborative, high-quality, and appropriate for this initial issue of renewal academic journal. Here, I would deeply appreciate every effort by editorial board members and authors. I hope these great efforts contribute further advances in this field from now on.

Review article

A neurovascular approach to clearing β-amyloid from the brain

Masafumi Ihara, MD, PhD
Department of Neurology, National Cerebral and Cardiovascular Center

Abstract

In the brain, arteries and veins do not run in parallel, and its perfusion system has characteristics not found in other organs. The presence of a tight blood-brain barrier and lack of authentic lymphatic vessels in the parenchyma means clearance of some waste products, such as β-amyloid (Aβ), is impeded. Aβ is thus cleared from the brain via at least four clearance pathways including 1) transcytotic delivery, 2) intramural periarterial drainage, 3) glymphatic drainage and 4) enzymatic or glial degradation. Failure in any four such pathways has been implicated in the pathophysiological processes behind Alzheimer's disease. In clinical trials of Aβ vaccination therapy, vascular Aβ deposition was paradoxically enhanced, with encephalitis subsequently occurring in a fraction of patients. This serious side effect may be associated with insufficient clearance of solubilized Aβ through clearance systems in response to immunotherapy. Transcytotic delivery, intramural periarterial drainage, and glymphatic drainage clearance pathways depend on vascular integrity and are partly driven by vascular wall motion; therefore arteriosclerosis or perfusion pressure reduction is assumed to increase Aβ accumulation. Strategies activating clearance systems may be helpful in the treatment of intractable disease through reduction of brain Aβ, therefore aiding development of neurovascular prevention strategies for Alzheimer's disease.

Key words: β-amyloid, glymphatic, IPAD, degrading enzyme, transcytosis

Correspondence:
Masafumi Ihara
Department of Neurology
National Cerebral and Cardiovascular Center
5-7-1 Fujishiro-dai, Suita, Osaka 565-8565, Japan
Phone: + 81-6-6835-5137
E-mail; ihara@ncvc.go.jp

Introduction

In order to maintain homeostasis and nerve function, the brain must manage ionic and amino acid concentrations through three types of strictly regulated barriers: 1) the blood-brain barrier between the blood and interstitial fluid (ISF), 2) the blood-cerebrospinal fluid (CSF) barrier between the blood and cerebroventricular CSF, and 3) the blood-CSF barrier between the blood and subarachnoid CSF [1]. The blood-brain barrier plays a major role, occupying 5000 times the area of the blood-CSF barrier [2]. Since the presence of these functions is essential for controlling ion gradients and neurotransmitter concentrations inside and outside the neuron, such systems likely possessed advantages from an evolutionary natural selection viewpoint. However, the development of these tight barriers has meant ISF containing waste products, such as amyloid β (Aβ), cannot easily return to the vascular lumen, leading to Aβ accumulation in the brain and possibly Alzheimer's disease (AD). However, to prevent accumulation of self-aggregating and misfolded proteins, including Aβ, several processing mechanisms take place in the brain. In this article, we focus on mechanisms behind cerebral clearance and peripheral metabolism of Aβ and its relationship with dementia causing diseases, in particular AD.

I. Clearance mechanisms of Aβ from the brain

Apart from juvenile AD, the main cause of sporadic AD in the elderly is thought to be a decrease in Aβ clearance [3].

The following four representative mechanisms (4-d) are thought to play a fundamental role in Aβ clearance (Figure 1) [4].

(1) Transcytotic delivery – clearance into the lumen of blood vessels by transcytosis through transporters such as lipoprotein receptor related protein-1 (LRP-1) [5] and P glycoprotein (also known as ABCB1) [6]. Aβ is transported by transcytosis from the abluminal (brain parenchyma) side to the luminal side. The receptor for advanced glycation end product (RAGE) transports Aβ from the vascular lumen to the brain parenchyma in an opposite direction to transcytosis and the RAGE inhibitor results in Aβ excretion out of the brain. Despite such theoretical evidence, a phase III trial of the RAGE inhibitor Azeliragon failed to demonstrate efficacy (TTP 488) in mild AD patients.

(2) Perivascular drainage – clearance through the perivascular lymphatic drainage pathway. Here the Aβ-containing ISF flows through the basal membrane layer of the blood vessel and is ultimately transported to the CSF space and cervical lymph nodes [7]. This route runs within the vessel wall and has thus been recently renamed 'intramural periarterial drainage' (IPAD) [8]. Since the breakdown of this drainage pathway is related to cerebral amyloid angiopathy pathology, therapies targeting such processes have been developed. Cilostazol, a vasoactive drug phosphodiesterase III inhibitor promotes the removal of Aβ from the vascular wall in a cerebral amyloid angiopathy model mouse [9]. Thus, an investigator-initiated clinical trial, the COMCID study, is currently being conducted in Japan in patients with mild cognitive impairment [10]. (ClinicalTrials.gov Identifier, NCT02491268)

3) Glymphatic drainage – this conduit system was originally reported in 1985 as the 'paravascular drainage pathway' [11] but recently renamed due to the pivotal role of glial cells in the system [12]. CSF flows into the brain parenchyma through the Virchow-Robin cavity around the artery and is transported into the parenchyma by the action of aquaporin 4 expressed in the foot processes of astrocytes. In the brain parenchyma, the CSF, together with ISF, dissolve Aβ and drain into the perivenous space [12]. They further drain into cerebral meningeal lymphatic vessels [13]. In Aβ -overexpressing mice, occlusion of the cerebral meningeal lymphatic vessels led to Aβ deposition in the lymphatic vessels, as well as the brain parenchyma, strengthening the importance of these systems in Aβ clearance [14].

4) Enzymatic and glial degradation – this is an Aβ degradation pathway through the action of proteases

such as neprilysin, insulin-degrading enzyme, plasmin, angiotensin-converting enzyme and glia (astrocytes and microglia) [15]. Recently, it was reported that microglia expressing triggering receptors expressed on myeloid cells 2 (TREM2) surround senile plaques and have a role in protecting neurons from Aβ, consistent with clinical findings that a loss-of-function mutation of *Trem2* was found in AD [16].

II. Drainage pathway of Aβ within vessel wall – IPAD

The presence of IPAD was suggested by Schwalbe in 1860s, who demonstrated that India ink injected into the cistern could be detected in the cervical lymph nodes within 1 minute [17]. Bradbury and Cserr et al. subsequently reported 1) tracer injected into the cerebral ventricle flowed into the cervical lymph node via the lamina cribrosa, 2) tracer injected into the caudate nucleus flowed into the cervical lymph node unrelated to CSF flow, and 3) radioisotope-labeled tracer injected into the brain parenchyma was observed along the arterial wall intracranially [18]. In the early 1990s, Weller et al. further showed that 1) India ink injected into the striatum of rats was present in close proximity to the dilated perivascular space, along the middle cerebral artery branch and the arterial circle of Willis, reaching the lamina cribrosa along the olfactory and ethmoidal arteries, and 2) further through the lamina cribrosa, extending from the nasal lymphatics to the cervical lymph nodes [19].

As a result of detailed observation by Carare et al., the capillary vessels in the brain and the basement membrane of the artery wall were shown to constitute the IPAD, with the route acting as a high-speed drainage system for ISF [20]. This lymphatic drainage is much faster than the rate at which molecules diffuse through the extracellular space and ISF is almost instantaneously cleared along the arterial wall within the brain and meninges, with a soluble tracer injected into the brain reaching the basement membrane of the meningeal blood vessel within 10 minutes. In a theoretical model [21], arterial pulsation is thought to be the driving force of IPAD, caused by centrifugal force generated by reflected waves following pulse waves originating in the heart.

Since Aβ is detected in the middle cerebral artery and the basilar artery wall but not in the cervical internal carotid artery [22], solutes flowing through the IPAD appear to leave the vessel wall at the base of the brain [7], or via the cerebral meningeal lymphatics [13], into the local lymph nodes.

III. Conditions in which glymphatic pathway works

The glymphatic pathway drainage system is gaining recognition in scientific literature. However, in the schematic diagram of the pathway, there are no barriers in the Virchow-Robin cavity and subarachnoid space, and CSF freely drains into the brain parenchyma [13]. This should be reconsidered as there is principally no space around arteries of the cerebral cortex [8]. Indeed, it is extremely rare to see the Virchow-Robin cavity in the cerebral cortex on MRI. Also, if ISF-containing Aβ is cleared around the vein, it is not clear why cerebral amyloid angiopathy is not observed at this site. In a study injecting fluorescence Aβ into the CSF space of mice at 6-10 months and 24-30 months of age, Aβ was found in the pial-glial basement membrane between the pia matter and astrocytes of the glia limitans, suggesting that CSF enters the brain along the pial-glial basement membrane but not through the Virchow-Robin periarterial space [8]. Nevertheless, one may not entirely exclude the possibility of the glymphatic pathway playing a role in pathological conditions or the aging process. Further elucidation of this pathway may clarify whether the permeability of the pia mater increases and the cortical Virchow-Robin cavity enlarges in the pathological conditions, leading to increased contribution of the glymphatic pathway in the clearance of waste products including Aβ.

IV. Conditions where IPAD fails

Interestingly, IPAD lymphatic drainage aligns with

the site of Aβ deposition in early cerebral amyloid angiopathy [23]. Accumulation of Aβ starts from the smooth muscle cell basement membrane, corresponding to the IPAD pathway. Thus, stagnation of this pathway may be closely related to cerebral amyloid angiopathy pathology. Indeed, ISF flow has been impaired in aged mice, as well as those with cerebral amyloid angiopathy [24]. Furthermore, artificial constriction of the bilateral common carotid arteries in a cerebral amyloid angiopathy model mouse results in worsening of the cerebrovascular Aβ deposition [25]. Therefore, a decrease in vascular pulsation due to aging, arteriosclerosis or Aβ deposition itself appears to act as an exacerbating factor of cerebral amyloid angiopathy. When dextran corresponding to the molecular weight of Aβ was injected into the brain and visualized by two-photon microscopy in real time, the efficiency of dextran clearance was shown to be impaired due to vascular occlusion and cerebral amyloid angiopathy [26]. The glymphatic pathway is promoted by vascular pulsation by dobutamine [12]. Furthermore, as levels of neprilysin or LRP-1 decrease, clearance of Aβ is impaired, causing cerebral amyloid angiopathy [4]. These Aβ clearance systems function in a complimentary manner to prevent accumulation of Aβ.

Disease conditions where clearance mechanisms fail and protein accumulates on the blood vessel wall may be collectively called protein-elimination failure arteriopathies (PEFA). Besides Aβ, gelsolin, cystatin C and transthyretin cause cerebral hemorrhage and dementia in familial cerebral amyloid angiopathy, and especially the latter two proteins accumulate in blood vessels of organs other than the brain. Also, in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), a hereditary vascular dementia caused by *Notch3* mutation, NOTCH3 produced from vascular smooth muscle cells accumulates in the blood vessel wall as granular osmiophilic material (GOM) [27], which is also thought to be a type of PEFA. Since GOM is also observed in peripheral blood vessels, including the skin, the breakdown of such a drainage route may be a phenomenon which can also occur in organs other than the brain.

