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Editorial policy of this journal

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It's my great honor to work as a chief editor of the Vas-Cog Journal. The aim of the Journal is to clarify vascular factors influencing cognitive impairment and behavior. At first, vascular factors affecting the central nervous system (CNS) mainly involve atherosclerotic changes in arteries. However, not only arteries but also an excretory clearance system involving veins and cerebrospinal fluid is related to neurodegenerative diseases[1]. Recent research about an excretory system in the CNS proposed two important pathways, called the glymphatic pathway and the perivascular pathway. The glymphatic pathway directs flows towards the venous perivascular and perineuronal spaces, clearing solutes from the neuropil into meningeal and cervical lymphatic drainage vessels[2]. The perivascular drainage system, an intramural peri-arterial drainage (IPAD) system, is along the basement membrane of capillary and arterial walls. Intraparenchymal material moves towards the leptomeningeal arteries at the surface of the brain through this pathway and, finally, to cervical lymph nodes[3]. However, it has been unclear whether the perivascular drainage and the glymphatic systems are distinct pathways, and whether they coexist or are competitive. New research is needed to clarify the roles of these pathways, and should be performed with cellular experiments, animal models, and human imaging studies. Molecular and physiological biomarkers are also important to clarify the role of vascular factors in cognitive impairment and behavior. This research presents a new approach for investigation of cognitive impairment. The Vas-Cog Journal welcomes all kinds of research concerning cognitive impairment and behavior from Japan and Asian countries.

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Review article

Blood-brain barrier disruption: A key interface between coronavirus disease 2019-related systemic inflammation and cognitive impairment

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Short Title: Inflammation in COVID-19, BBB disruption, and CI

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Abstract:

The prevalence of dementia has increased with the rising aging population worldwide, and aging and dementia are known risk factors for delirium, a condition that is closely related to inflammation, such as coronavirus disease 2019 (COVID-19). COVID-19 is caused by severe acute respiratory syndrome coronavirus 2. It originated in Wuhan city, China in early December 2019 and has spread rapidly worldwide ever since. The elderly population are at a higher risk of contracting the virus than other age groups. Evidence has shown that many patients with COVID-19 exhibit symptoms of delirium, disproportionally affecting the elderly, and this is concerning due to the close association between dementia and delirium. Impairment of cerebrovascular functions, especially the blood-brain barrier, plays a key role in delirium and subsequent dementia caused by inflammation from infectious diseases, such as COVID-19.

Key Words: Blood-brain barrier, systemic inflammation, COVID-19, cognitive impairment, infectious diseases, delirium

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Dementia and delirium

With the increasing aging population worldwide, cognitive impairment has become an unavoidable problem affecting both the medical and the healthcare system. The number of people suffering from dementia, a chronic neurodegenerative disease, increases every year with an estimate of up to 43 million worldwide and predicted to double within the next 20 years[1]. Delirium, an acute condition with similar symptoms of dementia, has shown to affect 50% of elderly people (aged 65 years and older)[2].

Risk factors for delirium can be divided into three categories: predisposing factors, facilitating factors, and precipitating factors. Predisposing factors

include old age (60 years and older), heavy alcohol consumption, depression, and history of ischemia or stroke and brain damage, such as dementia. Predisposing factors are important in screening high-risk patients. Facilitating factors do not directly contribute to causing delirium, and these include stress, sleep impairment, and changes in the physical environment or physical restraint. Precipitating factors can directly cause delirium, and these include the use of anesthetics, hypoxia, infection, and invasive surgery. However, with sufficient support from the medical staff, facilitating and precipitating factors can be improved to a certain degree, ultimately decreasing the risk of developing delirium.

Dementia and delirium are distinct health conditions that are closely related. Study has shown that a single episode of delirium could increase the chance of developing dementia later in life[2] and accelerates the rate of neurodegeneration. A study including 560 people aged 70 years or more without dementia found that those who were affected with delirium had significantly greater cognitive decline than those who were not[3]. Another cohort study including 309 acutely ill patients showed that 32% of patients experiencing delirium progressed towards dementia, while only 16% of those who were not delirious progressed to dementia[4]. A meta-analysis of 23 studies showed that patients who developed delirium during a hospital stay had a 2.3 times greater risk of developing dementia than those who did not[5]. Moreover, a study has shown that the duration of delirium could also be an important factor in developing dementia later in life, wherein patients with a longer duration of delirium experiencing worse global cognition and executive function at 3 and 12 months[6]. The reverse is also true, with delirium being more prevalent in patients with dementia. A study showed that 37% of patients with dementia experienced delirious attacks during their hospital stay.[7] Furthermore, vascular dementia (VaD) is often associated with delirium[8], and the pathological changes in patients with VaD are associated with cholinergic deficits[9], which is also a risk factor of delirium. Studies have shown that 40% to 50% of patients with VaD experience delirium, the prevalence of which exceeds that of patients with early-onset Alzheimer's disease (AD) or frontotemporal dementia[7,10].

While the relationship between dementia and delirium remains unclear, several mechanisms have been proposed. For example, certain insults to the brain such as metabolic derangements, certain drugs (e.g., anticholinergics), ischemia, and immunological stressors could alter neurotransmitter concentrations causing acetylcholine deficiency or dopamine excess, thus resulting in neuronal dysfunctions[11,12]. In addition, hypoxia and cerebral ischemia may directly cause cerebral dysfunction through impaired cerebral blood flow and metabolism[13]. Evidence also showed that certain anesthetics can directly contribute to the accumulation of beta-amyloids, which is also a fundamental part of AD[14]. Another theory known as the threshold hypothesis has also been proposed. As the brains of patients with dementia have fewer neuronal connections, it becomes more difficult to deal with inflammation and infection, not only resulting in delirium but also advancing the disease. Inflammation in response to an infection or other stress (i.e., surgery or acute illness) could also cause neuronal dysfunction. Cases such as this can occur in various mechanisms, such as apoptosis, activation of microglia and astrocytes, and altered neurotransmission[15]. All these studies provide valuable insights into the close relationship between dementia and delirium. In this review, we focus on the blood-brain barrier (BBB) changes associated with systemic inflammation, and how these changes link dementia and delirium.

Systemic inflammation and BBB

The exact molecular mechanism of the pathology of delirium remains unknown, which could be attributed to its multifactorial causation. However, evidence has shown that interaction between several biological factors might be the cause of the disruption of the large-scale neuronal network in the brain, leading to acute cognitive dysfunction[2]. These contributing factors of delirium include the

dysregulation of neurotransmitters, inflammation, physiological stressors, metabolic derangements, electrolyte disorders, and genetic factors. Other factors can also directly interact with neurotransmission or cellular metabolism, including drugs, hypercortisolism, electrolyte disturbances, hypoxia, and impaired glucose oxidation. This review will focus on the role of inflammation in delirium to better understand the relationship between coronavirus disease 2019 (COVID-19) and delirium.

The dysregulation of cytokines is believed to be the main factor in the involvement of inflammation in delirium. Studies have shown that the use of interleukins in rat models alters the acetylcholine levels and activity[16] and mediate exotoxic neurodegeneration[17]. A studyshowed that aging can alter the CNS and peripheral levels of certain cytokines (IL-1 beta and TNF alpha)[18]. On the contrary, other studyshowed that aging is not associated with cytokine level chages[19]. A study conducted on mice showed that changes in glial reactivity in the aging brain can exacerbate neuroinflammatory cytokine responses[20]. Symptoms associated with illness and delirium such as a decrease in cognition, depression of mood, and lethargy known as “sickness behavior” are now believed to have been caused by peripheral inflammatory cytokines[21].

A study showed that out of 261 patients with dementia, 19.4% experienced delirium, in which 34.4% were diagnosed with VaD, dementia with the highest precentile[22]. VaD is well associated with cerebrovascular pathologies, such as disruption of the BBB. Interestingly, 31.8 % of patients were diagnosed with dementia with Lewy bodies (DLB). Recent evidence showed that BBB of synucleinopathy patients, which was initially believed to be intact, may be disrupted through a proinflammatory response[23]. Studies have also shown that alpha-synuclein can cross the BBB bidirectionally, with LRP1 being a potential efflux transporter for alpha-synuclein[24]. LRP1 is also involved in the efflux of beta-amyloids and is downregulated in AD[25]. If this downregulation is also present in synucleinopathies, it can result in impairment of alpha-synuclein clearance and the accumulation of alpha-synclein in the brain. Furthermore, it is well known that acetylcholine deficiency occurs in DLB[26], a risk factor for delirium.

The BBB is composed of cerebrovascular endothelial cells between blood and the brain and selectively prevents substances in the blood from entering the CNS. In contrast to the leaky capillary endothelium in peripheral organs, the BBB is sealed by tight junctions and possesses various channels, receptors, and enzymes to allow substance transport. This allows transport across the BBB to be highly selective, which benefits the CNS in various ways. For example, pathogens, blood cells, and certain cytokines do not enter the CNS through the BBB. Antibodies and certain antibiotics are also prohibited from crossing the BBB, making drug and vaccine development difficult in some cases. Examples of molecules that are allowed to cross the BBB include insulin, leptin, TNF alpha, and epidermal growth factor, among others. The BBB is also important in supplying the brain with energy, as the brain lacks storage for carbohydrates. Disruption of the BBB can dramatically change the environment of the CNS. During systemic inflammation, the BBB can be changed both histologically and molecularly[27], resulting in cytokine entry into the CNS. As stated, cytokine dysregulation can lead to sickness behavior and delirium. This phenomenon likely occurs through the dysregulation of neurotransmitters and the activation of glial cells in the presence of certain inflammatory cytokines.

