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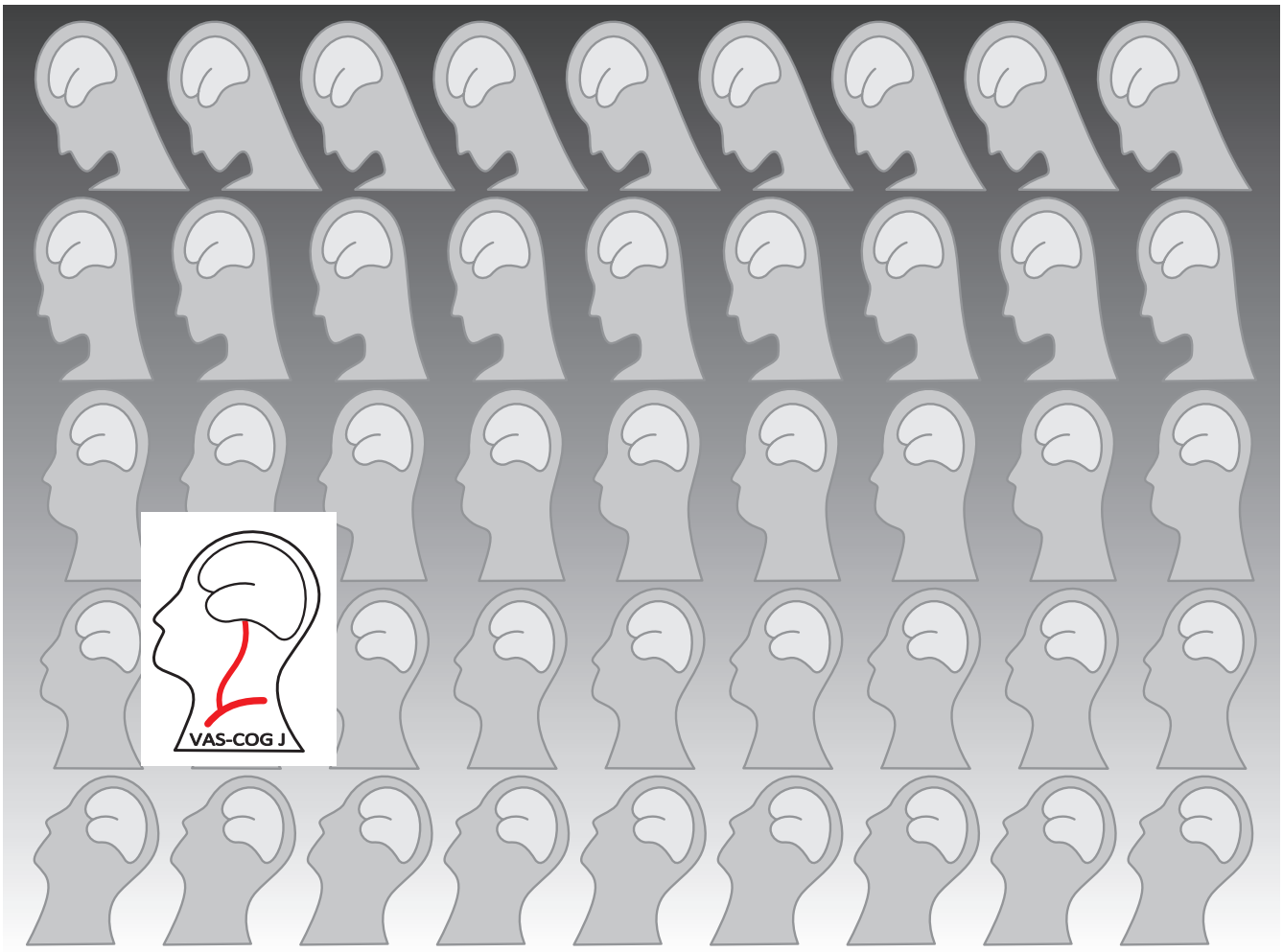

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運営事務局 株式会社プラスエス・アカデミー 〒591-8025 大阪府堺市北区長曽根町3番地 シュライククリエイティブセンター 201号
TEL 072-275-5723 FAX 072-275-5724 E-mail vas-cogj@plus-s-ac.com

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Table of Contents

Editorial

Toshiki Mizuno, MD, PhD
Professor of Neurology,
Kyoto Prefectural University of Medicine