V. Peripheral metabolism of Aβ

According to the sink hypothesis, Aβ is withdrawn from the brain parenchyma to the luminal space by the action of LRP-1 and P-glycoprotein, which bind to serum proteins such as sRAGE, sLRP-1, and ApoE. More than 60% of Aβ in blood is degraded in the liver: hepatocytes take up more than 90%, and phagocytic Kupffer cells less than 2% [28]. Aβ incorporated into hepatocytes is degraded and metabolized by proteases, such as neprilysin, insulin-degrading enzyme, plasmin and angiotensin-converting enzyme, and finally excreted into the bile (Fig. 2). The medicinal herb Ashwagandha, used In Indian traditional medicine, has been reported to significantly decrease the amount of Aβ in the brain by increasing the expression of LRP-1 and neprilysin in the liver in animal experiments, and may thus possess therapeutic properties to promote Aβ withdrawal [29]. Similar to this mechanism, solanezumab, an antibody against Aβ, forms a complex with Aβ in the blood, resulting in a central-to-peripheral gradient in Aβ concentration, potentially removing Aβ from the brain parenchyma. However, a clinical trial using solanezumab has failed to show efficacy against mild AD [30].

Conclusion

This article has outlined the mechanisms behind Aβ clearance. When vascular degeneration occurs with aging and/or cerebral amyloid angiopathy, Aβ clearance is impaired and accumulation accelerated. Therefore, prevention of vascular degeneration is also important for AD treatment. In the past, cerebrovascular disease was generally accepted to be distinct from AD resulting from a neurodegenerative process. However, it is clear that this simple dichotomy needs revision in light of the apparent vessel-dependent process of Aβ clearance.

Therefore, further elucidation of the physiologically and pathologically important Aβ clearance mechanism is warranted. AD research, when viewed from a neurodegenerative standpoint, has made considerable breakthroughs. However, it is apparent that this focus only represents part of the disease trajectory, which may explain the lack of efficacy in recent clinical trials. It is our hope that a more vascular approach may offer new avenues and treatments for AD in the near future.

Acknowledgements

The author would like to thank Dr. Ahmad Khundakar (Teesside University, UK) for his editorial assistance.

Disclosures: none

References

[1] Abbott NJ. Evidence for bulk flow of brain interstitial fluid: significance for physiology and pathology. Neurochem Int 2004;45:545–552. doi:10.1016/j.neuint.2003.11.006.

[2] Rapopart SI. Blood-brain barrier in physiology and medicine. New York: Raven Press; 1976.

[3] Mawuenyega KG, Sigurdson W, Ovod V, Munsell L, Kasten T, Morris JC, et al. Decreased clearance of CNS beta-amyloid in Alzheimer's disease. Science 2010;330:1774. doi:10.1126/science.1197623.

[4] Saito S, Ihara M. New therapeutic approaches for Alzheimer's disease and cerebral amyloid angiopathy. Front Aging Neurosci 2014;6. doi:10.3389/fnagi.2014.00290.

[5] Davis J, Xu F, Deane R, Romanov G, Previti ML, Zeigler K, et al. Early-onset and robust cerebral microvascular accumulation of amyloid beta-protein in transgenic mice expressing low levels of a vasculotropic Dutch/Iowa mutant form of amyloid beta-protein precursor. J Biol Chem 2004;279:20296–20306. doi:10.1074/jbc.M312946200 [doi]M312946200 [pii].

[6] Bartels AL. Blood-brain barrier P-glycoprotein function in neurodegenerative disease. Curr Pharm Des 2011;17:2771–2777.

[7] Weller RO, Djuanda E, Yow HY, Carare RO. Lymphatic drainage of the brain and the pathophysiology of neurological disease. Acta Neuropathol 2009;117:1–14. doi:10.1007/s00401-008-0457-0 [doi].

[8] Albargothy NJ, Johnston DA, MacGregor-Sharp M, Weller RO, Verma A, Hawkes CA, et al. Convective influx/glymphatic system: tracers injected into the CSF enter and leave the brain along separate periarterial basement membrane pathways. Acta Neuropathol 2018;136:139–152. doi:10.1007/s00401-018-1862-7.

[9] Maki T, Okamoto Y, Carare RO, Hase Y, Hattori Y, Hawkes CA, et al. Phosphodiesterase III inhibitor promotes drainage of cerebrovascular β-amyloid. Ann Clin Transl Neurol 2014;1:519–533. doi:10.1002/acn3.79.

[10] Saito S, Kojima S, Oishi N, Kakuta R, Maki T, Yasuno F, 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;2. doi:10.1016/j.trci.2016.10.001.

[11] Rennels ML, Gregory TF, Blaumanis OR, Fujimoto K, Grady PA. Evidence for a "paravascular" fluid circulation in the mammalian central nervous system, provided by the rapid distribution of tracer protein throughout the brain from the subarachnoid space. Brain Res 1985;326:47–63.

[12] Iliff JJ, Wang M, Zeppenfeld DM, Venkataraman A, Plog BA, Liao Y, et al. Cerebral Arterial Pulsation Drives Paravascular CSF-Interstitial Fluid Exchange in the Murine Brain. J Neurosci 2013;33:18190–18199. doi:10.1523/JNEUROSCI.1592-13.2013.

[13] Da Mesquita S, Fu Z, Kipnis J. The Meningeal Lymphatic System: A New Player in Neurophysiology. Neuron 2018;100:375–388.

doi:10.1016/j.neuron.2018.09.022.

[14] Da Mesquita S, Louveau A, Vaccari A, Smirnov I, Cornelison RC, Kingsmore KM, et al. Functional aspects of meningeal lymphatics in ageing and Alzheimer's disease. Nature 2018;560:185–191. doi:10.1038/s41586-018-0368-8.

[15] Boland B, Yu WH, Corti O, Mollereau B, Henriques A, Bezard E, et al. Promoting the clearance of neurotoxic proteins in neurodegenerative disorders of ageing. Nat Rev Drug Discov 2018;17:660–688. doi:10.1038/nrd.2018.109.

[16] Ulland TK, Colonna M. TREM2 — a key player in microglial biology and Alzheimer disease. Nat Rev Neurol 2018;14:667–675. doi:10.1038/s41582-018-0072-1.

[17] Schwalbe G. Der Arachnoidalraum, ein Lymphraum und sein Zusammenhang mit dem Perichoroidalraum. Zentralb Med Wiss 1869;7:465–467.

[18] Bradbury MW, Cserr HF, Westrop RJ. Drainage of cerebral interstitial fluid into deep cervical lymph of the rabbit. Am J Physiol 1981;240:F329-36.

[19] Zhang ET, Richards HK, Kida S, Weller RO. Directional and compartmentalised drainage of interstitial fluid and cerebrospinal fluid from the rat brain. Acta Neuropathol 1992;83:233–239.

[20] Carare RO, Bernardes-Silva M, Newman TA, Page AM, Nicoll JA, Perry VH, et al. Solutes, but not cells, drain from the brain parenchyma along basement membranes of capillaries and arteries: significance for cerebral amyloid angiopathy and neuroimmunology. Neuropathol Appl Neurobiol 2008;34:131–144. doi:NAN926 [pii]10.1111/j.1365-2990.2007.00926.x [doi].

[21] Schley D, Carare-Nnadi R, Please CP, Perry VH, Weller RO. Mechanisms to explain the reverse perivascular transport of solutes out of the brain. J Theor Biol 2006;238:962–974. doi:S0022-5193(05)00308-5 [pii]10.1016/j.jtbi.2005.07.005 [doi].

[22] Shinkai Y, Yoshimura M, Ito Y, Odaka A, Suzuki N, Yanagisawa K, et al. Amyloid beta-proteins 1-40 and 1-42(43) in the soluble fraction of extra- and intracranial blood vessels. Ann Neurol 1995;38:421–428. doi:10.1002/ana.410380312.

[23] Bakker ENTP, Bacskai BJ, Arbel-Ornath M, Aldea R, Bedussi B, Morris AWJ, et al. Lymphatic Clearance of the Brain: Perivascular, Paravascular and Significance for Neurodegenerative Diseases. Cell Mol Neurobiol 2016;36:181–194. doi:10.1007/s10571-015-0273-8.

[24] Hawkes CA, Härtig W, Kacza J, Schliebs R, Weller RO, Nicoll JA, et al. Perivascular drainage of solutes is impaired in the ageing mouse brain and in the presence of cerebral amyloid angiopathy. Acta Neuropathol 2011;121:431–443. doi:10.1007/s00401-011-0801-7.

[25] Okamoto Y, Yamamoto T, Kalaria RN, Senzaki H, Maki T, Hase Y, et al. Cerebral hypoperfusion accelerates cerebral amyloid angiopathy and promotes cortical microinfarcts. Acta Neuropathol 2012;123:381–394. doi:10.1007/s00401-011-0925-9.

[26] Arbel-Ornath M, Hudry E, Eikermann-Haerter K, Hou S, Gregory JL, Zhao L, et al. Interstitial fluid drainage is impaired in ischemic stroke and Alzheimer's disease mouse models. Acta Neuropathol 2013;126:353–364. doi:10.1007/s00401-013-1145-2.

[27] Ishiko A, Shimizu A, Nagata E, Takahashi K, Tabira T, Suzuki N. Notch3 ectodomain is a major component of granular osmiophilic material (GOM) in CADASIL. Acta Neuropathol 2006;112:333–339. doi:10.1007/s00401-006-0116-2.

[28] Ghiso J, Shayo M, Calero M, Ng D, Tomidokoro Y, Gandy S, et al. Systemic catabolism of Alzheimer's Abeta40 and Abeta42. J Biol Chem 2004;279:45897–45908. doi:10.1074/jbc.

M407668200.

[29] Sehgal N, Gupta A, Valli RK, Joshi SD, Mills JT, Hamel E, et al. Withania somnifera reverses Alzheimer's disease pathology by enhancing low-density lipoprotein receptor-related protein in liver. Proc Natl Acad Sci U S A 2012;109:3510–3515. doi:10.1073/pnas.1112209109.

[30] Honig LS, Vellas B, Woodward M, Boada M, Bullock R, Borrie M, et al. Trial of Solanezumab for Mild Dementia Due to Alzheimer's Disease. N Engl J Med 2018;378:321–330. doi:10.1056/NEJMoa1705971.