Various conditions have also been associated with the disruption of BBB. Neuroinflammation following ischemic stroke is shown to disrupt the BBB. Following a stroke, the tight junction integrity in the BBB decreases, which can lead to vasogenic edema, hemorrhagic transformation, ultimately increasing mortality. The levels of inflammatory cytokines, such as IL-1 beta and TNF-1 alpha, are upregulated in the brain following cerebral ischemia, with evidence pointing that inflammatory cytokines can increase the permeability of the BBB[28]. Neurotransmitters

released from hypoxic neurons during an ischemic stroke can also cause permanent neurotoxic damage to neural tissues, of which the BBB regulates[29]. Another condition associated with changes to the BBB is multiple sclerosis (MS). MS is an autoimmune disease characterized by the infiltration of lymphocytes and macrophages through the BBB and subsequent breakdown of the myelin sheath in neurons. A feature of MS involves the early breakdown of the BBB, allowing lymphocyte entry[30].

Changes to the BBB may also play an important role in AD via the accumulation of beta-amyloid through intake at the BBB and the decrease of the clearance of beta-amyloids. Evidence suggests that 85% of beta-amyloid clearance is through the BBB, via LRP-1, LRP-2, and APOJ[31]. Some studies have shown that vascular factors such as hypertension[32], diabetes[33], hyperlipidemia[34], and cardiovascular disease[35] can be risk factors of AD. Several AD animal models, which include models derived from mutations in APOE4, APP, and PSEN1 have shown to develop an early BBB breakdown[36]. Cerebral amyloid angiopathy (CAA) is also related to the BBB breakdown. CAA is the pathology that involves the accumulation of beta-amyloid on the walls of cerebral vessels. While CAA can be observed in physiological changes related to aging, it is known to be more prevalent in AD. In CAA, beta-amyloids are known to accumulate in the outer and middle layers of vascular smooth muscle cells. The main component of the accumulated beta-amyloid is amyloid-beta 40, which is in contrast to the main component of amyloid plaques or amyloid-beta 42. The accumulation of beta-amyloid on the walls of cerebral vessels can lead to the degeneration of tunica media and endothelium, resulting in the disruption of the BBB. Studies with animal models and postmortem brain of patients with AD suggest that CAA is not accompanied by the increase in production of APP, the precursor to beta-amyloid, but is caused by the dysfunction of beta-amyloid clearance from the brain[37]. Beta-amyloids in brain interstitial fluid are known to be excreted to the cerebral spinal fluid through the perivascular space. However, if this mechanism is obstructed, the flow of beta-amyloids can stagnate and accumulate on the walls of blood vessels. During severe systemic inflammation where vascular endothelial cells are potentially damaged by inflammatory cytokines, the BBB disruption caused by CAA can be possibly amplified. In addition, the accumulation of beta-amyloids can induce inflammation, i.e., CAA in itself can cause vascular inflammation. Albumin quotient, a common biofluid marker of BBB breakdown, is shown to elevate in AD[38]. This phenomenon is believed to be induced by vascular inflammation caused by CAA and BBB disruption. As beta-amyloids in CAA disrupt the BBB, peripheral inflammation can have a stronger influence on the CNS. This event can be the mechanism causing delirium accompanied by systemic inflammation and eventually resulting in the onset of dementia.

COVID-19, dementia, and delirium

Coronavirus disease 2019 (COVID-19) was first identified in Wuhan city, China in early December 2019 and has spread rapidly worldwide, with over 100 million confirmed cases and over 2.5 million deaths to date[39]. It is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). COVID-19, delirium, and dementia all disproportionally affect the elderly. Age is the major risk factor for neurodegenerative diseases, and over 50% of elderly people in hospitals are affected by delirium[2], while older patients with COVID-19 experience the most severe and prolonged course of the disease[40]. Data have shown that up to 67% of patients with COVID-19 exhibit signs of delirium (Table 1). Differences in the prevalence of delirium as reported in various studies could be attributed to the differences in the average age of the cohorts and the difficulty of diagnosing delirium. As shown, delirium can be listed as a feature of COVID-19. Signs of delirium could sometimes be present without the usual febrile responses such as cough or fever. With data suggesting that 40% of all cases have no radiographic abnormalities on presentation[41], currently, there are proposals listing delirium as one of

Table 1.
Prevalence of delirium in patients with COVID-19

Reference	Study size	Age	Prevalence of delirium in COVID-19 patients
Pun, Brenda T. et al., 2021[57]	2088	64 (median)	55%
Helms, J. et al., 2020[58]	58	—	67%
Kennedy, M. et al., 2020[56]	817	77 (mean)	28%
Ticinesi, A. et al., 2020[59]	852	73 (mean)	11%
Mao, L. et al., 2020[60]	214	52 (mean)	8%
Khan, Sikandar H. et al., 2020[61]	268	58 (mean)	29%

the diagnostic criteria for COVID-19, because the possibility of overlooking a potential COVID-19 case without considering delirium exists. While the exact cause of this phenomenon remains unknown, it could be attributed to the multifactorial nature of delirium. Many aforementioned risk factors of delirium can be associated with COVID-19, such as inflammation, ischemia, and anesthetics. A mass cohort study has shown that patients with COVID-19 have a higher risk of developing complications including dementia, mood disorder, insomnia, and ischemic stroke than influenza patients 6 months after the diagnosis[42].

One of the main features of severe COVID-19 is systemic inflammation known as the "cytokine storm." As previously stated, systemic inflammation can lead to undesirable changes to the BBB, which presents as sickness behavior or delirium. During some cases of systemic inflammation caused by sepsis, sepsis-associated encephalopathy[43] and sepsis-associated delirium[44] were observed. The sepsis-associated encephalopathy can often trigger severe cognitive impairments and exacerbates neurodegenerative pathology[44]. It has been suggested that the systemic inflammation triggered by some severe COVID-19 cases is similar in scale to that of sepsis[45], thus similar cognitive deterioration can occur and will boost existing neurodegenerative pathologies. Since some neurodegenerative diseases are associated with BBB changes, it is likely that the BBB change caused by the systemic inflammation can directly contribute to the development of some neurodegenerative diseases.

There is evidence showing that the SARS-Cov-2 can directly infect the brain, via various proposed pathways. The virus infects the cell by the binding of the receptor-binding domain of the spike protein to the receptor angiotensin-converting enzyme 2 (ACE2), after cleavage by furin[46]. Many neurons and neuroglia with high vascularization and permeable BBB express both ACE2 and furin, therefore prone to SARS-CoV-2 infections. Another pathway suggests that SARS-CoV-2 enters the brain through the nasal epithelium, which brings the virus into the olfactory bulb[47]. Studies also showed that neuropilin-1 may also be involved in the viral infection of SARS-CoV-2 into the brain[48], and tests showed that monoclonal anti-neuropilin-1 antibody can significantly reduce viral infection[49]. However, in all cases, the SARS-CoV-2 infection to the brain is yet to be fully understood.

Another clinical symptom of COVID-19 is the decrease in blood oxygenation caused by pneumonia. In severe cases, widespread inflammation of the lung is associated with respiratory failure and severe hypoxia. This omnipresent hypoxia is likely to affect the brain and may have negative effects including respiratory alkalosis and energy deprivation. A decrease in arterial oxygen saturation below 75% can cause impairment of neuronal activity[50]. Hypoxia can also cause damage to neural cells due to the rapid

increase in reactive oxygen species, against which the weak brain antioxidative defenses have few ways to defend.

Systemic inflammation associated with COVID-19 is known to increase blood levels of fibronectin, likely through the stimulation of its liver synthesis[51]. This phenomenon can facilitate blood clot formation, and it has been shown that approximately 20% to 50% of COVID-19 cases were complicated by thrombotic and thromboembolic manifestations[52], with stroke reported in approximately 5% of hospitalized patients[53]. Stroke is associated with secondary neurodegeneration and increased risk of both VaD and AD. Therefore, the relationship can be drawn linking COVID-19 associated thrombosis and neurodegenerative diseases.

Furthermore, the indirect effects of COVID-19 can be seen when considering the nature of the pandemic. The risk of developing delirium can be reduced up to 40% with steps such as having a family member assisting the patient with self-orientation[54], which is a difficult task when dealing with COVID-19[55]. The psychological stresses involved in coping with COVID-19 infection, the lack of physical contact, and the isolation from family are likely to trigger depression, which in itself is a well-known risk factor of dementia.

Conclusion

BBB is key in understanding CNS conditions, such as dementia and delirium. As BBB is highly important in maintaining the environment of the CNS, changes to the BBB may lead to drastic results. For example, the pathology of CAA involves the accumulation of beta-amyloid protein in cerebrovascular walls through the impairment of the clearance of beta-amyloids, most of which occurs across the BBB. Other conditions such as DLB, MS, and stroke also involve BBB changes, the mechanism which is likely to be necessary for understanding the said conditions.

Dementia and delirium are two closely linked conditions that are prevalent worldwide with the increasing aging population. Patients who have experienced a delirious attack are more likely to develop dementia than those who have not, thus making the understanding of the mechanism linking dementia and delirium an important task for both the medical and scientific communities. Studies have also shown that cerebrovascular pathologies are likely key interfaces in linking dementia and delirium. CAA pathologies seen in dementia, such as AD, can disrupt BBB, and this BBB disruption can cause delirium through the entry of various cytokines and dysregulation of neurotransmitters. Changes to the BBB independent of dementia may also cause delirium, weakening the brain and increasing the risk of developing dementia.

COVID-19 exhibits diverse clinical symptoms, the understating of which will be key for overcoming the pandemic. Recent evidence has shown that delirium presents as a clinical feature of COVID-19[56]. We proposed the following mechanism linking COVID-19, delirium, and the risk of developing dementia later in life. Infection caused by various pathogens, including SARS-CoV-2, can cause systemic inflammation, resulting in BBB disruption. As a result, the disruption allows inflammatory cytokines to enter the CNS, dysregulating neurotransmitters and activating glial cells, causing delirium. Furthermore, SARS-CoV-2 can directly infect the brain, and although not proven, it possible may be the cause of delirium observed in COVID-19. Through various neuropathologies, delirium can ultimately cause dementia, and pathologies present in dementia can cause additional BBB disruption, resulting in a vicious cycle (Figure 1).