We are entering an era of fundamental change in the treatment of Alzheimer's disease. Following FDA approval of Aducanumab in the US in 2021 and Lecanemab in 2023, the PMDA is currently investigating these drugs for approval in Japan. If these drugs are approved, PET tests for Alzheimer's disease biomarkers, and also blood and spinal fluid tests, could also be covered by insurance. For prescribing these antibody drugs, the Japanese government may require performance of these tests to diagnose Alzheimer's disease accurately. Testing will also be needed to manage patients safely by detecting the onset of ARIA during treatment . In Japan, free access to health care is available, which means that many dementia patients seeking new drugs may be seen, so changes to the healthcare system will certainly be required. In addition, it will be necessary to consider how much these therapies will contribute to society. We should consider these issues now that antibody therapies for Alzheimer's disease are available,. On the other hand, these antibody therapies are currently not effective in all patients with Alzheimer's disease. The antibody therapy has only been tested in patients in the early stages and may be limited, e.g. with risk factors such as APOE4 . We need to know how to select patients for antibody therapy and how to inform patients and families of possible risk and benefit. Medically, as noted with ARIA, further research is needed into the link between Alzheimer's disease and cerebral blood vessels. In particular, it needs to be clarified whether the drainage system from the brain and its pathways are impaired by ageing and atherosclerosis. Previous findings in hereditary Alzheimer's disease have emphasized the gain of toxic function of Abeta, and therapies have been developed using genetically modified models based on this hypothesis. However, the development of animal models and therapies based on the role of the degradation and efflux systems in Alzheimer's disease occurring in human ageing has only just begun. The VAS-COG Japan Society would like to further support the progress of research towards the development of treatments for this age-related loss of function.

Special Lecture (review article)

The relationship between amyloid-β accumulation and cerebrovascular disease in Alzheimer's disease: role of amyloid positron emission tomography

Hiroo Kasahara, MD, PhD[1)]; Masaki Ikeda, MD, PhD[2)]; Yoshio Ikeda, MD, PhD[1)]

1) Department of Neurology, Gunma University Graduate School of Medicine, Maebashi, Japan.
2) Division of General Education (Neurology), Faculty of Health and Medical Care, Saitama Medical University, Hidaka, Japan.

Abstract:

The relationship between Alzheimer's disease (AD) and cerebrovascular disease (CVD) is attracting attention. To investigate this complex relationship, it is necessary to focus on biomarkers that can assess AD pathophysiology. Positron emission tomography (PET) to detect amyloid-β (Aβ) can visualize the distribution of Aβ accumulation in the brains of AD patients. Amyloid PET imaging has been evaluated qualitatively, but a quantitative evaluation has also been developed to allow better comparison of data across institutions. Quantitative amyloid PET analysis has been used in the development of many disease-modifying drugs against AD. Cerebrospinal fluid and serum biomarkers have also been developed to investigate Aβ pathology, but the advantage of amyloid PET imaging is its ability to assess Aβ accumulation in a site-specific manner.

Spatial assessment of Aβ accumulation by amyloid PET is useful when investigating its association with CVD. We have revealed that more severe CVD findings are associated with milder Aβ accumulation in patients with AD. Simultaneous presence of Aβ and CVD pathologies, compared to the presence of either pathology alone, has been shown to significantly accelerate the onset of clinical dementia and cognitive decline. To prevent cognitive decline in AD patients, it is important to manage vascular risk factors and prevent CVD.

Key Words: Alzheimer's disease; dementia; white matter lesion; amyloid-β; cerebrovascular disease; positron emission tomography

Correspondence to:

Yoshio Ikeda, MD, PhD

Department of Neurology, Gunma University Graduate School of Medicine, 3-39-22 Showa-machi, Maebashi, Gunma 371-8511, Japan.