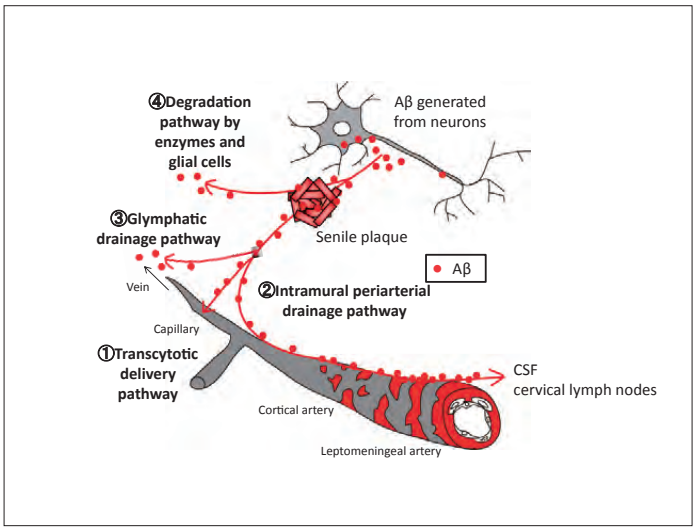

Figure 1. Clearance mechanism of A β (4-d)

Representative pathways of Aβ clearance pathways from the brain include (1) transcytotic delivery, (2) intramural periarterial drainage (IPAD), (3) glymphatic drainage and (4) enzymatic or glial degradation. These clearance mechanisms seem to work in a complimentary manner to prevent the accumulation of Aβ. However, once the equilibrium is disrupted as a result of aging and/or arteriosclerosis accumulation of Aβ may start in the brain.

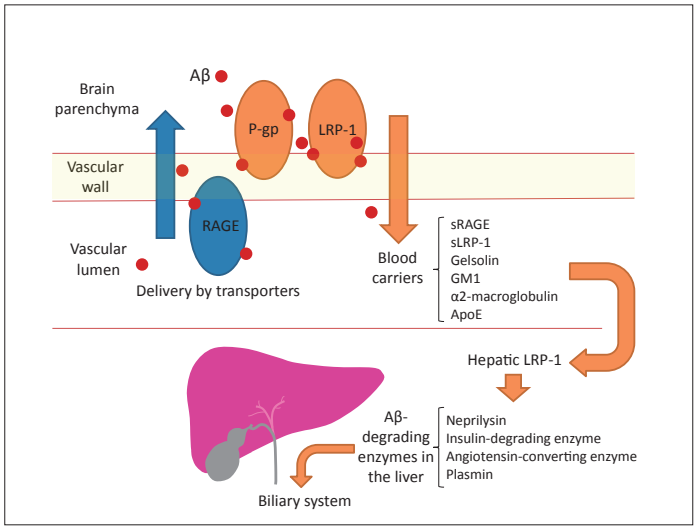

Figure 2. Peripheral metabolism of A β

According to the sink hypothesis, Aβ is withdrawn from the brain parenchyma to the vascular lumen by transporters, such as LRP-1 and P glycoprotein (P-gp), and transported by various carriers in the blood. After being transported to the liver, LRP-1 in hepatocytes incorporate Aβ, which is degraded by Aβ-degrading enzymes (sRAGE, sLRP-1, gelsolin, GM1, α2-macroglobulin, and ApoE) and excreted into the biliary system. Therefore, by accelerating such peripheral degradation, the brain-blood equilibrium of Aβ shifts, leading to increased withdrawal of Aβ from the brain parenchyma into the blood. Since RAGE is involved in the transport of Aβ from the vascular lumen to the brain parenchyma, inhibition of RAGE may result in Aβ clearance.
Abbreviations: ApoE, apolipoprotein E; GM1, ganglioside GM1; LRP-1, low density lipoprotein receptor-related protein 1; P-gp, P-glycolipid; RAGE, receptor for advanced glycation end product; sLRP-1, soluble low density lipoprotein receptor-related protein 1

Review article

New insights into the role of lifestyle-related diseases on vascular dementia and Alzheimer's disease

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

Abstract

Lifestyle-related diseases, such as diabetes mellitus, hypertension, and dyslipidemia, are known to promote arteriosclerosis and increase the risk of vascular dementia. Recent epidemiological studies have revealed that these lifestyle-related diseases are risk factors not only for vascular dementia but also for Alzheimer's disease. Such findings suggest a common molecular pathology between vascular dementia and Alzheimer's disease, which is mediated by biological pathways associated with lifestyle-related diseases, including the renin-angiotensin system and insulin signaling. There is a complicated interplay in mutual modifications among lifestyle-related diseases, vascular dementia, and Alzheimer's disease. It is important to take the complex and multifactorial nature of the disease into account when considering the underlying disease mechanisms of individual patients with dementia. It is also becoming evident that the molecules related to the pathogenesis of Alzheimer's disease, such as β-amyloid, have a direct impact on cerebrovascular damages, which could also be important for understanding the link between vascular dementia and Alzheimer's disease, and how it is influenced by lifestyle-related diseases. Given the rapid growth of the aging population, the treatment strategy for dementia is necessarily shifting to earlier-stage interventions and prevention. Understanding how lifestyle-related diseases contribute to the pathogenesis of both vascular dementia and Alzheimer's disease could be a key in tackling dementia.

Key words

Vascular dementia, Alzheimer's disease, lifestyle-related disease, β-amyloid, cerebral amyloid angiopathy

Correspondence to:
Shuko Takeda
Department of Clinical Gene Therapy, School of Medicine, Osaka University
2-2 Yamada-oka, Suita 565-0871, Japan
Tel: 81-6-6210-8351, Fax: 81-6-6210-8354
Email: takeda@cgt.med.osaka-u.ac.jp

Introduction

Vascular dementia (VaD) is a general term describing a cognitive decline caused by cerebrovascular disease (CVD), and it is the second most-frequent form of dementia after Alzheimer's disease (AD). The pathogenesis and pathology of VaD are extremely diverse. According to the commonly used diagnostic criteria of the National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN), VaD is divided into: 1) multi-infarct dementia, 2) strategic single-infarct dementia, 3) small vascular-lesion dementia, 4) low-perfusion VaD, and 5) cerebral hemorrhagic VaD. To understand the underlying disease mechanism and choose an appropriate medication and therapeutic strategy for each patient with dementia, it is important to note that VaD is not a single concept.

VaD and AD are two of the most-common forms of dementia among the elderly and often occur together. Classically, AD has been distinguished from VaD on the basis of having its unique neuropathological features, senile plaques, and neurofibrillary tangles instead of the severe cerebrovascular changes observed in the brain of VaD. However, a growing body of evidence from clinical and basic studies suggests that they have common molecular mechanisms.[1] Separating them as individual diseases, based on their classical concepts, is not only clinically difficult, but it could also show an extremely inadequate understanding of the pathogenesis of dementia.

Whereas lifestyle-related diseases, such as hypertension, diabetes mellitus, and dyslipidemia, are well known to induce arteriosclerosis in cerebrovasculature and increase the risk of developing VaD, accumulating evidence suggests that these factors are also independent risk factors for AD.[2,3] This implies a biological interplay among these pathological conditions. There seems to be a very complicated pathologic interaction in the brain, where VaD, AD, and lifestyle-related diseases mutually modify their biological mechanisms.

This review outlines the relationship among VaD, AD, and lifestyle-related diseases and how lifestyle-related diseases affect the pathologic link between VaD and AD, focusing on the potential common mechanisms.

Relationship between lifestyle-related diseases and dementia

Lifestyle-related diseases are associated with an increased number of dementia cases.[4] Hypertension is the greatest risk factor for arteriosclerosis—the presence of hypertension in middle and old ages raises the relative risk for the development of VaD up to approximately 10 times.[5] Recent studies have shown that hypertension in midlife is associated with AD development later in life.[3] Furthermore, the use of antihypertensive drugs is shown to reduce the incidence of dementia, including AD.[6-8]

It has been shown that diabetes mellitus increases the risk of CVD through arteriosclerosis, which leads to the development of VaD in later life.[5] Importantly, impaired glucose tolerance, which is a very early stage of diabetes, is shown to increase the risk of developing VaD, suggesting that early detection and intervention of a glucose metabolism abnormality are very important for preventing VaD.[9] Multiple studies have shown that diabetes mellitus significantly raises the risk of developing AD as well, which provides a new insight about biological mechanisms underlying AD.[2,10,11] Although the mechanism by which hypertension and diabetes mellitus increase the risk, development of AD is largely unknown, cerebrovascular alteration mediated by AD-related amyloid-β (Aβ) may partly account for it.

Biological link between hypertension and AD

Recent evidence suggests a biological link between hypertension, or alteration of the renin-angiotensin system (RAS), and AD. The central nervous system is known to have its own RAS mediating physiological and pathological brain functions.[12] Most RAS components are present in the central nervous

system, not only in the cerebrovasculature but also in the neuronal and glial cells. Angiotensinogen is detected in the choroid plexus and astrocytes at a high concentration. Angiotensin II has been identified within synaptic vesicles together with a high concentration of angiotensin receptor. Renin and angiotensin-converting enzymes are widely distributed throughout the brain.[13] Multiple studies have reported RAS activation in the brain of AD patients[14,15], supporting the idea that RAS could be a potential target for cognitive dysfunction and AD.

In this regard, some clinical studies suggest an association between the use of angiotensin receptor blockers (ARB) and a lower incidence of AD.[8] Takeda et al. have reported a beneficial effect of ARB on AD-related cognitive impairment, which is independent of its blood-pressure-lowering effect. Treatment with ARB prevented Aβ-induced vascular dysregulation by reducing oxidative stress on the cerebrovasculature, leading to improved cognitive function in AD mice.[16] The molecular mechanisms contributing to the beneficial effects of RAS modulation may be complex and pleiotropic.

Biological link between diabetes mellitus and AD

The association between diabetes mellitus and AD can partially be explained by cerebrovascular damage due to diabetes, which directly affects cognitive function. However, findings from clinical studies imply that the association exists independently of vascular factors,[10] raising the possibility that diabetic conditions may have a direct impact on the pathogenesis of AD.

It is becoming increasingly apparent that insulin is involved in the neuronal functions in the brain via mechanisms that are potentially independent of glucoregulatory function. Insulin receptors can be detected in the neurons of the hippocampus and cerebral cortex, and a downregulation of insulin and insulin-signaling pathway molecules has been shown in the postmortem brain of AD.[17,18]

Insulin potentially plays a role in the development of AD neuropathology. Senile plaque (extracellular deposits of Aβ) and neurofibrillary tangle (intracellular aggregates of tau) are major neuropathological hallmarks of AD. Insulin reportedly regulates Aβ concentration by modulating the enzyme responsible for Aβ production or by modulating Aβ degradation by competing with Aβ-degrading enzymes, including insulin-degrading enzymes.[19,20] Insulin is also known to affect tau pathology via activation of glycogen synthase kinase (GSK)-3β, which is one of the kinases involved in tau phosphorylation. Downregulation of insulin signaling leads to hyper-activation of GSK-3β and subsequent phosphorylation of tau, resulting in intracellular aggregation and formation of neurofibrillary tangle.[21]

Takeda et al. explored a mechanistic link between diabetes mellitus and AD by establishing unique diabetic-AD mouse models.[11] The diabetic-AD mice showed an early-onset cognitive impairment compared to the normal AD mouse model. One of the most striking changes in the diabetic-AD mice was impaired brain-insulin signaling. The diabetic-AD mice had lower levels of insulin in the brain, and the insulin signaling pathway was severely impaired.