Delirium and dementia are and may continue to be a challenge for the world that requires urgent intervention. With the global COVID-19 pandemic, both dementia and delirium will more likely become more prevalent in the future due to the direct and indirect interaction between COVID-19, delirium, and dementia. We believe this review will provide valuable insights to the existing literature to better understand the cerebrovascular mechanism involved in linking the three conditions.

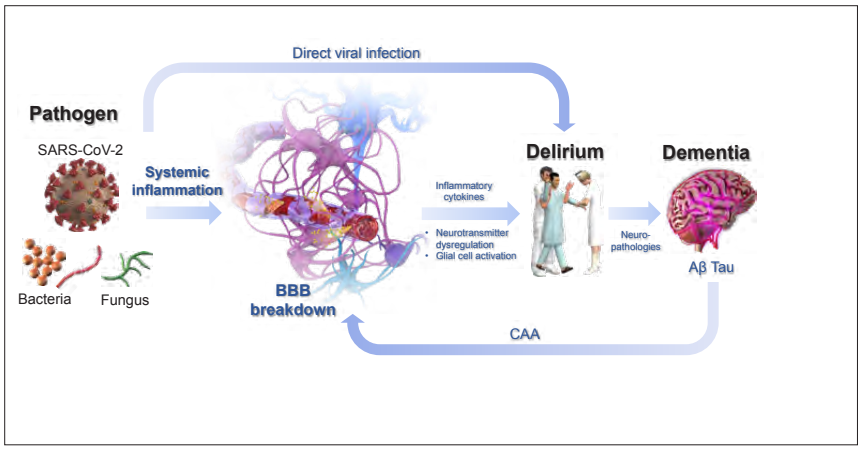

Figure 1.

Proposed mechanism of pathogen-induced delirium through BBB breakdown resulting in the development of dementia.

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Review article

The application of positron emission tomography to vascular dementia

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Short title : PET for vascular dementia

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Abstract :

Positron emission tomography (PET), one of the functional imaging modalities, visualizes the brain function based on the retention of radioisotope-labeled ligands. PET facilitates imaging of localized or diffuse metabolic disturbances responsible for cognitive impairment, and it is effective for differentiating vascular dementia (VaD) from degenerative dementia such as Alzheimer disease (AD). However, the confounding pathology and interaction between VaD and AD have become a focus of interest. Cerebrovascular disease and AD not only occur together but they also interact.

This review overviews the role of structural and functional imaging to diagnose vascular dementia, and summarizes the usefulness of PET to analyze the pathophysiology and differentially diagnose vascular dementia, using data on oxygen metabolism and amyloid accumulation in the brain.

In our study, cerebral cortical retention of Pittsburgh compound-B (^{11}C-PIB) was noted in more than half of VaD patients. Various types of low perfusion of cerebral blood flow were observed in patients, but low perfusion areas were not associated with cortical PIB retention, and the oxygen extraction fraction (OEF) was increased in 3/5 of those with retention.

Key Words : positron emission tomography, vascular dementia, Pittsburgh compound-B (PIB), oxygen extraction fraction (OEF)

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I. Introduction

Positron emission tomography (PET), one of the functional imaging modalities, visualizes the brain function based on the retention of radioisotope-labeled ligands. PET facilitates imaging of localized or diffuse metabolic disturbances responsible for cognitive impairment, and this tool is effective for differentiating vascular dementia from degenerative dementia such as Alzheimer disease (AD). It can also detect inflammatory changes and their interaction with amyloid deposition, leading to the development of mixed dementias after stroke[1].

In this review, firstly, we overview the role of structural and functional imaging to diagnose vascular dementia. Next, we summarize the useful application of PET to analyze the pathophysiology and differentially diagnose vascular dementia (VaD). Lastly, we introduce our data on oxygen metabolism

and amyloid accumulation in the brains of patients with VaD.

II. Vascular dementia and neuroimaging

VaD is defined based on the clinical diagnosis of dementia and cerebrovascular disease derived from the clinical course and imaging, and their causal association[2]. Typical VaD leads to dementia after a stroke episode (post-stroke dementia) or step-wise progression of dementia with repeated stroke episodes.

Although cerebral infarcts are important to identify patients with dementia, their presence does not necessarily mean that they are the cause of the dementia or that they have contributed to it. It remains controversial whether a specific set of lesions, based on their size and anatomic distribution, are the cause of or contribute to the development of dementia[3].

To investigate the association between vascular lesions and cognitive decline, structural imaging such as computed tomography (CT) or magnetic resonance imaging (MRI) and functional imaging including PET have been used in research and clinical practice. Whereas CT and MRI are able to detect morphological lesions, these modalities cannot determine the functional consequences of the underlying pathological changes. On the other hand, PET can support the clinical diagnosis by visualizing cerebral functions in typically affected brain regions[3] (Fig. 1).

III. Vascular dementia and positron emission tomography

PET can be applied to measure regional cerebral blood flow, oxygen consumption, glucose metabolism, which reflects synaptic alteration, and molecular changes. The data improve the assessment of the causal pathology and differential diagnosis. After the 1980s, PET scanners and radioisotope ligands could be used to measure regional brain perfusion and metabolism and were clinically applied[4]. In Japan, PET study using ^{15}O-tracer was approved for clinical use in 1996, and that using ^{18}F-fluorodeoxyglucose (FDG) to screen for cancer in 2002. Whole-body PET using FDG has spread rapidly for the purpose of evaluating patients with malignant tumors.

● Oxygen metabolism and cerebral blood flow

Quantitative assessment of brain perfusion and metabolism using an ^{15}O-tracer has been applied to evaluate the perfusion grade or indication of surgery in patients with cerebral artery stenosis or occlusion. The observation of hypoperfusion or hypometabolism patterns with ^{15}O-labeled compounds provides important information on cerebral blood flow and the

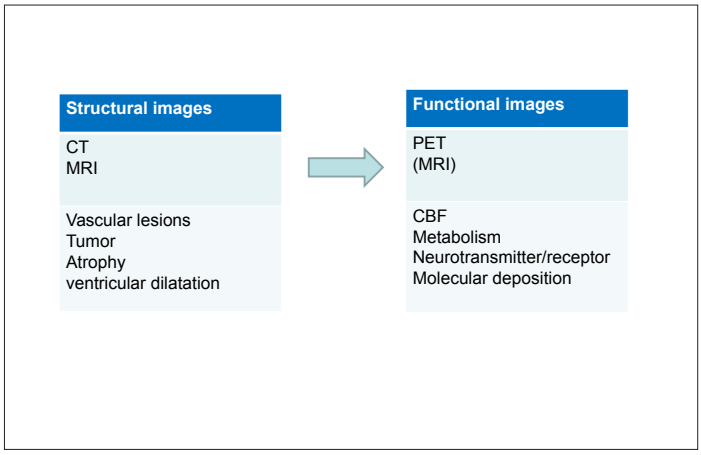

Fig.1 Structural and functional images

PET is a functional imaging modality and can measure cerebral blood flow, metabolism, neurotransmitters and receptors, and molecular deposition in the brain.

metabolic reserve that are considered to be key factors in the diagnosis and treatment of brain ischemia[5].

● Glucose metabolism

PET scanners have rapidly become used widely in research centers, and many clinical studies of dementia patients using FDG-PET have clarified features of brain metabolism in various types of dementia, such as AD, frontotemporal lobar degeneration (FTLD), and dementia with Lewy bodies (DLB)[6]. Degenerative dementias show characteristic patterns of regional hypometabolism. AD patients show hypometabolism in temporoparietal and frontal association areas but relative recessing of primary cortical areas, basal ganglia, and the cerebellum. FTLD patients exhibit distinct frontal or frontotemporal metabolic impairments, typically asymmetrically centered in the frontolateral cortex and anterior pole of the temporal lobe. DLB patients showed reduced glucose metabolism in the primary visual cortex in addition to that in the posterior association areas[3].

Comparing VaD with other forms of dementia, lower-level metabolism in the deep gray nuclei, cerebellum, primary cortices, middle temporal gyrus, and anterior cingulate cortex could be used to differentiate VaD from AD, whereas lower-level metabolism in the hippocampal region, and orbitofrontal, posterior cingulate, and posterior parietal cortices differentiated AD from VaD[7]. Decreases in perfusion and glucose metabolism distributed in vascular territories were noted bilaterally and involved the frontal lobes in VaD[8]. FDG-PET can clearly differentiate scattered areas of focal cortical and subcortical hypometabolism in VaD from the typical metabolic pattern in AD[3]. Other studies reported that vascular groups including patients without dementia exhibited decreased metabolism in frontal and parietal lobes but not in temporal lobes nor the precuneus. In addition, a VaD group showed decreased metabolism bilaterally in deep nuclei, specifically the caudate nucleus, globus pallidus, and thalamus[9].

● PET/CT and PET/MRI

The vascular pattern of specifically injured cerebral regions is always displayed as a hypometabolic area in PET. MRI and CT add an anatomical navigation function to PET due to their spatial resolution, so hybrid PET/CT and PET/MRI facilitate improved anatomical detail. They have been installed in research centers and become useful tools to obtain data on brain activity with good spatial resolution as well as morphological information[10].

● Amyloid and tau

PET tracers have enabled the detection of pathogenetic depositions such as amyloid and tau in AD. Amyloid accumulation can be imaged by Pittsburgh compound-B (^{11}C-PIB)[11] or several newer ^{18}F-labeled tracers[12,13]. Tau imaging is the newest tool for noninvasive assessment of neurodegenerative conditions such as AD and non-AD tauopathies[14]. Postmortem and tau-imaging studies generate data on not only the amount of tau deposition but also its topographical distribution in a brain, and so tau imaging might be more relevant and more closely associated with neurodegeneration and cognitive decline than Aβ[15,16].