Tel: +81 27 220 8060 Fax: +81 27 220 8067

E-mail: ikeday006@gunma-u.ac.jp

Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disease with increasing prevalence and is characterized by cognitive impairment and behavioral disturbances. Interestingly, pathological indicators of AD and cerebrovascular disease (CVD) are often seen simultaneously in the brains of older adults, and the relationship between AD and CVD is attracting attention. However, the role of CVD in AD pathogenesis has not been clarified. To investigate the relationship between AD and CVD, it is necessary to focus on biomarkers that can reflect the disease status of AD. Neuropathological hallmarks of AD brains include neurofibrillary tangles (NFTs) which contain phosphorylated tau protein and senile plaques which contain extracellularly deposited amyloid-β (Aβ) protein fibrils[1,2)]. Previous studies on biomarkers for AD have been conducted focusing on these pathological features. With the establishment of biomarkers for AD using cerebrospinal fluid (CSF) sampling and positron emission tomography (PET) scans, the recent diagnostic procedure of AD no longer relies solely on classical neuropsychological testing but instead assesses patients based on biomarkers. $A\beta_{42}$ levels in CSF and amyloid PET findings have been validated as biomarkers of Aβ pathology (A), while phosphorylated tau in CSF and tau PET findings have been established as biomarkers of tau pathology (T). In addition, total tau in CSF, decreased glucose metabolism on ^{18}F-fluorodeoxyglucose PET, and brain atrophy on magnetic resonance imaging (MRI) are established biomarkers of neurodegeneration (N). The National Institute on Aging and Alzheimer's Association (NIA-AA) proposed diagnostic criteria for AD based on biomarkers of Aβ, tau, and neurodegeneration, called the A/T/N biomarkers[3)]. Of these biomarkers for AD diagnosis, Aβ is the first biomarker to become abnormal in carriers with a pathogenic AD mutation[4)]. This finding suggests that abnormalities in biomarkers of Aβ dysregulation may solely serve as a defining AD signature. Amyloid PET, such as ^{11}C-labeled Pittsburgh Compound B PET (^{11}C-PiB PET), can detect cerebral Aβ deposition *in vivo* and visualize the distribution of Aβ accumulation in AD brains[5)]. Postmortem studies have revealed that increased ^{11}C-PiB uptake on PET

images corresponds to areas of abundant senile plaques[6]. Herein we describe the characteristics of amyloid PET and discuss the relationship between Aβ accumulation and CVD.

Advancements in radiotracers for amyloid PET and methods for image analyses

The first radiotracer to visualize brain Aβ deposition in AD patients was ^{18}F-2-(1-{6-[(2-fluoroethyl)(methyl)amino]-2-naphthyl}ethylidene) malononitrile (^{18}F-FDDNP)[7]. However, ^{18}F-FDDNP is not capable of efficiently binding Aβ, while also binding to NFTs, making it less frequently used at present[8]. PiB is an uncharged derivative of thioflavin-T that has a high affinity for Aβ fibrils and shows very low binding to NFTs and is therefore widely used in clinical studies[9]. On the other hand, ^{11}C-PIB use is limited because of the short half-life of ^{11}C, and several radiotracers labeled with ^{18}F have been developed as alternatives. Among them, ^{18}F-flutemetamol is a derivative of thioflavin-T, which has a chemical structure almost identical to ^{11}C-PIB. ^{18}F-flutemetamol has a high affinity for Aβ but exhibits higher white matter uptake[10]. Moreover, ^{18}F-florbetapir and ^{18}F-florbetaben with trans-stilbene derivatives have been developed, and the synthesis devices have been approved under the Japanese Pharmaceuticals and Medical Devices Act (PMDA). Furthermore, two of the above radiotracers (^{18}F-florbetapir and ^{18}F-flutemetamol) are marketed as diagnostic agents in Japan.

In general, the amyloid PET images are rated as positive or negative by inspection; they are rated as "positive" if the uptake level in the cerebral cortex is higher than that in the white matter. The standardized uptake value ratio (SUVR) represents a quantitative measure of tracer uptake, which is normalized to the average uptake in a reference region. As it is known that radiotracer uptake in the cerebellar cortex does not differ between AD patients and healthy controls[6], it is commonly used as the reference region in amyloid PET analysis. Generally, qualitative evaluation of amyloid PET imaging by inspection shows consistent results across institutions. While SUVR values are useful for quantitative assessment, there is considerable variation in the reported SUVR measurement methods used among institutions. A common quantitative output value, regardless of the tracer or method, would allow better comparison of amyloid PET data across institutions. For this reason, the main objective of the Centiloid Project is to standardize amyloid PET results and reconstruct objective quantitative data[11]. The tracer results were standardized by a quantitative index of amyloid imaging, by scaling the outcome of each particular analysis method or tracer to a 0 to 100 scale, anchored by young controls (≤ 45 years old) and typical AD patients; the unit of measurement used in this scale was named "Centiloid"[12]. Quantitative amyloid PET analysis, as described above, has been introduced in the development of many disease-modifying drugs targeting AD pathology. Ongoing Phase 2 and 3 clinical trials for AD are dominated by disease-modifying drugs that target Aβ, and a significant number of these studies are evaluating changes in Aβ accumulation using amyloid PET evaluation before and after treatment.