Notably, the diabetic-AD mice showed an accelerated diabetic phenotype compared to normal diabetic mice, suggesting reciprocal actions between diabetes mellitus and AD. This reciprocity also supports the idea that diabetes and AD share common biological mechanisms.

Synergistic effect of lifestyle-related diseases on the pathogenesis of dementia

Because lifestyle-related diseases are associated with both VaD and AD, it is necessary to consider that a patient with lifestyle-related diseases is potentially at a high risk for developing both types of dementia and their pathologic interaction in the brain (Fig. 1). Hypertension and diabetes mellitus have synergistic effects on developing CVD through arteriosclerosis. Chronic hyperglycemia and hyperinsulinemia due to diabetes mellitus impair the vascular endothelial cells through oxidative stress and increase inflammatory cytokines.[22] Inflammatory

cells infiltrating the vascular wall through the damaged endothelial cells cause degeneration of the vascular wall, leading to the progression of arteriosclerosis in the cerebral vessels. Cognitive function can be impaired when cerebral blood flow falls below the lower limit of maintaining physiological neuronal activities in the brain. Reduction of cerebral blood flow can be caused by functional alteration (decrease in the physiological dilatory capacity of the cerebral artery to maintain enough blood flow and energy for the activated brain area) or structural changes (narrowing of the blood-vessel lumen or thrombus formation) of the blood-vessel walls, both of which have root cause in vascular endothelial damage or dysfunction. Hypertension is also tightly associated with endothelial impairment and cerebrovascular arteriosclerosis; hypertension and diabetes mellitus have synergistic effects on the risk of development of CVD by up to two- to threefold.[23] Studies using AD animal models show that diabetes mellitus and hypertension can increase the production rate of Aβ in the brain[24] or impair the clearance mechanism of Aβ from the brain,[25] both leading to Aβ plaque formation.

Aβ aggregates are known to accumulate not only in the brain parenchyma but also in the cerebral blood vessels (cerebral amyloid angiopathy [CAA]).[26] Aβ has been shown to have vasoconstrictor activity, and it is becoming evident that Aβ accumulation causes direct damage to the cerebral blood vessels.[16] Recent studies also report that the vascular-damaging activity of Aβ becomes more evident in the presence of hypertension.[24] This suggests that AD-related Aβ plays a role in the development of hypertension-induced CVD.

CAA, lifestyle-related diseases, and pathogenesis of dementia

CAA may be a key player linking lifestyle-related diseases, VaD, and AD. Although CAA can be part of a normal aging process, which is observed in the brains of healthy elderly people, it occurs much more frequently and severely in the brains of those with AD. CAA is often accompanied by multiple cerebral microbleeds and is also known to contribute to the pathogenesis of VaD.[27]

Emerging evidence from clinical and basic research suggests that lifestyle-related diseases may exacerbate CAA.[27] Ellis et al. reported a significant correlation between the severities of CAA and cerebrovascular atherosclerosis in a study of 117 autopsy-confirmed AD cases,[28] suggesting an interplay between AD pathogenesis and atherosclerosis, both of which can be influenced by the presence of lifestyle-related diseases. An *in vivo* study using an AD animal model with a diabetic condition reported a significant deposition of Aβ in the cerebral vessels of diabetic AD mice, which was associated with an increase in the inflammatory responses of the cerebrovasculature, leading to an exacerbation of the cognitive impairment of the mice.[11]

Deposition of Aβ in CAA induces the degeneration of the cerebrovascular walls, such as fibrinoid necrosis, microaneurysmal change, and stenosis. Progression of CAA leads to cerebrovascular breakdown causing hemorrhagic or ischemic lesions that, in turn, exacerbate cognitive dysfunction.[29] Increasing numbers of studies support a direct association between lifestyle-related diseases and CAA.[30] Stricter management of lifestyle-related diseases can be important in a patient with suspected CAA (a patient with multiple cerebral microbleeds on MRI image), especially when with multiple CVD risk factors in terms of prevention of cognitive impairment and dementia.

Conclusion

Lifestyle-related diseases raise the risk of developing VaD through arteriosclerotic changes. Recent research reveals that: 1) lifestyle-related diseases are risk factors not only for VaD but also for AD, 2) VaD and AD may have common biological mechanisms, and 3) CAA is involved in the pathogenesis of both VaD and AD. As the number of

dementia cases is expected to increase rapidly with the aging of society, it is becoming more important to understand the biological linkage among lifestyle-related diseases, VaD, and AD (Fig. 3). Better understanding of the mechanisms underlying the biological interplay among these pathological conditions may contribute to the development of a new therapeutic strategy for dementia.

Acknowledgements

This work was supported by JSPS KAKENHI Grant Number 17H05080 (grant-in-Aid for Young Scientists (A)).

Disclosures; ST has no potential conflicts.

References

1. Attems, J. & Jellinger, K.A. The overlap between vascular disease and Alzheimer's disease--lessons from pathology. *BMC medicine* **12**, 206 (2014).
2. Takeda, S., Sato, N., Rakugi, H. & Morishita, R. Molecular mechanisms linking diabetes mellitus and Alzheimer disease: beta-amyloid peptide, insulin signaling, and neuronal function. *Molecular bioSystems* **7**, 1822-1827 (2011).
3. Takeda, S., Sato, N., Ogihara, T. & Morishita, R. The renin-angiotensin system, hypertension and cognitive dysfunction in Alzheimer's disease: new therapeutic potential. *Frontiers in bioscience : a journal and virtual library* **13**, 2253-2265 (2008).
4. Livingston, G., *et al.* Dementia prevention, intervention, and care. *Lancet (London, England)* **390**, 2673-2734 (2017).
5. Ninomiya, T., *et al.* Midlife and late-life blood pressure and dementia in Japanese elderly: the Hisayama study. *Hypertension (Dallas, Tex. : 1979)* **58**, 22-28 (2011).
6. Forette, F., *et al.* Prevention of dementia in randomised double-blind placebo-controlled Systolic Hypertension in Europe (Syst-Eur) trial. *Lancet (London, England)* **352**, 1347-1351 (1998).
7. Khachaturian, A.S., *et al.* Antihypertensive medication use and incident Alzheimer disease: the Cache County Study. *Archives of neurology* **63**, 686-692 (2006).
8. Li, N.C., *et al.* Use of angiotensin receptor blockers and risk of dementia in a predominantly male population: prospective cohort analysis. *BMJ (Clinical research ed.)* **340**, b5465 (2010).
9. Matsuzaki, T., *et al.* Insulin resistance is associated with the pathology of Alzheimer disease: the Hisayama study. *Neurology* **75**, 764-770 (2010).
10. Ott, A., *et al.* Diabetes mellitus and the risk of dementia: The Rotterdam Study. *Neurology* **53**, 1937-1942 (1999).
11. Takeda, S., *et al.* Diabetes-accelerated memory dysfunction via cerebrovascular inflammation and Abeta deposition in an Alzheimer mouse model with diabetes. *Proceedings of the National Academy of Sciences of the United States of America* **107**, 7036-7041 (2010).
12. Wright, J.W., Reichert, J.R., Davis, C.J. & Harding, J.W. Neural plasticity and the brain renin-angiotensin system. *Neuroscience and biobehavioral reviews* **26**, 529-552 (2002).
13. Csikos, T., Chung, O. & Unger, T. Receptors and their classification: focus on angiotensin II and the AT2 receptor. *Journal of human hypertension* **12**, 311-318 (1998).
14. Savaskan, E., *et al.* Cortical alterations of angiotensin converting enzyme, angiotensin II and AT1 receptor in Alzheimer's dementia. *Neurobiology of aging* **22**, 541-546 (2001).
15. Barnes, N.M., *et al.* Angiotensin converting enzyme density is increased in temporal cortex from patients with Alzheimer's disease. *European journal of pharmacology* **200**, 289-292 (1991).
16. Takeda, S., *et al.* Angiotensin receptor blocker prevented beta-amyloid-induced cognitive impairment associated with recovery of neurovascular coupling. *Hypertension (Dallas, Tex. : 1979)* **54**, 1345-1352 (2009).

17. Freude, S., *et al.* Neuronal IGF-1 resistance reduces Abeta accumulation and protects against premature death in a model of Alzheimer's disease. *FASEB journal : official publication of the Federation of American Societies for Experimental Biology* **23**, 3315-3324 (2009).
18. Rivera, E.J., *et al.* Insulin and insulin-like growth factor expression and function deteriorate with progression of Alzheimer's disease: link to brain reductions in acetylcholine. *Journal of Alzheimer's disease : JAD* **8**, 247-268 (2005).
19. Eckman, E.A. & Eckman, C.B. Abeta-degrading enzymes: modulators of Alzheimer's disease pathogenesis and targets for therapeutic intervention. *Biochemical Society transactions* **33**, 1101-1105 (2005).
20. Farris, W., *et al.* Insulin-degrading enzyme regulates the levels of insulin, amyloid beta-protein, and the beta-amyloid precursor protein intracellular domain in vivo. *Proceedings of the National Academy of Sciences of the United States of America* **100**, 4162-4167 (2003).
21. Rad, S.K., *et al.* Mechanism involved in insulin resistance via accumulation of beta-amyloid and neurofibrillary tangles: link between type 2 diabetes and Alzheimer's disease. *Drug design, development and therapy* **12**, 3999-4021 (2018).
22. Kim, J.A., Montagnani, M., Koh, K.K. & Quon, M.J. Reciprocal relationships between insulin resistance and endothelial dysfunction: molecular and pathophysiological mechanisms. *Circulation* **113**, 1888-1904 (2006).
23. Hu, G., *et al.* The impact of history of hypertension and type 2 diabetes at baseline on the incidence of stroke and stroke mortality. *Stroke* **36**, 2538-2543 (2005).
24. Faraco, G., *et al.* Hypertension enhances Abeta-induced neurovascular dysfunction, promotes beta-secretase activity, and leads to amyloidogenic processing of APP. *Journal of cerebral blood flow and metabolism : official journal of the International Society of Cerebral Blood Flow and Metabolism* **36**, 241-252 (2016).
25. Hong, H., *et al.* Downregulation of LRP1 [correction of LPR1] at the blood-brain barrier in streptozotocin-induced diabetic mice. *Neuropharmacology* **56**, 1054-1059 (2009).
26. Noguchi-Shinohara, M., *et al.* Cerebral Amyloid Angiopathy-Related Microbleeds and Cerebrospinal Fluid Biomarkers in Alzheimer's Disease. *Journal of Alzheimer's disease : JAD* **55**, 905-913 (2017).
27. Yamada, M. Predicting cerebral amyloid angiopathy-related intracerebral hemorrhages and other cerebrovascular disorders in Alzheimer's disease. *Frontiers in neurology* **3**, 64 (2012).
28. Ellis, R.J., *et al.* Cerebral amyloid angiopathy in the brains of patients with Alzheimer's disease: the CERAD experience, Part XV. *Neurology* **46**, 1592-1596 (1996).
29. Saito, S. & Ihara, M. New therapeutic approaches for Alzheimer's disease and cerebral amyloid angiopathy. *Frontiers in aging neuroscience* **6**, 290 (2014).
30. Yamada, M. Risk factors for cerebral amyloid angiopathy in the elderly. *Annals of the New York Academy of Sciences* **977**, 37-44 (2002).