Since Alzheimer pathology and cerebral vascular lesions commonly coexist, the interaction between the two pathologies has been of marked interest. Jang et al. reported that the association between Aβ/tau brain accumulation detected by PET and cognitive decline was stronger in a subcortical vascular cognitive impairment group compared with an AD-related cognitive impairment group[17].

● Active microglia and inflammation

The common neuropathological events in both vascular and degenerative disorders induce inflammation and proliferation of microglia and astrocytes as well as activation and upregulation of several inflammatory compounds. This reactive inflammation can be imaged by radiolabeled ligands for the peripheral benzodiazepine receptor, called the translocator protein (TSPO), not only in the area of the infarct but also in degenerating projection areas remote from the primary ischemic lesion[18]. The interaction of an inflammatory reaction and amyloid deposition may be associated with the development of post-stroke dementia and can be studied by PET

with a TSPO ligand, PK 11195, and PIB[19]. PET studies were reported involving small vessel disease regarding the association between active microglia and vascular lesions[20] in addition to amyloid imaging[21]. In a PET study using a TPSO ligand with neuropathological comparison, elevated TPSO binding provided evidence of inflammatory activation localized to vessel walls and perivascular spaces in cerebral small vessel disease[20]. Sample data in human stroke patients are reported, suggesting the possibility of being able to differentiate two separate pathological mechanisms: an Aβ-dependent cortical mechanism and a non-Aβ-dependent, neuroinflammation-related subcortical mechanism[21].

● Benzodiazepine ligands

^{11}C-flumazenil, (FMZ), a ligand binding to central benzodiazepine receptors, is useful for evaluating neuronal viability. In a report of patients with extensive leukoaraiosis, the presence of dementia was associated with a reduced distribution volume of FMZ in widespread areas of the cerebral cortex[22]. Differences in neuronal integrity in the cerebral cortex might determine whether patients with leukoaraiosis become symptomatic. ^{123}I-iomazenil, a benzodiazepine receptor ligand of single photon emission computed tomography (SPECT), may also reveal underlying pathophysiological differences in the frontal lobe among VaD, mixed AD/VaD dementia, and AD, reflecting the neuronal integrity in the cerebral cortex[23].

● Neurotransmitters and receptors

PET tracers facilitate the study of selectively affected neurotransmitter and receptor systems, the cholinergic system in AD or the dopaminergic system in DLB[24,25]. In the evaluation of parkinsonism using PET, dopamine pre- and post-synaptic functions can be measured separately, and latent neurodegenerative pathological findings or dopaminergic neuronal damage caused by vascular lesions can be detected[26].

● A diagnostic algorithm for PET

Chételat et al. proposed a diagnostic algorithm with optimal time-points for PET biomarkers: structural imaging as a first step and three main diagnostic pathways with distinct biomarker sequences, in which amyloid PET, ^{18}F-FDG-PET, and dopamine transporter SPECT are assigned different orders on diagnostic evaluation depending on clinical presentation[27]. In another algorithm, the initial part in tertiary memory clinics involves routine tests for typical dementing disorder (e.g., amnestic AD, vascular dementia) including structural imaging. When the diagnosis is unclear, they suggest performing FDG-PET, and then using amyloid biomarkers[28]. Since vascular dementia is diagnosed based on clinical symptoms and vascular lesions, pure vascular dementia is not a PET-applicable dementia. However, vascular dementia is sometimes associated with AD or other neurodegenerative pathologies. Amyloid PET and tau PET can be used to clearly resolve the comorbidity of amyloid and tau pathology when PET shows negative findings[29].

IV. Amyloid accumulation and oxygen metabolism in vascular dementia

The confounding pathology and interaction between VaD and AD have attracted interest, such as amyloid accumulation in VaD and the contribution of vascular factors to AD. Cerebrovascular disease and AD not only occur together but they also interact, as shown in the Nun study[30]. The high manifestation rate of clinically relevant cognitive impairment after stroke might be related to the interaction of vascular risks and metabolic changes leading to AD. A hypothesis based on recent reports supports the view that vascular lesions may modify the pathophysiology of AD (AD with vascular lesions), while they may be a direct cause of cognitive decline[31]. Cognitive decline in VaD may be associated with the amyloid pathology: latent amyloid pathology or cerebral amyloid angiopathy directly affecting the cognition, or the amyloid pathology may reciprocally contribute to vascular lesions.

We introduce our data on oxygen metabolism and amyloid accumulation in the brains of ten VaD patients (Table 1). Eight of them had diagnoses consistent with probable VaD based on the

Table 1 Characteristics of vascular dementia patients

M: male, F: female, PIB: Pittsburgh compound-B, PIB+: apparent cerebral cortical retention, PIB ±: cortical retention in focal small areas, PIB-: no cortical retention. OEF: oxygen extraction fraction, MMSE: mini-mental state examination, FAB: frontal assessment battery, MoCA: Montreal cognitive assessment.

Case	age (years)	gender	education (years)	PIB	subtype of VaD	increased OEF	MMSE	FAB	MoCA
1	84	M	16	+	strategic	+	17	8	14
2	77	F	9	+	subcortical	-	24	14	11
3	86	M	9	+	cortical	+	15	9	6
4	82	M	16	+	subcortical	+	26	13	13
5	83	M	12	+	subcortical	-	25	5	13
mean	82.4		12.4				21.4	9.8	11.4
6	79	M	20	±	subcortical	-	25	14	19
7	87	M	9	±	subcortical	+	20	10	14
8	72	M	9	±	subcortical	-	23	14	16
mean	79.3		12.7				22.7	12.7	16.3
9	85	M	11	-	subcortical	-	23	17	15
10	77	M	9	-	subcortical	-	29	11	22
mean	81.0		10.0				26.0	14.0	18.5

Association Internationale pour la Recherché et l'Enseignement en Neurosciences (NINDS-AIREN) criteria[2], and the remaining two (cases 2 and 10) were diagnosed according to diagnostic criteria of subcortical ischemic vascular dementia[32]. Subtypes of vascular dementia[33] were strategic single infarct dementia (one patient: case 1), cortical vascular dementia (one patient: case 3), and subcortical vascular dementia (eight other patients).

In our study, 50% (5/10) of VaD patients exhibited apparent cerebral cortical retention of PIB (Fig.2) and PIB retention of focal small areas in three patients. Mini-mental state examination (MMSE) and Frontal assessment battery (FAB) scores were not significantly different between PIB-retention and non-retention groups. However, the Montreal cognitive assessment (MoCA) score of the PIB-retention group was significantly lower than that of the partial-retention and non-retention groups (Fig. 3). Age and education showed not significant difference between groups. PIB retention areas were not associated with low perfusion areas, and the patient with dementia after cortical infarcts (Case 3) showed diffuse cortical PIB retention in the remaining hemisphere. Three patients exhibiting AD-like hypoperfusion were revealed to be PIB-positive (Cases 1, 2, and 5) and one of them showed hippocampal atrophy (Case 1), while decreased perfusion areas also included frontal lobes, basal ganglia, and the thalamus. The additional hypoperfusion areas were consistent with a previous report on VaD[9]. Three of five PIB-positive patients showed lobar microbleeds on *T2-MRI (Cases 2, 3, and 5), and these patients may have suffered from cerebral amyloid angiopathy.

We provide further information on four patients with increased oxygen extraction fraction (OEF).

Case 1: An 84-year-old male, with dementia after left thalamic infarction, MMSE score of 17, and a vascular risk of hypertension. MRI showed leukoaraiosis and lacunas in white matter and the left thalamus. PET showed PIB retention in the bilateral frontal inferior portion and right parietal medial portion, low perfusion in bilateral frontal, temporal, and parietal areas without sensory-motor areas, and mildly increased OEF in bilateral frontal and parietal areas (Fig. 4).

Case 3: An 86-year-old male, with dementia after multiple infarcts (cerebellum, occipital lobes, left

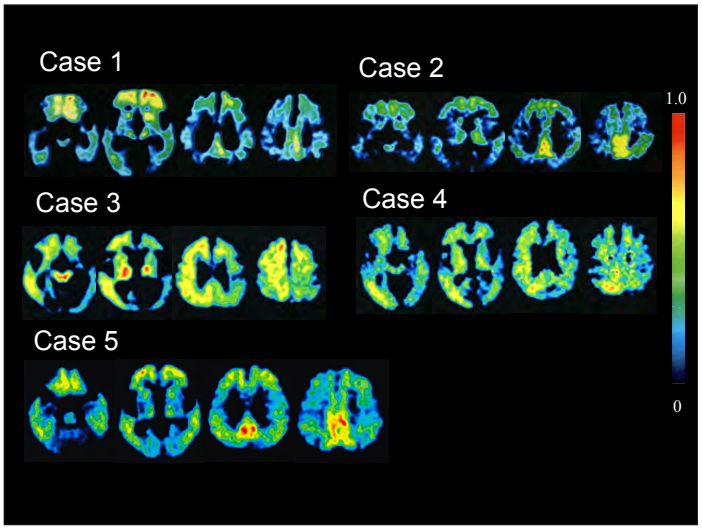

Fig. 2 ^{11}C-PIB-PET of vascular dementia patients with apparent cortical retention

N-Methyl-[^{11}C]2-(4-methylaminophenyl)- 6-hydroxybenzothiazole (PIB) was prepared at Nishijin Hospital, Kyoto.
PIB radiosynthesis was performed using a simplified method.
The PIB retention outcomes that were evaluated were based on Distribution Volume Ratio (DVR) measures.
DVRs were generated using the cerebellum as a reference.