The advantages and disadvantages of amyloid PET

Although amyloid PET is used frequently in both clinical practice and research, Poul *et al*. indicated the following problems with amyloid PET[13]. Firstly, amyloid PET imaging biomarkers for assessing Aβ deposition have insufficient *in vivo* specificity. It has been shown that uncharged derivatives of thioflavin-T (^{11}C-PiB and ^{18}F-flutemetamol) can be nonspecifically retained by tissue targets other than Aβ, including estrogen sulfotransferase, an enzyme that is elevated during brain inflammation[14,15]. Additionally, quantification of the signal in gray matter is particularly problematic when there is cortical atrophy, as observed in AD brains.

In addition to amyloid PET, immunological measurements, such as $A\beta_{42}$ levels in CSF, have also recently been used as markers of Aβ pathology. Reduction of $A\beta_{42}$ levels in CSF is significantly correlated with Aβ deposition in amyloid PET[16]. Recently, serum Aβ biomarkers have been developed and are shown to correlate with CSF biomarkers[17].

Since immunoserological biomarkers are being developed at a lower cost than amyloid PET, amyloid PET imaging would need to confer advantages over immunoserological biomarkers. Indeed, the biggest advantage of amyloid PET seems to be its ability to assess Aβ accumulation in a site-specific manner. For example, Hwang *et al*. reported that AD with Aβ accumulation in the occipital region showed a younger onset than AD without occipital Aβ accumulation[18], an example of the advantage of using amyloid PET to identify Aβ distribution to inform clinical characteristics. Another example is the use of amyloid PET for investigating differences in cerebral Aβ deposition at normally appearing white matter and white matter with high intensity lesions in T2-weighted MRI. Use of ^{18}F-florbetapir PET revealed that retention of the tracer in white matter is associated with demyelination in AD[19]. Taken together, these data suggest that amyloid PET will play an important role in studies requiring to evaluate Aβ accumulation at specific brain regions.

The relationship between Aβ accumulation and CVD in AD

The pathologies of AD and CVD often overlap in the brains of older individuals, and epidemiological studies indicate that comorbid AD and CVD is common[20]. Several studies have reported that vascular risk factors (VRFs), such as hypertension, hypercholesterolemia, and diabetes mellitus, are associated with an increased risk of developing AD[21,22,23]. Furthermore, it has been reported that VRFs are correlated with CVD[24]. The most common comorbidity in AD is stroke, and

more specifically, ischemic infarction[25]. A recent cohort study has provided evidence that a history of stroke conferred a more than 2-fold increase in the risk of late-onset AD[26]. Cerebral MRI is useful to visually assess the extent of CVD and cerebral white matter lesions (WML), thus constituting imaging biomarkers of CVD[27,28].

Using amyloid PET to assess Aβ accumulation in different brain regions is useful when investigating the association between cerebral ischemic changes and Aβ accumulation. We used ^{11}C-PiB PET and MRI to investigate the association between cerebral Aβ accumulation and CVD in AD patients[29] and revealed that higher WML scores significantly correlated with lower mean cortical SUVRs, especially in the frontal region, suggesting that more severe ischemic MRI findings are associated with milder Aβ accumulation in AD patients. We concluded that CVD may hasten the onset of cognitive decline and promote early detection of dementia. Supporting our findings, others have reported that the simultaneous presence of Aβ and CVD pathologies, compared to either pathology alone, significantly accelerates the rate of cognitive decline[30]. The results of various clinical studies on amyloid PET indicate that CVD and Aβ accumulation are thought to be independent processes in the clinical course of AD but additively affect cognitive decline[30,31]. On the contrary, Bannai *et al*. indicated that the reduced blood flow observed in the cerebral arteries attenuated the dynamics of the interstitial fluid leading to congestion and subsequently facilitated Aβ aggregation in the AD mouse model[32]. These findings suggest an interaction between CVD and Aβ accumulation in AD patients; further investigations and clinical studies are required to clarify this complex relationship.