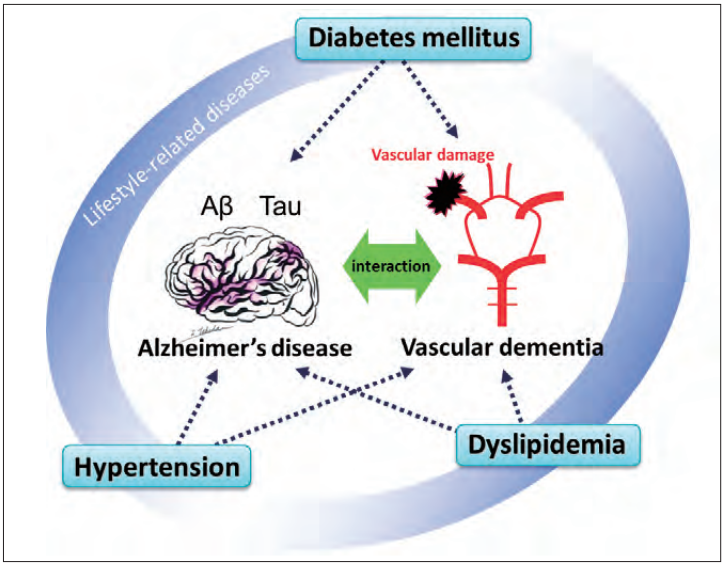

Figure 1 Relationship between lifestyle-related diseases, VaD, and AD

Lifestyle-related diseases, such as diabetes mellitus, hypertension, and dyslipidemia, are common risk factors for both VaD and AD. There is a complex interaction among these pathological conditions. VaD, vascular dementia; AD, Alzheimer's disease.

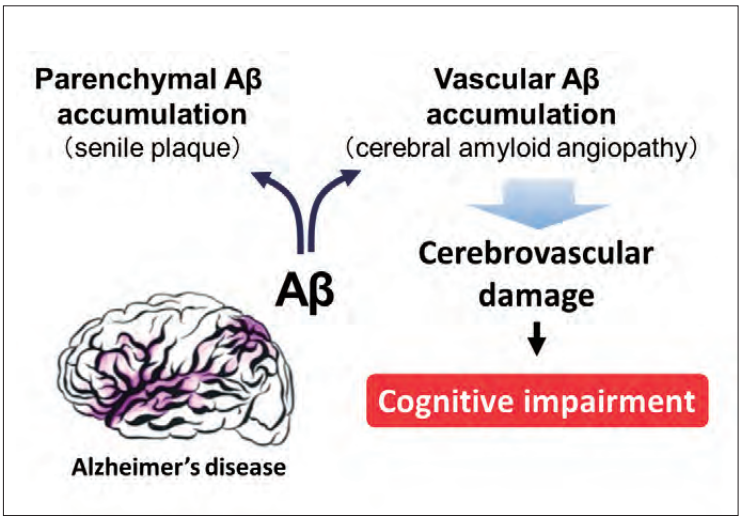

Figure 2 Impact of AD-related A β peptide on cerebrovascular function and cognitive impairment

AD-related Aβ peptide does not only accumulate in the brain parenchyma, forming senile plaques, but also deposits on cerebral blood vessels developing cerebral amyloid angiopathy. Aβ causes functional or structural cerebrovascular alterations, resulting in impairment of cognitive function. AD, Alzheimer's disease; Aβ, β -amyloid.

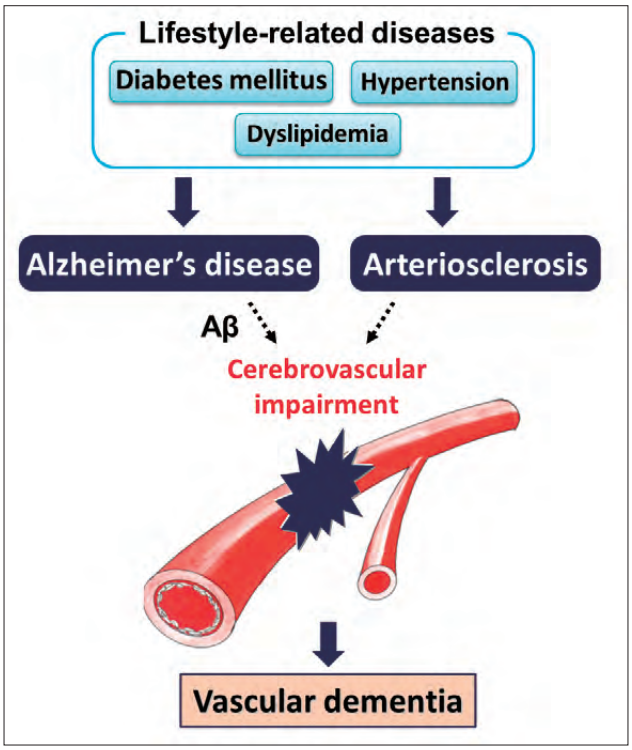

Figure 3 Lifestyle-related diseases and AD synergistically impair cerebrovascular function and exacerbate VaD

Lifestyle-related diseases induce arteriosclerosis in cerebrovasculature, which leads to VaD. Lifestyle-related diseases are also known to affect AD pathology. AD-related Aβ peptides have a direct impact on cerebrovasculature, causing functional and structural damage. Lifestyle-related diseases and AD synergistically exacerbate the pathogenesis of VaD. VaD, vascular dementia; AD, Alzheimer's disease; Aβ, β-amyloid.

Case report

A Japanese family of autosomal dominant cerebral small vessel disease with heterozygous *HTRA1* mutation showing dementia, gait disturbance and subarachnoid hemorrhage

Toru Yamashita, MD, PhD [a]; Hiroaki Nozaki, MD, PhD [b]; Yosuke Wakutani, MD, PhD [c]; Koh Tadokoro, MD [a]; Emi Nomura, MD [a]; Yoshiaki Takahashi, MD [a]; Kota Sato, MD, PhD [a]; Nozomi Hishikawa, MD, PhD [a]; Mami Takemoto, MD, PhD [a]; Jingwei Shang, MD, PhD [a]; Yasuyuki Ohta, MD, PhD [a]; Osamu Onodera, MD, PhD [b]; Koji Abe, MD, PhD [a]

[a] Department of Neurology, Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama University
[b] Department of Neurology, Brain Research Institute, Niigata University
[c] Department of Neurology, Kurashiki Heisei Hospital

Abbreviations: CARASIL, cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy; DSWMH, deep and subcortical white matter hyperintensity; FLAIR, fluid-attenuated inversion recovery; HTRA1, high temperature requirement A serine peptidase 1; MCA, middle cerebral artery; MMSE, mini-mental state examination; MRI, magnetic resonance imaging; PCR-RFLP, PCR-restriction fragment length polymorphism; PVH, periventricular hyperintensity; SAH, subarachnoid hemorrhage; SPECT, single photon emission computed tomography; TGF-β, transforming growth factor-β; TIA, transient ischemic attack; yo, years old.

Abstract

Homozygous mutations of high temperature requirement A serine peptidase 1 (*HTRA1*) gene cause an autosomal recessive cerebral small vessel disease, namely cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL). Meanwhile, heterozygous mutations of the *HTRA1* can also cause an autosomal dominant small vessel disease with a milder clinical phenotype. Here we described 2 patients in a Japanese family with the same heterozygous *HTRA1* mutation (c.496 C>T, p.R166C), showing a unique clinical history of traumatic subarachnoid hemorrhage (SAH), no alopecia or spondylosis, in addition to previously similar clinical phenotypes such as cognitive impairment, gait disturbance, and hyperreflexia. The present cases suggest that traumatic SAH may be an important risk of the heterozygous *HTRA1* mutation (c.496 C>T, p.R166C), especially in Asia.

Key words: cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL), high temperature requirement A serine peptidase 1 (HTRA1), subarachnoid hemorrhage (SAH).

Corresponding author: Koji Abe
Address: Department of Neurology, Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama University, 2-5-1 Shikatacho, Okayama 700-8558, Japan
Phone: +81-86-235-7365, Fax: +81-86-235-7368
E-mail: tooy@d1.dion.ne.jp

Introduction

High temperature requirement peptidase A1 (HTRA1) is a serine protease, which inhibits transforming growth factor β (TGF-β) signaling pathway[1]. Homozygous mutations of the *HTRA1* gene cause a hereditary cerebral small vessel disease characterized by leukoencephalopathy, early-onset alopecia and lumber spondylosis, and referred to as cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL)[2, 3]. However, recent evidence noted that heterozygous mutations of *HTRA1* could also cause small vessel disease with a dominant inheritance pattern[4-6]. Here we described 2 patients in a Japanese family with the heterozygous *HTRA1* mutation (c.496 C>T, p.R166C) showing a unique clinical history of traumatic SAH different from previous reports.

Case Reports

Patient II-4 is a 77-year-old (yo) man. When he was 71, he experienced a sudden episode of vertigo that disappeared within 2 days. He was aware of gait disturbance at 73 yo, which became more severe at 75 yo and cognitive function was impaired, but he did not show alopecia or lumbar spondylosis. He visited a local hospital where old multiple lacunar infarctions were detected in brain magnetic resonance imaging (MRI), and then drug treatment started with clopidogrel (75 mg). He was a non-smoker and his blood pressure was normal at 117/70 mmHg. His cognitive function was impaired to mini-mental state examination (MMSE) score of 12/30 and Hasegawa dementia scale-revised score of 7/30. Affective function was also diminished, showing Abe's BPSD score of 8/44. Neurological examination showed hyperreflexia and slight cogwheel rigidity (R>L) in all extremities, but no evident pathological reflexes or sensory disturbances in his extremities. A fluid-attenuated inversion recovery (FLAIR) image of MRI showed hyperintensity in the periventricular white matter with atrophic splenium of corpus callosum (Fig. 1b & 1c, an arrow), whereas the tip of the temporal lobe was spared. At 77 yo, he stumbled and received a blow to the left side of his head, when a slight traumatic subarachnoid hemorrhage (SAH) was detected by head CT scan (Fig. 1d, an arrowhead). Despite this, he recovered within 3 days without sequela.