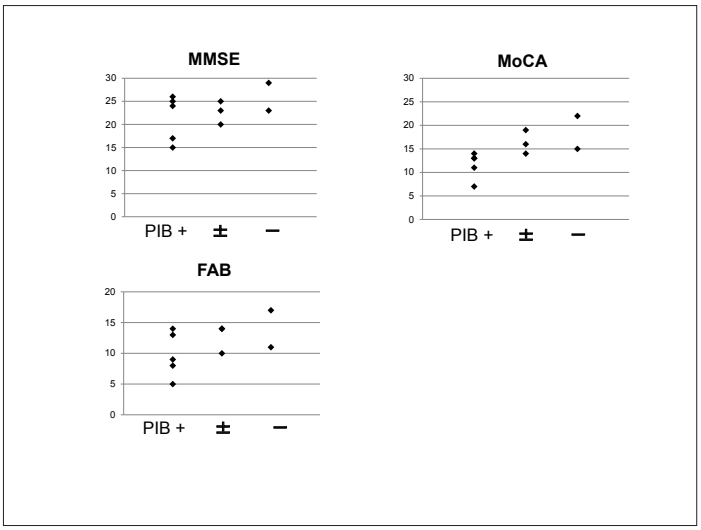

Fig. 3 Comparison of cognitive tests between PIB-positive and -negative groups

PIB: Pittsburgh compound-B, PIB+: apparent cerebral cortical retention,
PIB ± : cortical retention in focal small areas, PIB-: no cortical retention.
Although MMSE and FAB scores showed no significant difference between groups,
the MoCA score in the PIB+ group was significantly lower (Kruskal-Wallis test p=0.039).

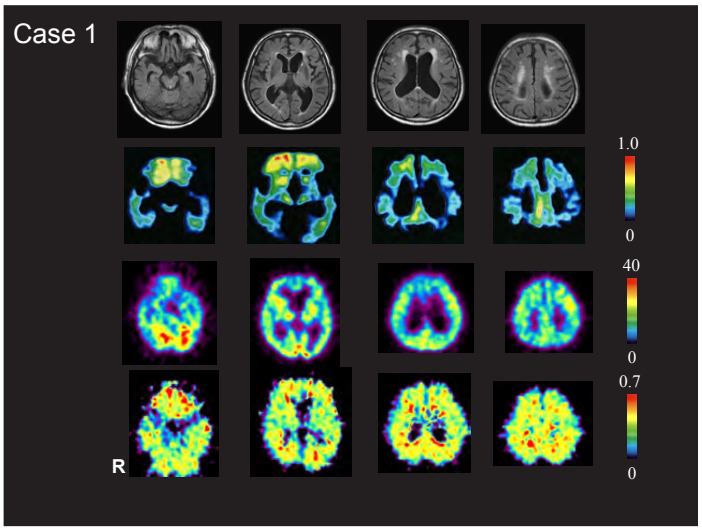

Fig. 4 MRI and PET of Case 1

The first row is brain MRI, the second row is ^{11}C-PIB-PET, the third row is cerebral blood flow (CBF), and the fourth row is the oxygen extraction fraction (OEF) using PET and ^{18}O-compounds.
MRI showed leukoaraiosis and lacunas in the white matter and left thalamus. PET showed PIB retention in the bilateral frontal inferior portion, right parietal medial portion, low perfusion in bilateral frontal, temporal, and parietal areas without sensory-motor areas, and mildly increased OEF in bilateral frontal and parietal areas.

thalamus, and left frontal lobe), MMSE score of 15, and a vascular risk of hypertension. MRI showed multiple brain infarctions in vertebro-basilar and left middle cerebral artery areas. PET showed PIB retention right-dominantly in frontal, temporal, and parietal areas and the right parietal medial portion, low perfusion in left frontal, temporal, and parietal areas, bilateral occipital areas, and prominently increased OEF in bilaterally diffuse cerebral areas (Fig. 5).

Case 4: An 82-year-old male, with dementia after left hemiparesis and gait disturbance, MMSE score of 26, and vascular risks of hypertension, diabetes mellitus, and hyperlipidemia. MRI showed leukoaraiosis and lacunas in white matter. PET showed PIB retention in right temporo-occipital and parietal areas, low perfusion right-dominantly in bilateral frontal areas, and mildly increased OEF in bilateral frontal and parietal areas (Fig. 6).

Case 7: An 87-year-old male, with dementia with parkinsonism, mild left hemiparesis, MMSE score of 20, and a vascular risk of hypertension. MRI showed leukoaraiosis and lacunas in white matter and the right thalamus. PET showed PIB focal retention in the left frontal area, low perfusion in the right frontal area, and mildly increased OEF in bilateral frontal and parietal areas (Fig. 7).

Increased OEF patients did not show significantly lower scores in MMSE, FAB, or MoCA than patients with non-increased OEF. Those showing an increase in OEF included three PIB-positive patients and one patient with PIB focal retention, but no PIB-negative patient. They showed no apparent arterial stenosis detected by MRA or cervical ultrasonography, suggesting misery perfusion in vessels smaller than those detected by the devices. Our data suggest that an increase of OEF might be caused by lower perfusion at a smaller artery or capillary level. A PIB-positive patient with prominently increased OEF in diffuse areas (case 3) showed lower scores of MMSE, FAB, and MoCA. Such a patient may have suffered from a complicated pathophysiology involving smaller artery dysfunction and an amyloid pathology.

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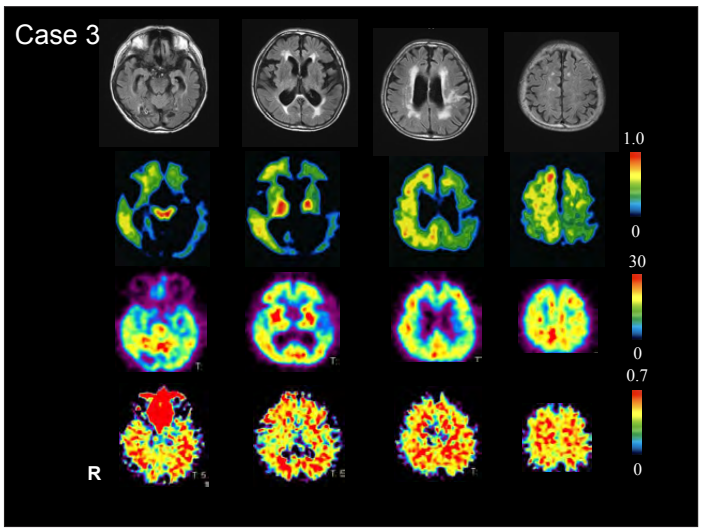

Fig. 5 MRI and PET of Case 3

MRI showed multiple brain infarctions in vertebro-basilar and left middle cerebral artery areas.
PET showed right-dominant PIB retention in frontal, temporal, and parietal areas and the right parietal medial portion, low perfusion in left frontal, temporal, and parietal areas, and bilateral occipital areas, and prominently increased OEF in bilaterally diffuse cerebral areas.

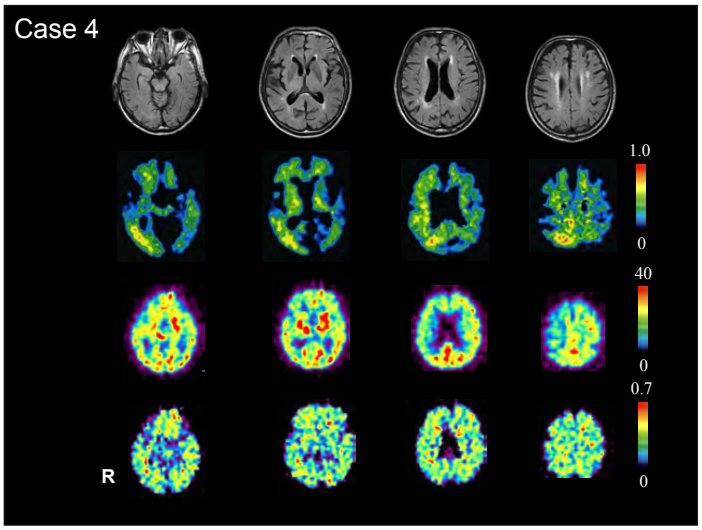

Fig. 6 MRI and PET of Case 4

MRI showed leukoaraiosis and lacunas in white matter. PET showed PIB retention in the right temporo-occipital and parietal areas, right-dominant low perfusion in bilateral frontal areas, and mildly increased OEF in bilateral frontal and parietal areas.

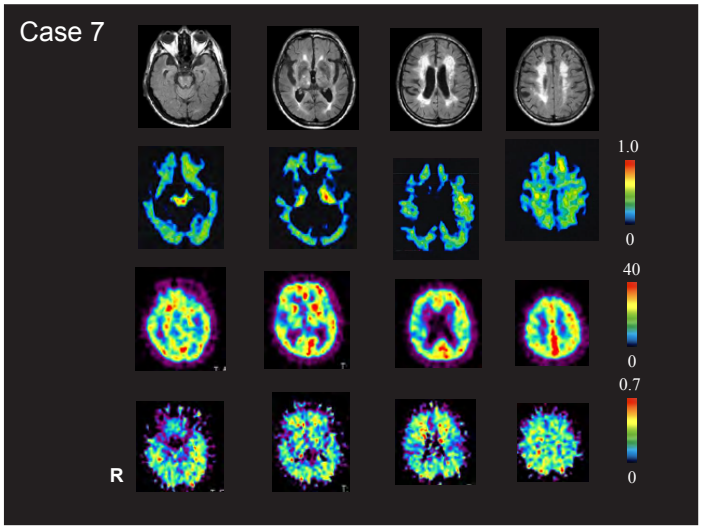

Fig. 7 MRI and PET of Case 7

MRI showed leukoaraiosis and lacunas in white matter and the right thalamus. PET showed PIB focal retention in the left frontal area, low perfusion in the right frontal area, and mildly increased OEF in bilateral frontal and parietal areas.

PET study was performed in cooperation with Nishijin Hospital.