Conclusions

In conclusion, amyloid PET can be used to evaluate Aβ accumulation in different brain regions and is useful when investigating the association between Aβ accumulation and CVD. Various studies describe the association between Aβ accumulation and CVD and have shown that CVD in AD patients may accelerate the occurrence of cognitive decline. To prevent cognitive decline in AD patients, it is important to manage VRFs and prevent any degradation with the progression of CVD.

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Review article

Cellular and Molecular Neuropathology of Cerebral Small Vessel Disease and Dementia

Raj N Kalaria FRCPath, FMedSci[1)]; Yoshiki Hase MD PhD[1)]; Roxana O. Carare MD PhD[2)]

1) Neurovascular Research Group, Translational and Clinical Research Institute, Newcastle University, Newcastle upon Tyne, United Kingdom
2) Faculty of Medicine, University of Southampton, UK

Abstract:

Cerebrovascular disorders are inherently heterogenous. They entail a variety of clinical, pathological and cognitive features. In recent years, cerebral small vessel disease (SVD) has been at the forefront mainly because it is attributed to a common cause of strokes and responsible for long-term sequalae including disability. Advances in neuroimaging, particularly magnetic resonance imaging (MRI) have expounded on the radiological definition of SVD involving white matter hyperintensities and parenchymal changes whereas it is difficult to appreciate covert pathology in intracranial arteries and arterioles. SVD pathology incorporates small cortical and subcortical infarcts, microinfarcts, microbleeds, perivascular spacing and white matter attenuation. Cerebral vessels undergo loss of smooth muscle cells and disruption of the extracellular matrix within basement membranes with consequences on interstitial fluid drainage. The distribution and quantity of SVD pathology involving both parenchymal lesions and arteriopathy vary with age, gender, vascular risk factors and genetically determined disorders. However, both types of lesions invariably correlate with progression of impairment or worsen cognitive function. SVD is part and parcel of almost all types of dementias. The incorporation of SVD as a biomarker is much warranted in the biological definition of dementia. Therapeutic interventions to reduce SVD pathology via risk control will have a major impact on the burden of dementia.

Key Words: age, arteriolosclerosis, CADASIL, cerebral amyloid angiopathy, Collagen IV, familial dementia, small vessel disease, vascular brain injury, white matter hyperintensity

Correspondence to:

Professor Rajesh N. Kalaria, Translational and Clinical Research Institute, Newcastle University, Campus for Ageing and Vitality, Newcastle upon Tyne, NE4 5PL, United Kingdom.
Tel: +44-(0)191-208-1352; Fax: +44-(0)191-208-1301
E-mail : raj.kalaria@newcastle.ac.uk

INTRODUCTION

Cerebral small vessel disease (SVD) is increasingly described on magnetic resonance imaging (MRI) to denote parenchymal changes, particularly white matter hyperintensities (WMH).[1-3)] The most common consequences of SVD are (i) lacunar (small deep) infarcts; (ii) primary non-traumatic intracerebral brain haemorrhage (ICH) and (iii) subcortical ischaemic vascular dementia, which may be caused by multiple lacunar infarcts or by diffuse white matter ischaemic damage. In addition to age, hypertension and diabetes mellitus appear the main risk factors for SVD. These risk factors are almost equally important for non-lacunar infarcts[4)] and are a cause of cognitive impairment and dementia (Table 1). The pathogenesis of lacunar infarcts has been the topic of intensive research[5)] and imaging studies have suggested that the majority (>90%) of lacunes are found at the edge or have proximal predilection to WMH.[6)] However, the pathological definition of SVD implies much more and emphasizes distinct covert changes within walls of cerebral vessels. Small cerebral vessels bearing smooth muscle cells or myocytes have diameters from 40 up to 900 μm and they emerge from the leptomeningeal arteries, enter the brain parenchyma from the surface of the brain to extend a variable depth into the parenchyma comprising both basal and pial penetrators. The major structural pathologies described in penetrating small arteries in SVD are arteriolosclerosis, fibrinoid necrosis and micro-aneurysms. Small cerebral arteries and arterioles change with age and are actually affected in many disorders including hereditary angiopathies, inflammatory and infective vasculitides and toxic disorders.