Patient III-1 is a 56 yo man, the proband of the present family, and a nephew of patient II-4. His mother, who also showed cognitive dysfunction, was diagnosed with Alzheimer`s disease in a local hospital at 79 yo, and died of aspiration pneumonia at 85 yo. At 53 yo, he experienced an acute episode of dysarthria and visited a local hospital, where multiple small infarctions were pointed out in the left middle cerebral artery (MCA) territory on a brain MRI. Drug treatment with aspirin (100 mg) started, and the above symptom resolved in a week. At 56 yo, he displayed dysarthria once again and newly obtained gait disturbance and cognitive dysfunction. When he visited our hospital, he did not show alopecia or lumbar spondylosis. He was a non-smoker and his blood pressure was normal at 125/90 mmHg. His cognitive function was mildly impaired with MMSE score of 26/30, Hasegawa dementia scale-revised score of 21/30, frontal assessment battery score of 9/18, and Montreal cognitive assessment score of 23/30. He was depressive with geriatric depression scale of 10/15, and apathetic with apathy score of 23/42, but no BPSD showing Abe's BPSD score of 0/44. A neurological examination showed dysarthria as well as hyperreflexia in all extremities, but no evident pathological reflexes nor sensory disturbances in his extremities. Serum analysis showed normal LDL-cholesterol (128 mg/dl, normal 65-165 mg/dl), triglycerides (71 mg/dl, normal 40-234 mg/dl), fasting blood glucose (100 mg/dl, normal 73-109 mg/dl), HbA1c (5.7%, normal 4.9-6.0%), homocysteine (10.3 nmol/ml, normal 3.7-13.5 nmol/ml), protein C activity (115%, normal 64-146%), and protein S (95%, normal 60-150%). Serum very long chain free fatty acids were also normal. A cerebrospinal fluid examination revealed 1 leucocyte/μl with 100% mononucleosis and normal glucose (58 mg/dl) but an increased level of protein (78 mg/dl). The MRI (FLAIR) images showed hyperintensity in the deep and periventricular white matter with atrophic splenium of corpus callosum

(Fig. 1f & 1g). Despite no significant stenosis in the major artery (Fig. 1e), cerebral blood flow showed hypoperfusion of bilateral frontal lobes, bilateral parietal lobes, and the left temporal lobe (Fig. 2). Due to this small vessel disease, cilostazol (100 mg) was added to aspirin. However, at 58 yo, after he fell and hit his head on the floor, CT scan showed a massive traumatic SAH (Fig.1h, arrowheads) with right subdural hematoma (Fig.1h, arrow). Despite craniotomy to remove the hematoma, he deceased.

For DNA analysis, written informed consent was obtained from the father and the 2 affected patients with approval of the research ethics committee of Okayama University (#329) and Niigata University (#802). Genomic DNA was extracted from the peripheral blood leukocytes of the father and both patients, and Sanger sequence analysis of *CSF1R* (exons 12-22) and *Notch3* (exons 2-24) were performed only in Patient III-1, but were normal. Then direct sequencing of *HTRA1* exons with the Sanger method was performed in the father and the 2 affected patients as previously reported[6]. Both affected patients showed a heterozygous point mutation from C to T coding 496, resulting in substitution of the 166th arginine to cysteine located in exon2 of the *HTRA1* gene (c.496 C>T, p.R166C) (Fig. 3a). The point mutations of c.496 C>T in *HTRA1* were confirmed by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) with *Hha*I, and an uncut PCR product band (276 bp) was detected in both patients (Fig. 3b). Based on the above data, we diagnosed the 2 patients as having an autosomal dominant cerebral small vessel disease with heterozygous *HTRA1* mutation (c.496 C>T, p.R166C).

Discussion

Here we described 2 patients in a Japanese family with similar clinical phenotypes such as cognitive impairment, gait disturbance, hyperreflexia, history of traumatic SAH without alopecia or spondylosis, caused by a heterozygous *HTRA1* mutation (c.496 C>T, p.R166C). The same p.R166C mutation was previously reported in Greece[4], in which a patient of heterozygous *HTRA1* mutation (p.R166C) showed cognitive impairment, gait disturbance, hyperreflexia and alopecia without spondylosis (Table 1). Although the same heterozygous *HTRA1* mutation may cause a different clinical spectrum, the present Japanese cases showed a unique clinical history of traumatic SAH, different from the Greek case (Table 1).

HTRA1 is a serine protease that represses the transforming growth factor β (TGF-β) signaling pathway, whereas mutated *HTRA1* cannot repress the production of TGF-β. As a result, overproduced TGF-β is believed to cause cerebral small vessel disease characterized by recurrent ischemic stroke, multiple lacunar infarctions, and leukoencephalopathy[1,3]. In patients with a homozygous/heterozygous *HTRA1* mutation, cerebral small vessels show pathological changes such as initial thickening with fibronectin, splitting of the elastic lamina and loss of smooth muscle cells[7,8], which has been assumed to induce cerebral ischemia. However, Asian patients, including Taiwanese, Chinese, and Japanese with heterozygous *HTRA1* mutations, sometimes showed intracerebral hemorrhage[9-11], indicating that the *HTRA1* mutation may cause vulnerability of cerebral artery. In fact, both Japanese patients in this paper developed traumatic SAH, although use of anti-platelet drugs may also be related. Hemorrhagic stroke is more common in Asian people than in Caucasian[12], so intracerebral hemorrhage and traumatic SAH may be a greater and/or important risk of heterozygous *HTRA1* mutation (c.496 C>T, p.R166C) in Asian patients than in Caucasian.

Conflicts of interest

The authors disclose no potential conflicts of interest.

Acknowledgements

This work was partly supported by a Grant-in-Aid for Scientific Research (B) 17H04196, (C) 17K10827 and Challenging Research 15K15527, and by Grants-in-Aid from the Research Committees (Mizusawa H, Nishizawa M, Sasaki H, and Aoki M) from the Ministry of Health, Labour and Welfare of Japan.

References

1. Oka C, Tsujimoto R, Kajikawa M, et al. HtrA1 serine protease inhibits signaling mediated by Tgfbeta family proteins. *Development* 2004; 131: 1041-1053.
2. Fukutake T and Hirayama K. Familial young-adult-onset arteriosclerotic leukoencephalopathy with alopecia and lumbago without arterial hypertension. *Eur Neurol* 1995; 35: 69-79.
3. Hara K, Shiga A, Fukutake T, et al. Association of HTRA1 mutations and familial ischemic cerebral small-vessel disease. *N Engl J Med* 2009; 360: 1729-1739.
4. Bougea A, Velonakis G, Spantideas N, et al. The first Greek case of heterozygous cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy: An atypical clinico-radiological presentation. *Neuroradiol J* 2017; 30: 583-585.
5. Nozaki H, Kato T, Nihonmatsu M, et al. Distinct molecular mechanisms of HTRA1 mutants in manifesting heterozygotes with CARASIL. *Neurology* 2016; 86: 1964-1974.
6. Verdura E, Herve D, Scharrer E, et al. Heterozygous HTRA1 mutations are associated with autosomal dominant cerebral small vessel disease. *Brain* 2015; 138: 2347-2358.
7. Ito J, Nozaki H, Toyoshima Y, et al. Histopathologic features of an autopsied patient with cerebral small vessel disease and a heterozygous HTRA1 mutation. *Neuropathology* 2018; 38: 428-432.
8. Oide T, Nakayama H, Yanagawa S, et al. Extensive loss of arterial medial smooth muscle cells and mural extracellular matrix in cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL). *Neuropathology* 2008; 28: 132-142.
9. Kono Y, Nishioka K, Li Y, et al. Heterozygous HTRA1 mutations with mimicking symptoms of CARASIL in two families. *Clin Neurol Neurosurg* 2018; 172: 174-176.
10. Lee YC, Chung CP, Chao NC, et al. Characterization of heterozygous HTRA1 mutations in Taiwanese patients with cerebral small vessel disease. *Stroke* 2018; 49: 1593-1601.
11. Zhang WY, Xie F and Lu PL. Two novel heterozygous HTRA1 mutations in two pedigrees with cerebral small vessel disease families. *Neurol Sci* 2018; 39: 497-501.
12. Poon MT, Bell SM and Al-Shahi Salman R. Epidemiology of intracerebral haemorrhage. *Front Neurol Neurosci* 2015; 37: 1-12.

heterozygous HTRA1 mutation cases showing SAH

Table 1. Characteristics of Patients

	Case II-4	Case III-1	Bougea et al. (2017)
Heterozygous HTRA1 mutation	c.496 C>T (p. R166C)	c.496 C>T (p. R166C)	c.496 C>T (p. R166C)
Gender	M	M	M
Age at onset, y	71	53	29
Age at examination, y	77	56	31
Duration of illness, y	4	3	2
Family history	+	+	+
Hypertension	—	+	—
Hyperlipidemia	—	+	—
Smoking	—	—	—
Initial symptom	gait disturbance	dysarthria and dysphasia	migraine
History of TIA or ischemic stoke	+	+	—
History of traumatic SAH	+	+	-
Cognitive impairment(MMSE)	+ (12)	± (26)	+ (24)
Gait disturbance	+	+	+
Hyperreflexia	+	+	+
Alopecia	—	—	+
Spondylosis	—	—	—
Hearing loss	—	—	+
PVH	+	+	+
DSWMH	+	+	+
Multiple lacunar infarcts	+	+	+
Microbleeds	—	—	—

TIA, transient ischemic attack; SAH, subarachnoid hemorrhage; MMSE, mini-mental state examination; PVH, periventricular hyperintensity; DSWMH, deep and subcortical white matter hyperintensity.

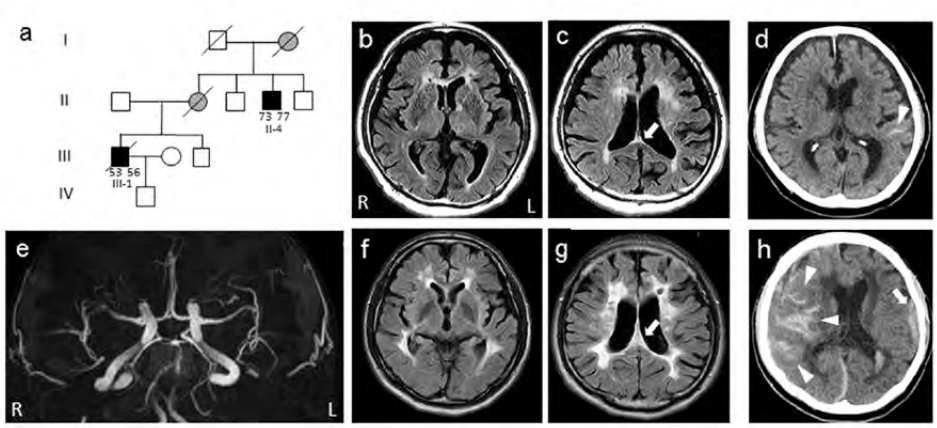

Figure 1.

(a) Family tree of the patients. (b, c) FLAIR images of patient II-4 showing white matter hyperintensities with atrophic corpus callosum (an arrow). (d) Head CT of patient II-4 detecting a slight SAH on the surface of the left temporal lobe (an arrowhead). (e) MR angiography of patient III-1 showing no evident stenosis of the major artery. (f, g) FLAIR images of patient III-1 pointing out diffuse hyperintensities involving periventricular and deep white matter with atrophic corpus callosum (an arrow). (h) Head CT of patient III-1 showing a massive SAH (arrowheads) with right subdural hematoma (an arrow).