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Case report

A Unique Case of Takayasu arteritis with Leukoencephalopathy

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

Abstract

Takayasu arteritis is primarily a granulomatous large vessel vasculitis mainly involving the aorta and its main branches. Here we report a 45-year-old woman developing gait disturbance and visual loss with abnormal lesions in bilateral pons, left cerebellum and bilateral occipital to parietal areas on brain magnetic resonance imaging (MRI). Her symptoms and brain MRI findings were refractory to initial steroid therapy, but muscle weakness in left upper limb later occurred with new abnormal lesion in right frontal area with Gadolinium-enhancement. The brain biopsy finally demonstrated a marked gliosis and demyelination with cytotoxic helper T cell and microglia accumulation predominantly around the small vessel, and the new brain lesion plus new neurological symptoms improved after the second steroid therapy except for visual loss. The present case reported a unique intracranial small vessel involvement in the course of Takayasu arteritis.

Key words: Takayasu arteritis, leukoencephalopathy, brain biopsy, small vessel, IL-6

Abbreviations: CD, cluster of differentiation; CSF, cerebrospinal fluid; CT, computed tomography; ESR, erythrocyte sedimentation rate; ^{18}F-FDG PET, Fluorine-18 fluorodeoxyglucose positron emission tomography; FLAIR, fluid attenuated inversion recovery; Gd, Gadolinium; IgG, immunoglobulin G; IL-6, interleukin-6; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging.

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Introduction

Takayasu arteritis known as “pulseless disease” is primarily a granulomatous large vessel vasculitis mainly involving the aorta and its main branches, as well as coronary and pulmonary arteries[1]. Cerebral lesions associated with Takayasu arteritis are supposed to be mainly caused by ischemia due to large vessel stenosis. However, small vessel ischemic lesions are also reported on brain magnetic resonance imaging (MRI) with hyperintense white matter lesions on T2-weighted image[2]. Here we report a first case of cerebral lesions with Takayasu arteritis, who demonstrated a marked gliosis and demyelination with cytotoxic T cell and microglia accumulation around the small vessel confirmed by brain biopsy.

Case report

A 45-year-old woman developed a progressive gait disturbance (left >> right) in two months. She had an immediate history of Takayasu arteritis treated with aspirin for previous 6 months. Although she admitted to a nearby hospital found hyperintensities in bilateral occipital to parietal areas on T2-weighted image of brain MRI on day -46, she was not treated there because autoantibodies and cerebrospinal fluid (CSF) analysis were normal. However, the symptoms were getting worse, and thus she admitted to our hospital for further examination.

On admission (day 1), bilateral bruits were audible at supraclavicular fossa, and neurological examinations showed diminished visual acuity and truncal ataxia. Neither papilledema nor inflammatory change in fundi was found. There were no other abnormal neurological findings in motor, sensory or autonomic systems. Serum analyses showed normal white blood cells count (6,740 /μL, normal 3,300-8,600/μL) with increased erythrocyte sedimentation rate (ESR, 64 mm/h, 103 mm/2h), and mild elevation of C-reactive protein (0.4 mg/dL, normal 0.00-0.14 mg/dL), immunoglobulin G (IgG, 1,917 mg/dL, normal 861-1,747 mg/dL), and elevation of immunoglobulin A (721.8 mg/dL, normal 93-393 mg/dL) and immunoglobulin E (1,494 IU/mL, normal < 170 IU/mL). Serum autoantibody test showed elevation of anti-thyroglobulin antibody (11.1 IU/mL, normal < 5.0 IU/mL) and anti-cardiolipin IgG antibody (34 U/mL, normal < 9 U/mL), and serum interleukin-6 (IL-6) was greatly elevated (2,680 pg/mL, normal < 4.0 pg/mL).

A CSF study showed normal pressure (initial 130 and terminal 50 mmH_2O), mildly elevated cell counts (11 /μL, monocyte 100%) and protein (100 mg/dL, normal 10-40 mg/dL) with normal glucose level (47 mg/dL) and IL-6 (3.5 pg/mL, normal < 4.3 pg/mL). CSF oligoclonal bands were detected.

Whole body computed tomography (CT) revealed aortic stenosis with calcification in descending aorta (Fig. 1A, arrowhead) and CT angiography revealed right subclavian artery stenosis (Fig. 1B, arrowhead). Brain magnetic resonance angiography (MRA) revealed no obvious stenosis (Fig. 1C). Brain MRI showed high intensity lesions in bilateral tegmentum of pons, left cerebellar hemisphere and bilateral occipital to right dominant bilateral parietal areas on fluid-attenuated in version recovery (FLAIR) images (Fig. 1D) without enhancement on Gadolinium (Gd) -enhanced T1-weighted images (Fig. 1E). Fluorine-18 fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) revealed decreased uptake of the tracer in the above lesions (Fig. 1F, arrowheads) on day 8. Because an autoimmune encephalopathy was suspected at this moment, three cycles of intravenous high-dose methylprednisolone (1000 mg per day, 3days) were started on day11. Although visual loss was sustained, truncal ataxia was gradually improved. She discharged from our hospital on day 46 and transferred to a different hospital for rehabilitation.

However, she later noticed muscle weakness in left upper limb around day 60 and gradually worsen. Thus, she came to our hospital on day 99 again. Serum analyses showed a normal ESR (8 mm/h, 21 mm/2h) and C-reactive protein (0.09 mg/dL), and a mild elevation of IL-6 (4.3 pg/mL). A CSF study showed normal cell counts (1 /μL, monocyte 100%), mildly elevated protein (100 mg/dL, normal 10-40 mg/dL) and IL-6 (4.5 pg/mL). Brain MRI showed a new high intensity lesion on FLAIR image (Fig. 1G, arrowhead) with Gd-enhancement appeared in right frontal area (Fig. 1H, arrowhead). ^{18}F-FDG PET revealed a further decreased uptake in the right frontal to parietal lesions (Fig. 1I, arrowheads) on day 105. In order to confirm the diagnosis, brain biopsy was performed from white matter lesions of right frontal and parietal lobe by stereotaxic technique on day 115. Pathological study found a marked gliosis with demyelination and a diffuse accumulation of lymphocytes predominantly around small vessel (Fig. 2). Elastica van Gieson (EVG) stain revealed that there was perivascular space without internal elastic lamina or smooth muscle in the small vessel. Immunohistological examination showed that monocytes were mainly positive for cluster of differentiation 3 (CD3), CD8 and CD68, weakly

Figure1

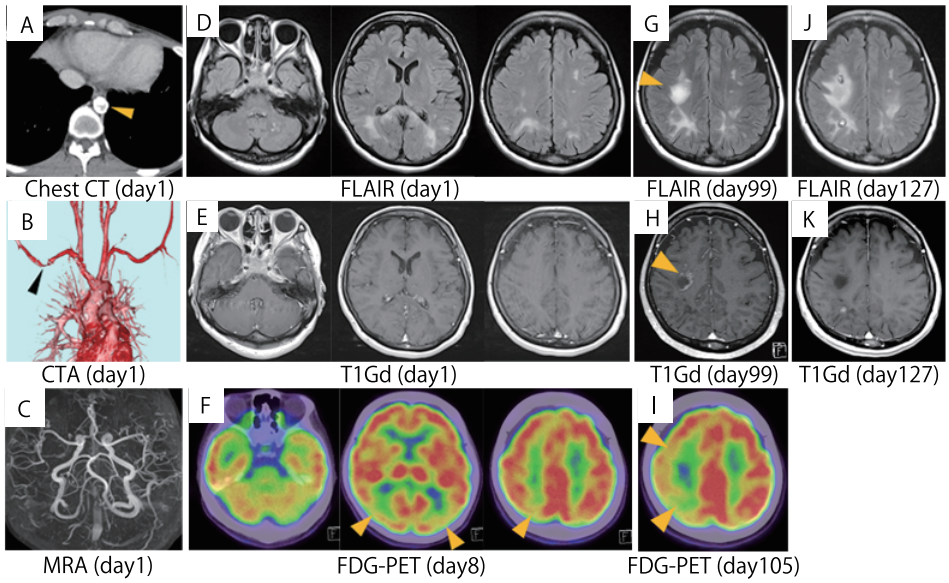

Figure 1

(A) Whole body CT shows aortic stenosis with calcification in descending aorta (arrow), and (B) CT angiography shows right subclavian artery stenosis (arrow). (C) Brain MRA shows no obvious stenosis. Brain MRI shows (D) high intensity lesions in pons, left cerebellar hemisphere and bilateral occipital to parietal areas on FLAIR images (E) without enhancement on Gd-enhanced T1-weighted images. (F) ^{18}F-FDG PET on day 8 shows a decreased uptake of the tracer in the above lesions (arrows). (G) Brain MRI showed a new high intensity lesion on FLAIR image (arrow) on day 99 (H) with Gd-enhancement appeared in right frontal area (arrow). (I) ^{18}F-FDG PET on day 105 shows a further decreased uptake in the right frontal to parietal lesions (arrows).

positive for CD4, and negative for CD20 (Fig. 2), suggesting that cytotoxic T cell and microglia accumulation in the lesions. After the brain biopsy, three cycles of intravenous high-dose methylprednisolone (1000 mg per day, 3days) were started again on day 117, and administration of oral prednisolone (20 mg/day) was started in day 134. With those therapies, weakness in the left limb was gradually improved. On day 127, brain MRI showed high intensity lesions were slightly expanded on FLAIR image (Fig. 1J), whereas frontal enhanced lesion disappeared on Gd-enhanced T1-weighted image (Fig. 1K). Finally, she discharged on day 144.