In recent times, C Miller Fisher should probably receive the credit for meticulous analysis of cerebral SVD or arteriolar pathology. Fisher suggested segmental arterial disorganization and small vessel atherosclerosis are the two most common causes of lacunar infarcts leading lacunar syndromes, whereas fibrinoid necrosis was associated with large lacunes and ICH.[7)] Intracranial atherosclerosis occurs in very old age, particularly in the branches of the main cerebral arteries.[8)] There are few

qualitative differences in atherosclerotic plaques and the repertoire of the reactive cells associated with atherosclerosis in carotid versus intracranial arteries. In this review article, we focus on recent updates in the understanding of arteriolar pathology in the context of sporadic and familial SVD type of disorders (Table 1).

Features of Vascular Pathology in SVD

Arteriolosclerosis, Fibrinoid Necrosis and Micro-Aneurysms

Arteriolosclerosis describes non-fibrinoid hyaline thickening in arteriolar vessels of 40–300 μm-diameter.[9,10] Normal intracerebral arteries are relatively thin-walled and have a wide lumen in relation to the wall thickness with their sclerotic index normally being <0.3. Arteriolosclerosis tends to be more associated with ischaemic white matter disease and vascular dementia or vascular cognitive impairment rather than lacunar infarcts.[11] The thickened walls narrow the lumen and increase the sclerotic index (SI = 1 – [internal diameter/ external diameter]), a measure devised to indicate severity of degenerative fibrous thickening of the tunica media.[12,13] Previous studies indicate thickened fibrotic arteries seldom rupture.

Fibrinoid necrosis appears not to be necessarily very different[14] from Miller Fisher's description of lipohyalinosis.[15] In the early stages, the walls are thickened by eosinophilic fibrinoid material, composed mainly of plasma proteins, with abundant fibrin, formed by leakage of the blood-brain barrier (BBB) together with remnants of smooth muscle cells. At this fibrinoid-necrosis stage of SVD, the BBB is disrupted and the affected vessels are prone to rupture. In time, the fibrinoid material is replaced by collagen produced by fibroblasts and the arteriolar walls become 'glassy' in appearance. Lipids are usually only a minor component in these lesions, and hyalinosis refers to acellular fibrosis.[9] It has been recommended that the term 'lipohyalinosis' should therefore be abandoned and replaced by descriptions based on appropriate stains: fibrinoid change if histological or immunocytochemical stains verify the presence of fibrin, and fibrosis if collagen is the main constituent of thickened arterial walls. The homogeneous eosinophilia in haematoxylin- and eosin (H&E)-stained sections may result from either fibrinoid change or collagenous fibrosis. These two are probably consecutive changes and can be readily distinguished by use of special stains but appear deceptively similar to H&E.[14] A description probably better describing these vessels would be fibro-hyalinosis, a term implying a rather uniform SVD change extending also to non-hypertensive regressive conditions.

According to the traditional view, Charcot–Bouchard or miliary micro-aneurysms arise in the context of hypertension, at weakened sites in vessel walls.[14] They resemble small sacs, 0.3 to 2 mm across, arising from parent arteries/arterioles 100–300 μm in diameter. The walls of the aneurysms consist of hyaline connective tissue, damaged smooth muscle cells and elastica interna. Rupture of microaneurysms typically produces globular haemorrhages; if 'healed' by thrombosis and fibrosis, these are transformed into fibrocollagenous balls.

Alkaline phosphatase histochemistry and high-resolution micro-radiography showed the great majority of 'micro-aneurysms' to be complex tortuosities. These are most common at the interface between the grey and white matter and their numbers increase with age, but hypertension has no effect on their prevalence. Micro-aneurysms are also not found in relation to lacunar infarcts. However, definitive identification of microaneurysms in routine diagnostic analysis is very rare.