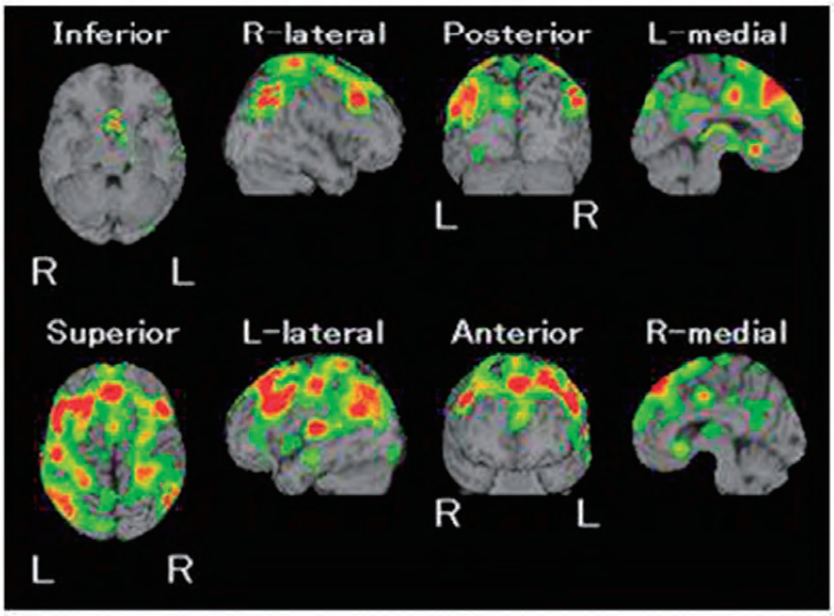

Figure 2.

^{99m}Tc-ECD-single photon emission computed tomography (SPECT) of patient III-1 shows hypoperfusion of bilateral frontal lobes, bilateral parietal lobes, and the left temporal lobe.

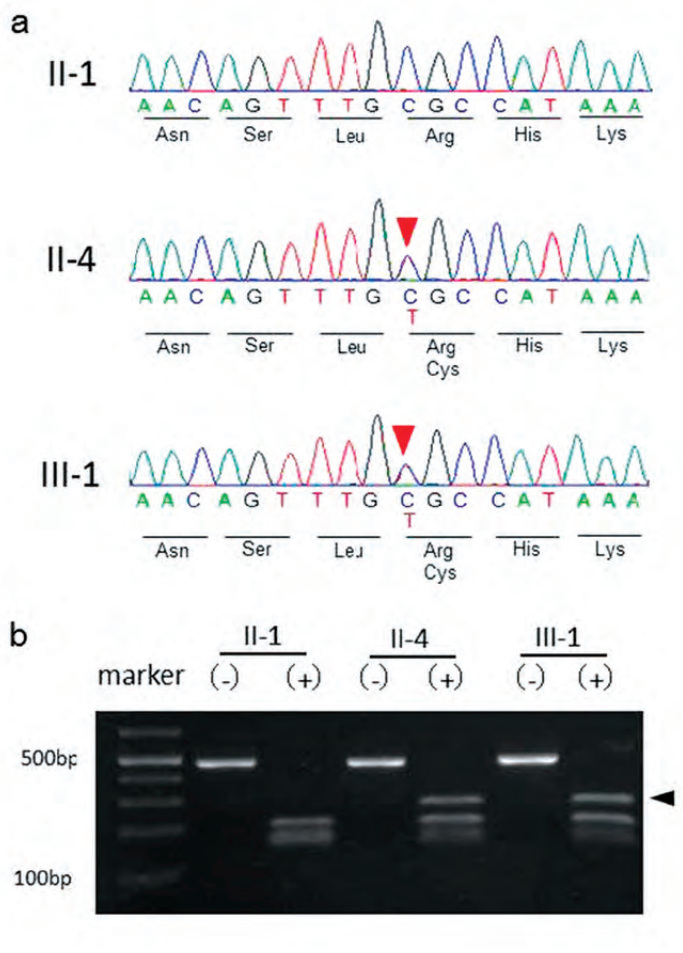

Figure 3.

(a) The 2 patients (II-4 and III-1) carried the same heterozygous point mutation from C to T coding 496 (arrowheads), resulting in substitution of the 166th arginine to cysteine located in exon2 of the *HTRA1* gene. (b) A point mutation of c.496 C>T (p.R166C) in *HTRA1*, confirmed by PCR-RELP with *Hha*I. An uncut PCR product band was found in both patients even after *Hha*I digestion (an arrowhead).

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 9th 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. I would like to express my sincere gratitude to all members of Vas-Cog 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 2019, we have 143 active members, including 26 directors and 54 councilors, and the membership is expected to increase in the future. Furthermore, the financial structure has been going very well. 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 9th Annual Meeting of Vas-Cog Japan was successfully held August 4–5, 2018, at Beppu Convention Center (B-ConPlaza) in Oita, organized by chairpersons Prof. Katsuya Urakami and Prof. Etsuro Matsubara. 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 10th annual meeting will be held at "Sola City Conference Center" in Tokyo on August 3, 2019, with Prof. Yoshio Ikeda and Prof. Masahiro Akishita as the chairpersons. We are extremely excited about the 10th anniversary meeting and expecting many of you to attend. Our affiliate Vas-Cog Asia plays an increasingly significant role in the field of vascular dementia research. The 7th meeting held in Jakarta on September 6, 2018 was a huge success with Vas-Cog Asia Director, Prof. Koji Abe. The 8th annual meeting of Vas-Cog Asia will be held in Manila on October 3, 2019, in conjunction with the APSC2019 meeting.

We are 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, 2019

Reports of the Vas-Cog Japan 2018

Katsuya Urakami, MD, PhD
Section of Environment and Health Science,
Department of Biological Regulation, Faculty of Medicine, Tottori University

The Vas-Cog Japan 2018 was held at the Beppu International Convention Center (B-con Plaza), August 4-5, 2018.

Japan faces a super-aging society in which the number of patients suffering from dementia has soared. Nobody doubt that this is the urgent problem that should be settled from a socioeconomic standpoint. Recently, it becomes clear that life-style related disease as well as the vascular lesions occurring afterwards are heavily involved in the onset and exacerbation of dementia such as Alzheimer's disease. This meeting focused on the relationship between the vascular pathophysiology and the onset of dementia. Our society also needs to nurture and recruit young physicians and researchers having great energy to fight against dementia. In the Vas-Cog Japan 2018, we performed "Elucidation of the significance of vascular lesions in dementia-aiming to nurture young physicians and researchers-" as a theme. A wonderful lecture was given by Prof. Ouchi, director of Toranomon hospital, and meaningful discussion was held at the symposiums and many presentations.

The Vas-Cog Japan 2018 was the first time that we have a two-day meeting, which allows you to participate and visit for a great deal of information regarding vascular cognitive impairments. As you know, Beppu is a hot spring town representing "Onsen-ken Oita". After an appropriate stimulation to the brain at the meeting, we are sure that you were able to refresh both mind and body with the delicious sake and seasonal food as well as a hot spring. We are looking forward to seeing you again in the Vas-Cog Japan 2019 (Tokyo).

VAS-COG Japan 2018 Report

Etsuro Matsubara, MD, PhD
Department of neurology,
Oita University Faculty of Medicine

A host city

The ninth annual meeting of VAS-COG Japan 2018 was held on August 4-5, 2018, in Beppu, Oita. The president of this meeting was Prof. Katsuya Urakami from Tottori University and me. It was our great honor and pleasure to host the first meeting on the island of Kyushu. The two-day meeting is also the first trial, which is the touchstone issue for a host local city like OITA. I was afraid that young doctors might hesitate to attend the meeting, but we had as many as participants with 170 attendees.

The title of the meeting was on "how to clarify the significance of vascular abnormality on dementia". Special lecture, symposium, and 36 oral and poster presentations were scheduled on the first day of the meeting. Dr. Ohuchi gave us a special lecture regarding metabolic syndrome and dementia. In the following symposium 1 titled with "Vascular lesions in dementia", four guest speakers had introduced 4 topics, cardiovascular lesions as a risk factor, different strategy from a therapeutic viewpoint of cerebral amyloid angiopathy, glymphatic pathway and anti-amyloid effect of cilostazol. We also had poster and oral presentations, including candidates for young investigator award (YIA). At the following welcome party, I am sure that all participants enjoyed seasonal, fresh foods of OITA, and thereafter unwound from the fatigue at the "BEPPU ONSEN".

On the second day morning, I organized 3-hr intense brainstorming session under the title "Paradigm shift (pre-emptive therapy): how to reconsider the relationship between AD and vascular abnormality". We invited 11 speakers from a variety of background, and discussed about "community revitalization and smart aging", "relationship between AD pathology and cerebrovascular abnormality", and "preemptive medicine from a view point of geriatrics". In the afternoon sessions, two educational lectures focused on intestinal environment and help for a healthy brain-now. Current and future vision for the dementia prevention was also discussed in the symposium 2.

Finally, we cordially thank all participants and contributors for the big success of this VAS-COG JAPAN 2018.

Welcome to Vas-Cog Japan 2019

The University of Tokyo
Masahiro Akishita, MD, PhD

Gunma University
Yoshio Ikeda, MD, PhD

It is our great pleasure to welcome you to the 10th annual meeting of the Japanese Society for Vascular Cognitive Impairment (Vas-Cog Japan 2019). This year's meeting will be held on August 3rd, 2019 at Ochanomizu Sola City Conference Center, Tokyo.

Recent studies clarified that the vascular factors such as diabetes mellitus, hypertension, dyslipidemia were involved in the appearance of not only vascular dementia but also Alzheimer's disease. 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 will be given by Prof. Takuya Takahashi from Yokohama City University. Other featured lectures or symposia are now under consideration by the program committees.

Because the venue for the meeting is convenient to access locating nearby Ochanomizu station, we are expecting many doctors and researchers would join the meeting. We also would like to encourage young investigators to present at the meeting. We are looking forward to seeing you at Vas-Cog Japan 2019!

10th Annual Meeting of the Japanese Society for Vascular Cognitive Impairment

第10回 日本脳血管・認知症学会総会

VAS-COG Japan 2019

「血管性因子と神経変性のクロストーク」

会期 2019年8月3日(土)

演題登録期間
2019年3月13日(水)～4月15日(月)

会場 御茶ノ水ソラシティカンファレンスセンター 2F
〒101-0062 東京都千代田区神田駿河台4丁目6

会長 池田 佳生 群馬大学大学院医学系研究科 脳神経内科学
秋下 雅弘 東京大学大学院医学系研究科加齢医学 東京大学医学部附属病院老年病科

総会事務局
〒371-8511 群馬県前橋市昭和町3-39-22
群馬大学大学院医学系研究科　脳神経内科学
池田 将樹、笠原 浩生

運営事務局
株式会社JTB 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:06-6252-5049　FAX:06-7657-8412
E-mail:mice-vas-cogj@jtb.com

© TCVB

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

Meeting report of Vas-Cog Asia 7 from Jakarta

Koji Abe, MD, PhD
Vas-Cog Asia President

I would like to celebrate the great success of Vas-Cog Asia 7, which was held in Jakarta on September 6 afternoon (2018) always jointing with Asia-Pacific Stroke Conference (APSC) based on the great supports by Professor Mursyid Bustami (APSC2018 chair), Professor Yohanna Kusuma (Program chair of APSC2018), and Professor Paulus Anam Ong (Host of Vas-Cog Asia 7, Jakarta). We had 42 participants from Japan, Indonesia, Taiwan, China, Hong Kong, Malaysia, 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.