Discussion

We described a patient who suffered from Takayasu arteritis, eventually developing gait disturbance and visual loss with high intensity lesions in bilateral pons, left cerebellum and bilateral occipital to parietal areas on FLAIR images (Fig. 1D) and a hypometabolism on ^{18}F-FDG PET (Fig. 1F). Clinically, her visual acuity gradually worsened as the high intensity lesions in bilateral occipital lobe extended to parietal lobe. Neither papilledema nor inflammatory change in fundi was found. Therefore, the indicated visual loss was might be due to inflammation-related damage in the tract to the visual cortex. Her symptoms and brain MRI findings were refractory to initial steroid therapy, but muscle weakness in left upper limb later occurred with new high intensity lesion in right frontal area with Gd-enhancement. The brain biopsy finally demonstrated a marked gliosis and demyelination with cytotoxic helper T cell and microglia accumulation (Fig. 2), and the new brain lesion plus new neurological symptoms improved after the second steroid therapy except for visual loss (Fig. 3).

Takayasu arteritis is primarily a granulomatous large vessel vasculitis, which is characterized by stenosis, occlusion and sometimes aneurysm of the

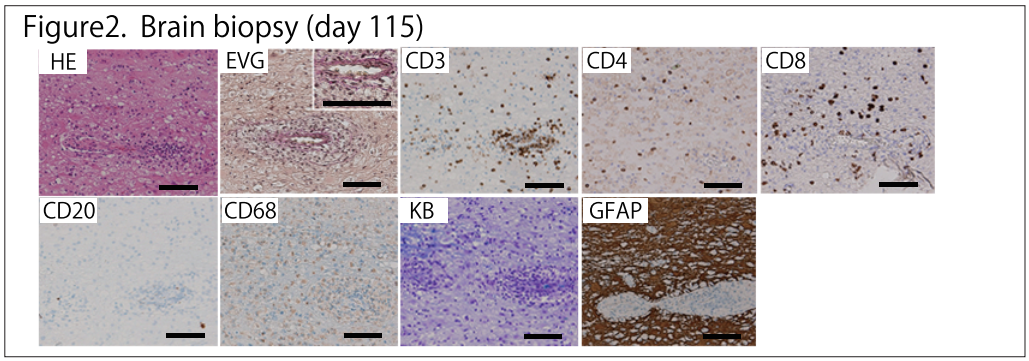

Figure 2

Pathological study on brain biopsy samples shows a marked gliosis with demyelination and a diffuse accumulation of lymphocytes predominantly around small vessel. EVG stain revealed that there was perivascular space without internal elastic lamina or smooth muscle in the small vessel. Immunohistological examination showed that monocytes were mainly positive for CD3, CD8 and CD68, weakly positive for CD4, and negative for CD20. Bar: 100μm.

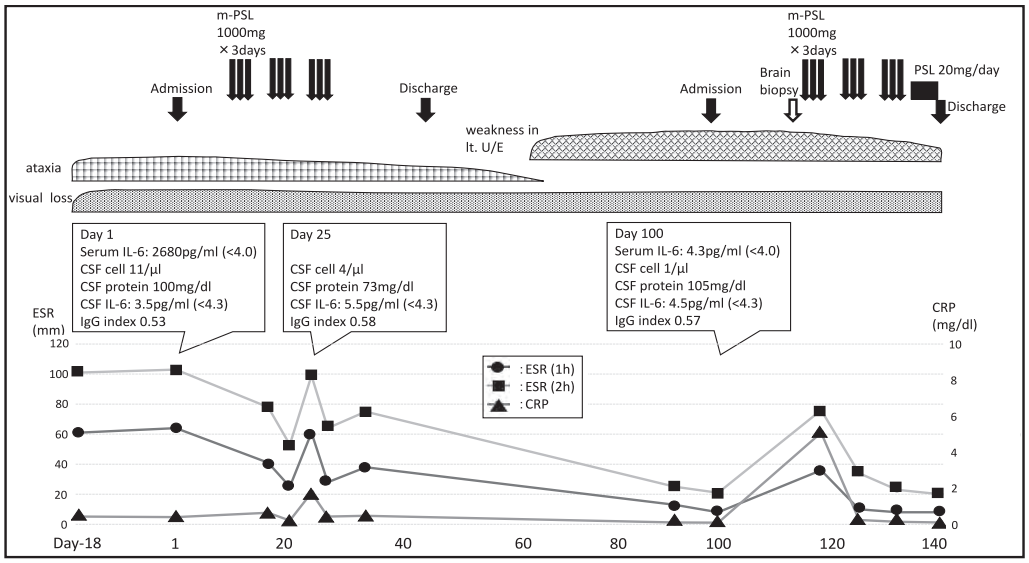

Figure 3

Clinical course of the present case.

aorta and its main branches[1,2]. The pathogenesis of Takayasu arteritis is cellular infiltration of CD3 positive, CD8 positive, but not CD4 positive cytotoxic T cell[3], macrophages, CD4 positive T cell, CD8 positive T cell, natural killer T cell and $\gamma\delta$ T cell[4] in aortic tissue. In the present case, the brain biopsy showed the accumulation of mainly CD68 positive microglia, and CD3 and CD8 positive cytotoxic T cell, weakly CD3 and CD4 positive helper T cell (Fig. 2), which happened predominantly around the small vessel. On the other hand, there was no eosinophilic red neurons which indicated acute ischemia in the lesion[5]. These findings suggested that inflammation of small vessels might reflect T2 high intensity of brain MRI. EVG stain revealed that there was perivascular space without internal elastic lamina or smooth muscle in the small vessel, and the diameter of this artery was about 30 to 100μm, therefore, this small vessel with inflammation was supposed to be a post-capillary venule[6], but is pathologically similar

to the previous pathological findings in the aortic tissue of the Takayasu arteritis.

IL-6 is a pro-inflammatory cytokine which is mainly synthesized by activated T cells and macrophages, and serum concentration of IL-6 is increased with Takayasu arteritis patients[7]. In the present case, serum concentration of IL-6 on first admission (day 1) was greatly elevated, however it turned better to almost normal range after three cycles of intravenous high-dose methylprednisolone therapy. Whereas CSF IL-6 level was slightly worsened after initial therapy (Fig. 3), suggesting a sustained intrathecal inflammation. Thus the second intravenous high-dose methylprednisolone therapy and oral prednisolone were effective.

Here we reported the first case of the leukoencephalopathy accompanied by Takayasu arteritis with the pathological characteristic of marked gliosis and demyelination with microglia and cytotoxic T cell accumulation predominantly around the small vessel. Our case suggested an interesting relation of leukoencephalopathy and Takayasu arteritis with microglia and cytotoxic T cell accumulation.

Conflicts of interest

The authors declared no potential conflicts of interest.

Acknowledgement

We appreciate the patient's cooperation. This work was partly supported by a Grant-in-Aid for Scientific Research (B) 17H0419611, (C) 15K0931607, 17H0975609, and 17K1082709, and by Grants-in-Aid from the Research Committees (Kaji R, Toba K, and Tsuji S) from the Japan Agency for Medical Research and Development 7211800049, 7211800130, and 7211700121.

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Greetings from Vas-Cog Japan, the Japanese Society for Vascular Cognitive Impairment

Ryuichi Morishita, MD, PhD

President: The Japanese Society for Vascular Cognitive Impairment

Since Vas-Cog Japan was first established at 11 years ago, it has developed considerably. The society progressed under the strong leadership of former Presidents Prof. Ken Nagata and Prof. Koji Abe, aiming to promote both basic and clinical research on vascular cognitive impairment and dementia. I took over as president of the society. I would like to express my sincere gratitude to all members of Vas-Cog Japan for their 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 2021, we have 183 active members, up from 143 last year, including 25 directors and 64 councilors, and the membership is expected to continue to increase in the future. Furthermore, the financial structure has been going very well, year by year. Under the guidance of Prof. Yoshio Ikeda, the Chairman of Financial Affairs, we can expect the society's finances to continue to grow in the future. I sincerely thank the members, councilors, and directors who have supported the society since its establishment for these achievements. Our society has now met the requirements in terms of member numbers, membership management, and publication of journals to apply to be registered as an academic organization with the Science Council of Japan. At present, the Chairman for the Promotion of Becoming a Society, Prof. Katsuya Urakami, is overseeing our application for registration. Regarding conflicts of interest (COI), we have set up a COI committee and prepare provisions under the direction of the chairman of this committee, Prof. Masahiko Suzuki

We have published an annual newsletter since 2014. The newsletter has been widely distributed to related academic societies in various countries and has been 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 the Vas-Cog Journal, a joint publication with Vas-Cog Asia. Last year, Prof. Toshiki Mizuno took over the role of chief editor of the journal. We continue to focus on improving the content of the journal in terms of the quality of published articles, as well as the look of the journal in terms of style and presentation.

The COVID-19 outbreak resulted in the cancelation of academic conferences worldwide, including the 11th annual meeting of Vas-Cog Japan 2020, which was intended to be held 12 and 13 September 2020 at Awa Kanko Hotel, Tokushima, with Prof. Masataka Sata, Department of Cardiovascular Medicine, Institute of Biomedical Sciences, Tokushima University Graduate School and Prof. Shunya Takizawa, Department of Neurology, Tokai University School of Medicine as the chairpersons. The conference is now scheduled to take place in the same venue on 28 August 2021. Hopefully, we will have a safe and exciting meeting this year. Up-to-date information on the conference will be available on the Vas-Cog Japan website closer to the scheduled date.

Our affiliate Vas-Cog Asia plays an increasingly significant role in the field of vascular dementia research. Vas-Cog Asia 9 was held on the web-based platform on 4 December, jointly with the Asia-Pacific Stroke conference. The 10th anniversary meeting of Vas-Cog Asia will be held in India this year.

The effects of the COVID-19 pandemic continue to be felt in many countries. It remains difficult to know how long the COVID-19 outbreak will last and when we will be able to get our lives back to normal. Recent studies have pointed to a relationship between COVID-19 and dementia. 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 develop effective therapeutics, fighting against the COVID-19 pandemic as well. The society has an exciting future, and we look forward to your participation in the society going forward.