Causes of Arteriopathies

The main causes of arteriolosclerosis are ageing, hypertension, cerebral amyloid angiopathy (CAA) and among common familial disorders such as cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) (Table 1). These can be distinguished by location and type of staining to demonstrate protein accumulation or loss of arterial vascular smooth muscle cells. Hypertension or ageing-related arteriolosclerosis is usually pronounced in subcortical arteries and arterioles. Longstanding hypertension likely increases risk of rupture of small arteries with consequent ICH. Arteriolosclerosis in CAA is largely leptomeningeal and cortical, and in CADASIL predominantly affects leptomeningeal and subcortical vessels, often sparing those in the cortex. Vessels affected by arteriolosclerosis show tinctorial staining for collagen and are intensely immunopositive for collagen I or collagen IV, for example. Arterioles with CAA are Congo Red and Thioflavin S positive, and remarkably often amyloid β (Aβ)-immunopositive. In CADASIL and other monogenic SVD disorders, arteriolar walls show granular basophilia in sections stained with H&E or Periodic Acid Schiff (PAS) but specificity can be shown by immunopositivity of fragments of mutated proteins such as the ectodomain of NOTCH3 in CADASIL[16] and others (Table 2).

Chronic Hypertensive Disease

Hypertension is not itself a disease of blood vessels, but its deleterious effects are mediated by structural changes in blood vessels, particularly in small arteries and arterioles. Chronic hypertension shifts the autoregulatory limits to the right, towards higher pressure values. This is a protective response allowing maintenance of a constant cerebral blood flow (CBF) even at increased arterial pressure and prevents the ill effects of the excessive systemic pressure on delicate capillaries involving specific molecular mechanisms.[17,18] To maintain the upper and lower limits of autoregulation resistance vessels or arteries must undergo gradual change within the vessel wall.[9] Symptoms of cerebral hypoperfusion develop when the mean arterial blood pressure falls to about 40 per cent of baseline

levels. In hypertensive patients, such a reduction is reached at a correspondingly higher level of arterial pressure than in normotensive people. Thus, one-third of asymptomatic hypertensive patients were found to have focal or diffuse cerebral hypoperfusion.[19] This may be exacerbated by excessive antihypertensive medication, to ischaemic levels severe enough to cause tissue damage in both grey and white matter, especially along the arterial border zones.[20] Similarly, in a hypertensive patient with stroke, decreases in blood pressure to levels tolerated by normotensives may worsen the ischaemia as a result of arterial changes.

Sporadic cerebral amyloid angiopathy

Sporadic CAA is predominantly a silent disease without overt clinical symptoms. The most common type of CAA is associated with deposition of Aβ (Aβ-CAA),[21,22] the cleavage product of Aβ precursor protein (APP). Deposition of Aβ in the walls of cerebral blood vessels occurs in sporadic CAA, Alzheimer disease, and Down syndrome but may also occur in other disorders such as dementia pugilistica,[23] and cerebral and spinal vascular malformations.[24] Aβ-CAA is also common in iatrogenic Creutzfeldt-Jakob disease (iCJD), observed in ~90% shared in both growth hormone and dura mater iCJD cases.[25] Sporadic Aβ-CAA rarely affects people <60 years of age. In those >60, the prevalence is a little over 30 per cent[26] and increases with age.[27]

Unlike detection of parenchymal Aβ deposition with tracers such as Pittsburgh compound B (PiB) there are no established methods to detect Aβ-CAA in the living brain.[28] Aβ-CAA is an independent risk for progressive dementia, associated with ischaemic damage to the white matter, and petechial cortical haemorrhages or infarcts. CAA comprises a group of protein misfolding disorders characterized by the extracellular deposition of fibrillar proteins with amyloid properties in the walls of blood vessels of the brain and meninges.[29] It is a relatively common cause of brain haemorrhage in the elderly.[30] Over 25 unrelated proteins are known to be involved in amyloidosis[31] and of these seven are associated with CAA (Table 1). Brains with CAA are often characteristic because of the distribution of the vascular disease, particularly SVD. The predominant form of Aβ that accumulates in arterioles and arteries is Aβ40, whereas that in capillaries is mainly Aβ42.[32] On the basis of different distributions, several ways of grading Aβ-CAA patterns have been devised over the years.[22,33] Each of the up to four patterns[33] is claimed to be distinct and are useful for quantification of research material but for routine purposes the system proposed by Thal et al[34] seems to have been most often applied.[35] Type 1 CAA corresponds to Aβ in cortical capillaries and other vessels whereas Type 2 involves leptomeningeal and cortical vessels, with the exception of cortical capillaries. The type 1 of Thal[34] corresponds to Type 3 described by Mann et al.[33] The differing patterns in CAA within subjects could reflect variations in the efficiency of Intramural Periarterial Drainage (IPAD), as its failure leads to CAA. Alternatively, it may relate to the relative amounts of Aβ, with higher levels of Aβ40 promoting a more 'aggressive' form of CAA.[33]