Professor Simeon Marasigan announced the Vas-Cog Philippines launch on next February 23 (2019) in Manila, and next Vas-Cog Asia 8 is going to be held again in Manila on October 3 (2019) under direction of our new President Tsong-Hai Lee (Taipei) and new Secretary General Toru Yamashita (Okayama). 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 2, 2018

An impression on VAS-COG Asia 2018

Shinichiro Uchiyama, MD, PhD
Professor, Clinical Research Center for Medicine,
International University of Health and Welfare
Director, Center for Brain and Cerebral Vessels,
Sanno Hospital and Sanno Medical Center

The VAS-COG Asia was held as a joint conference with the Asia Pacific Stroke Conference (APSC) 2018 in the Sultan Hotel & Residence Jakarta in the afternoon on September 6. This joint conference was started when I organized APSC 2012 as the Chair in Tokyo in cooperation with Prof. Koji Abe, and this was the 7th conference following the 6th joint conference with APSC 2017 in Nanjing. The VAS-COG Asia 2018 was very exciting because of a variety of presentations of basic and clinical studies with hot discussion, which were titled "promising biomarkers in vascular dementia", "vascular and beta-amyloid pathogenesis in MCI", "amyloid genesis and inflammation in animal model of vascular cognitive impairment", "chronic hypoperfusion accelerates Alzheimer's pathology in AD transgenic mice", "mortality risks for vascular dementia in Thai cohort", "rapid screening test for cognitive impairment using high-performance eye-tracking technology", and "Abe's BPSD score (ABS) for post-stroke cognitive impairment patients" by young and senior investigators. Dementia and stroke are leading causes of shortening health life span, which have been widely recognized to share vascular risk factors in the background, and thereby relationships between dementia and cerebrovascular disease have been paid more attention than ever. In addition, since dementia and stroke are steeply increasing in Asia, which occupies 60% of the world population, the role of VAS-COG Asia will definitely become more important in future. Recent evidence clarified that vascular risk factors are associated with not only vascular dementia but also any degenerative dementia including Alzheimer disease. In addition, epidemiological studies indicated that vascular risk factors are attributable to young and middle-aged dementia even more than advance-aged dementia. I hope many top leaders of dementia research as well as young physicians and researchers interested in this field will attend the conference, who will make a great contribution to the level up of the VAS-COG Asia. The APSC 2019 will be held on October 2-5 and the VAS-COG Asia 2019 on October 1 in the charming mega-city Manila, Philippines. Please join the Joint Conference of APSC 2019 and VAS-COG Asia 2019.

Reports of Vas-Cog Japan Council Meeting

Yoshio Ikeda, MD, PhD
Gunma University

The 10th board and council meeting for the Japanese Society for Vascular Cognitive Impairment was held together with 16 board members, 2 auditors and 23 councilors in the Reception Hall at Beppu International Convention Center on the 4th of August, 2018.

The representative director and committee members reported the topics shown below and all proceedings were approved by members.

[Membership]

162 regular members (As of July 31, 2018)

[Report from each committee leader]

* The leader of board for society promotion, Dr. Katsuya Urakami, discussed the necessity to increase payment of annual membership fee.
* 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.
* The chief editor of the academic magazine, Dr. Mikio Shoji, discussed the preparation status for improving the contents of Vas-Cog Journal No. 5.
* The leader for COI, Dr. Masahiko Suzuki, started to consider detailed regulations based on the discussion on the editorial committee.
* The leader of board for finance, Dr. Yoshio Ikeda, reported the necessity to increase payments of annual membership fees although a surplus exists this year. Both auditors, Dr. Shimamura and Dr. Matsumura reported that the accounting was properly conducted in the audit report.

[Plans for future meetings]

1. The 10th Meeting (August 3rd, 2019)
   Ochanomizu Sola City in Tokyo
   Chairmen: Dr. Masahiro Akishita and Dr. Yoshio Ikeda
2. The 11th Meeting (September 12th and 13th, 2020)
   Awa Kanko Hotel in Tokushima
   Chairmen: Dr. Shunya Takizawa and Dr. Masataka Sada
3. Refer to the last page for subsequent schedules

[Report of new board members / councilors]

* on the following pages indicates a new board member or councilor.

[Name list]

● Executive Advisor

Hiroshi Mori
(Osaka City University/Tamiya Hospital)

● President

Ryuichi Morishita (Osaka University)

● Executive Directors (General Affairs)

Yoshio Ikeda (Gunma University)

● Executive Directors

Masahiro Akishita (The University of Tokyo)
Shinichiro Uchiyama
(International University of Health and Welfare)
Nobuya Kawabata (Yachiyo Hospital)
Koichi Kozaki (Kyorin University)
Masataka Sata (Tokushima University)
Masahiko Suzuki
(The Jikei University School of Medicine)
Yasuo Terayama (Iwate Medical University)
Ken Nagata
(Research Institute for Brain and Blood Vessels)
Toshiya Fukui (Kawasaki Memorial Hospital)
Etsuro Matsubara (Oita University)
Shokei Mitsuyama (Kumamoto University)
Shuhei Yamaguchi (Shimane University)
Koji Abe (Okayama University)
Katsuya Urakami (Tottori University)
Kazuo Kitagawa (Tokyo Women's Medical University)
Issei Komuro (The University of Tokyo)
Mikio Shoji (Geriatrics Research Institute and Hospital)
Shunya Takizawa (Tokai University)
Hidekazu Tomimoto (Mie University)
Haruo Hanyu (Tokyo Medical University)
Masatsugu Horiuchi (Ehime University)
Toshiki Mizuno
(Kyoto Prefectural University of Medicine)
Masaru Mimura (Keio University)
Masahito Yamada (Kanazawa University)

● Auditors

Munehisa Shimamura (Osaka University)
Miyuki Matsumura
(Institute of Geriatrics
Tokyo Women's Medical University)

● Councilors

Hitoshi Aizawa (Tokyo Medical University)
Satoshi Abe (Shimane University Hospital)
Nobuyoshi Ishii (Oita University)
Masafumi Ihara
(National Cerebral and Cardiovascular Center)
Yumiko Uchiyama
(Tokyo Women's Medical University)
Takao Urabe (Juntendo University Urayasu Hospital)
Sumito Ogawa (The University of Tokyo)
Kenjiro Ono (Showa University)
Tatsushi Kamiya (Kamiya Clinic)
Noriyuki Kimura (Oita University)
Minoru Kouzuki (Tottori University)
Hisatomo Kowa (Kobe University)

Kenji Sakai (Kanazawa University Hospital)
Naoyuki Sato
(Center for Development of Advanced Medicine for Dementia)
Takayoshi Shimohata (Gifu University)
Yoshiki Takao (Kurashiki Heisei Hospital)
Ayumi Takamura (Tottori University)
Yasushi Takeya (Osaka University)
Hiroo Terashi (Tokyo Medical University)
Takahiko Tokuda
(Kyoto Prefectural University of Medicine)
Masao Nagayama (IUHW Atami Hospital)
Yasuto Higashi (Himeji Central Hospital)

Nozomi Hishikawa (Okayama University)
Kouki Makioka (Gunma University Hospital)

Toru Minamino (Niigata University)
Li-Juan Min (Ehime University)

Kenichi Meguro (Tohoku University)
Hideki Mochizuki (Osaka University)

Toru Yamashita (Okayama University Hospital)

Kouji Wakayama (The University of Tokyo)
Yasuhiro Aso (Oita University Hospital)
Masaki Ikeda (Gunma University Hospital)
Hiroo Ichikawa (Showa University Fujigaoka Hospital)
Jun Iwanami (Ehime University)
Ryoko Imazeki (Tokai University)

Takahiko Umahara (Tokyo Medical University)

Yasuyuki Ohta (Okayama University)
Haruhisa Kato (Tokyo Medical University)
Yumi Kameyama (The University of Tokyo Hospital)
Hitomi Kurinami (Osaka University)
Taro Kojima (The University of Tokyo)
Masaki Kondo
(Kyoto Prefectural University of Medicine)
Hirofumi Sakurai (Tokyo Medical University)
Masayuki Satoh (Mie University)

Kazuma Sugie
(Nara Medical University School of Medicine)
Daiki Takano (Yokohama General Hospital)
Shuko Takeda (Osaka University)
Kentarou Deguchi (Okayama University)
Takashi Tokashiki (Okinawa National Hospital)
Kazuaki Nagashima (Gunma University)

Yu Hasegawa (Kumamoto University)
Yukihito Higashi
(Research Institute for Radiation Biology and Medicine)
Yukio Fujita (Gunma University)
Yasuhiro Manabe
(National Hospital Organization Okayama Medical Center)
Takafumi Miyachi (Yanai Medical Center)
Kazuhiro Muramatsu
(Tokyo Dental College Ichikawa General Hospital)
Masaki Mogi (Ehime University)
Takashi Yamazaki
(Research Institute for Brain and Blood Vessels-Akita)
Hiroshi Yoshizawa
(Tokyo Women's Medical University)
Yosuke Wakutani (Kurashiki Heisei Hospital)

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.

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

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:_____

37) 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:_____

Editor's Note

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

The 5th issue of Vas-Cog Journal reports the outline of the 9th annual meeting, VAS-COG Japan 2018, hosted by Professor Katsuya Urakami and Professor Etsuro Matsubara on August 4-5, 2018, in Beppu, Oita. Special lectures, symposium, and 36 oral and poster presentations were presented of the meeting. As many as participants with 170 attendees joined the meeting. We also introduced the detail of 10th annual meeting, Vas-Cog Japan 2019 (Tokyo).

In this meeting, committee and attendance had decided on 2 important issues: Vas-Cog Japan is change to be the Academic Society and publishes the official journal. Based on this decision, editorial board made great efforts to publish 5th as the official journal of Vas-Cog Japan. As you can see, Vas-Cog journal has been refined and remarkable 2 reviews and a case report work were carried. I deeply appreciated every effort by president, members of editorial board and secretariat. And I would also deeply appreciate authors: Dr. Ihara, Dr. Takeda, and Dr. Yamashita, who submitted wonderful works for this initial issue of renewal academic journal. I hope these great efforts contribute further advances in this field.

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, 2020 (Tokushima) Chairman : Shunya Takizawa and Masataka Sata
The 12th Meeting : August, 2021 (planned) Chairman : Kazuo Kitagawa and Koichi Kozaki
The 13th Meeting : August, 2022 (planned) Chairman : Masahiko Suzuki

- to be continued -