10 March 2021

Welcome to Vas-Cog Japan 2021

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

Department of Neurology
Tokai University School of Medicine
Shunya Takizawa

It is our great honor to welcome you to the 11th annual meeting of the Japanese Society for Vascular Cognitive Impairment (Vas-Cog Japan 2021). This year's meeting will be held on August 28th, 2021 on WEB. The meeting, which was scheduled in September last year originally, has been postponed for one year due to COVID-19 pandemic. We are planning complete WEB meeting, where you can participate it on remote. Accumulating evidence suggests that life-style related diseases, such as hypertension, diabetes, and dyslipidemia, are risk factors not only for cardiovascular diseases but also for dementia. Thus, it would be fascinating opportunity for the expert researchers in atherosclerosis and dementia to communicate each other to understand recent advances in both areas. The main theme of the meeting is "Dementia practice from vascular and neurological medicine". We are focusing on the close relationship between the vascular diseases and the pathogenesis of neuronal degeneration causing dementia. The special lectures will be given by Prof. Takayoshi Shimohata from Gifu University and Prof. Tomoya Yamashita from Kobe University. Educational lectures will be given by Prof. Koji Abe from National Center Hospital, National Center of Neurology and Psychiatry and Prof. Yuishin Izumi from Tokushima University. We are organizing three symposia "Frontiers in researches in cerebrovascular blood flow and metabolism related to vascular dementia," "Dementia and cardiovascular diseases" and "Protective and exacerbating factors in vascular dementia." We are planning two special symposia organized by young investigators from vascular and neurological medicine.

We are expecting many doctors and researchers on neurology, geriatric medicine, cardiology, metabolic diseases and pharmacology to attend the meeting. We are looking forward to seeing you at Vas-Cog Japan 2021 on web!

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

第11回 日本脳血管・認知症学会総会

VAS-COG Japan 2021

「血管と神経から診る認知症」

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Welcome to Vas-Cog 2022
Theme: Cerebral small vessel disease and cognitive impairment, frailty, sarcopenia

Department of Neurology. Tokyo Women's Medical University

Kazuo Kitagawa

Department of Geriatric Medicine Kyorin University School of Medicine

Koichi Kozaki

It is our honor to host the 11th annual meeting of the Japanese Society for Vascular Cognitive Impairment (Vas-Cog Japan 2022). 11th annual meeting is scheduled to be held August 6th, 2022 in Tokyo with co-chairs of Professor Kitagawa and Kozaki. Although we are under the threat of detestable COVID-19 infection at this time June 2021, we are hoping that the conference will be held face-to-face in August 2022. This time we are planning to have a meeting with the theme of "Cerebral small vessel disease and cognitive impairment". Recent progress in the field of cerebral small vessel disease has been showing us a lot of things, especially a close relation of cerebral small vessel disease with cognitive impairment or possibly with frailty and sarcopenia, both are major cause of disability in the older adults.

Cerebral small vessel disease is closely related to lifestyle-related diseases such as hypertension, diabetes, dyslipidemia, and others. Cerebral small vessel disease is in part a cause of lacunar infarction and ischemic white matter lesion, so-called "leukoaraiosis". Lacunar infarction and ischemic white matter lesion can be the cause of vascular dementia in the form of "small-vessel type" in the NINDS-AIREN criteria. Recent evidence shows cerebral microbleeds, cortical microinfarction and amyloid angiopathy are also included in cerebral small-vessel disease.

Frailty and sarcopenia are the process of being disabled in the old age. Frailty is defined by 5-domains; body weight loss, physical weakness, slowness, and exhaustion, and physical inactivity. Sarcopenia is defined by muscle weakness, physical weakness and muscle loss. Recent findings are showing that both frailty and sarcopenia are in part related to cerebral small and large vessel disease.

Together, cerebral small vessel disease is a morbid condition causing cognitive impairment, dementia, frailty, and sarcopenia. We would like to revisit this important issue, and have a great time exchanging opinion with participants face-to-face. We hope 2022 Vas-Cog conference will shed the light on this important issue. We would like all the members to submit an abstract, attend the meeting and make active discussion next year. Please join us!

12th Annual Meeting of the Japanese Society for Vascular Cognitive Impairment

Vas-Cog J

第12回 日本脳血管・認知症学会総会

VAS-COG Japan 2022

VAS-COG JAPAN 2022 TOKYO

Vas-Cog J

Theme

Cerebral small vessel disease and cognitive impairment, frailty, sarcopenia

— 脳小血管病と認知機能低下、フレイル、サルコペニア —

会期 2022年8月6日(土)

会長 北川 一夫 東京女子医科大学 脳神経内科

神﨑 恒一 杏林大学医学部 高齢医学

演題登録 詳しくはHPにてご確認ください。

総会事務局 吉澤 浩志（東京女子医科大学脳神経内科）
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Meeting report of Vas-Cog Asia 9 from Busan

Koji Abe, MD, PhD
The first Vas-Cog Asia President

I would like to celebrate the great success of Vas-Cog Asia 9, which was held on the completely web-based style in Busan (Korea) on December 4 afternoon (2020) always jointing with Asia-Pacific Stroke Conference (APSC) based on the great supports by Professors Tan Kay Sin (APSO president, Malaysia) and Joung-Ho Rha (APSC2020 Chair, Korea) and Professors Hee-Joon Bae, Byung-Chul Lee, and Hye Won Yoon (Hosts of Vas-Cog Asia 9, Seoul). This Vas-Cog Asia 9 was originally planned to be held in Seoul on September 11 (2020). However, an unexpected pandemic of CORONA (Covid-19) beginning 2020 January in Wuhan (China) forced the postpone and the meeting place/style moving. Even under such difficult situations, we welcomed about 40 participants from Korea, Japan, Taiwan, Indonesia, and China. There were variety of important presentations in the present conference. Many basic science, translational research, clinical trials and evidence were discussed especially on the aspects of Alzheimer's disease (AD), vascular dementia (VD), behavioral and psychiatric symptoms of dementia (BPSD), and their important vascular involvement.

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

Next Vas-Cog Asia 10 anniversary is going to be held in India (2021) under direction of our President Tsong-Hai Lee (Taipei) and 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.

January 10, 2021

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* indicates new board member or councilor.

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Katsuya Urakami (Tottori University)

Yasuyuki Ohta *(Yamagata University)

Kenjiro Ono (Showa University)

Kazuo Kitagawa
(Tokyo Women's Medical University)

Koichi Kozaki (Kyorin University)

Issei Komuro (The University of Tokyo)

Masataka Sata (Tokushima University)

Munehisa Shimamura (Osaka University)

Takayoshi Shimohata (Gifu University)

Ken Shinmura (Hyogo College of Medicine)

Kazuma Sugie (Nara Medical University)

Masahiko Suzuki (The Jikei University)

Hidekazu Tomimoto (Mie University)

Yukihito Higashi (Hiroshima University)

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Miyuki Matsumura
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Hiroo Ichikawa (Fujigaoka Rehabilitation Hospital)
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Jun Iwanami (Ehime University)
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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.
Officers shall reach the mandatory retirement age on March 31st of the year in which they become 65 years old.

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

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

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

Chapter5.Council

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

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

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

Chapter6.Accounts

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

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

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

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

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

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

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

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

Vas-Cog Journal Submission Instructions for authors

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

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

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

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

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

Submission of Manuscripts:

At least the first author and corresponding author should be members of Japanese Society of Vascular Cognitive Impairment. All manuscripts must be submitted electronically through online submission system in the official web site of Japanese Society of Vascular Cognitive Impairment (http://www.plus-s-ac.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.plus-s-ac.com/vas-cogj/kaishi.html**) with all co-authors' signatures, and email it to the Editorial Office (**vas-cogj@plus-s-ac.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.

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Editor's Note

Shuko Takeda, MD, PhD.

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I would like to express my gratitude and admiration to the editorial board and all the members of Vas-Cog Japan for the successful publication of Vas-Cog Journal No.7 under the arduous conditions of the COVID-19 pandemic. Its impact on the medical world has been enormous, with the activities of many medical organizations and academic societies yet to return to the *new* normal. Under the present conditions, the successful publication of Vas-Cog Journal No. 7 after a delay of several months is no mean feat. I would also like to add that, without a shadow of a doubt that and in spite of COVID-19, we at Vas-Cog Japan will continue to carry out our academic and scientific activities.

There are indications that strongly suggest COVID-19 causes severe inflammation and the formation of thrombi. It has also emerged that strokes and cognitive dysfunction are serious sequelae of COVID-19. This all means the role Vas-Cog Japan will play in this pandemic and beyond will almost certainly be extremely significant.

The *brand-new* Vas-Cog Journal is now in its second year of using a submissions and peer-review procedure, which was introduced with the aim of establishing the publication as a fully-fledged academic journal of international repute. To further this aim, the intention is to collaborate with Vas-Cog Asia and Vas-Cog World to publish articles submitted by researchers from a wider geographical area. This is also the second year of the new editorial board under the chief editorship of Prof. Toshiki Mizuno, who took over from Prof. Mikio Shoji.

The current issue contains two review articles and a case report on vascular dementia. There are also reports on the Vas-Cog Japan Annual Meeting, which was postponed from last year, and the Vas-Cog Asia Meeting, which was held online.

The COVID-19 pandemic will continue into this year, and I very much hope that our members and readers will remain safe and in good health.

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 : August, 2021 (Tokushima) Chairman : Shunya Takizawa and Masataka Sata
The 12th Meeting : August, 2022 (Tokyo) Chairman : Kazuo Kitagawa and Koichi Kozaki
The 13th Meeting : August, 2023 (planned) Chairman : Masahiko Suzuki
The 14th Meeting : August, 2024 (planned) Chairman : Takayoshi Shimohata
The 15th Meeting : August, 2025 (planned) Chairman : Kazuma Sugie

- to be continued -