Electron microscopy reveals extracellular deposits of randomly orientated, straight, unbranched filaments of indefinite length with a diameter of approximately 6–9 nm. CAA tends to be associated with accentuated perivascular neurofibrillary pathology, particularly if the CAA is severe. Systematic morphometric analysis of sections of frontal, temporal and parietal cortex from 51 AD brains revealed that phospho-tau labelling of neurites around Aβ-laden arteries and arterioles significantly exceeded that around non-Aβ-laden blood vessels, which was, in turn, greater than cortical immunolabelling away from blood vessels.[36]

With respect to the pathogenesis of CAA three main sources of Aβ accumulation in vessel walls may be considered. (i) *Systemic*: Aβ is derived from cells throughout the body and is carried in plasma and transported bidirectionally to and from the brain parenchyma by specific receptors in the vessel walls.[37] (ii) *Vascular:* Aβ is produced locally by vascular smooth muscle cells, endothelium and pericytes,[38] all of which express APP.[424] (iii) *Drainage*: Aβ accumulates because of failure of IPAD from the CNS. Aβ formed by neurons within the CNS is cleared from the interstitial fluid by several processes, including enzymatic degradation within the brain parenchyma and the walls of blood vessels,[39,40] transcytosis across the BBB, with endothelial cell uptake mediated by specific receptors including lipoprotein receptor-related protein 1,[41] and IPAD, together with other constituents of the interstitial fluid, along the perivascular extracellular matrix to meningeal arteries and probably cervical lymph nodes. This drainage may be impaired in older people, as vascular disease reduces arterial pulsations (thought to supply the motive force for perivascular drainage), with resulting accumulation of Aβ in the arterial wall, which further impedes vascular pulsatility.[42] Precipitation within the perivascular extracellular matrix of amyloidogenic solutes such as Aβ in the course of their removal from the brain is probably the cause of most types of CAA.[43] Reduced Aβ-degrading enzyme activity within the vessel wall may be a contributory factor: Miners *et al*.[44] showed that neprilysin activity was lowest in meningeal blood vessels from patients with most severe CAA, even after adjusting for smooth muscle content, and that raising or lowering neprilysin activity respectively decreased or increased the death of human cerebrovascular smooth muscle cells on exposure to Aβ. Exclusively neuronal production of Aβ is sufficient to cause CAA.[45]

Affected blood vessels in Aβ-CAA may show segmental dilation or fibrinoid necrosis. Serial sectioning and computer-assisted three-dimensional image analysis suggest that the following sequential steps lead to blood vessel rupture and

haemorrhage:[46] (i) accumulation of amyloid in the arterial wall, (ii) destruction of smooth muscle cells, (iii) consequent dilation (formation of micro-aneurysms) of the artery and (iv) breakdown of the BBB, (v) deposition of plasma proteins in the vessel wall (fibrinoid necrosis), and finally (vi) rupture and haemorrhage. Fibrinoid change was more marked than deposition of amyloid at sites of dilation and rupture. This is consistent with the proposal that the deposition of Aβ in walls of cortical vessels may not directly cause microhemorrhages.[47] Fibrinoid change was also significantly associated with possession of *APOE ε2*,[48] which carries an increased risk of haemorrhage in Aβ-CAA. Loss of vascular smooth muscle cells in CAA seems to depend at least partly on their uptake of Aβ and this, in turn, is influenced by *APOE* genotype. Degradation of extracellular matrix proteins (e.g. MMP-9) weaken vessel walls and is pivotal in the rupture of Aβ-laden arteries.[49] Other changes in the vessel wall may aggravate the angiopathy. For example, iron accumulation and calcification of vessel walls has been reported in hereditary cerebral haemorrhage with amyloid angiopathy of the Dutch type (HCHWA-D) that correlate with the striped cortex observed on *in vivo* 7T MR scans.[50]

GENETICALLY DETERMINED SVDS

Hereditary amyloid β-peptide cerebral amyloid angiopathy (CAA)

Primarily Aβ-CAA occurs in Dutch (HCHWA-D) and Flemish (HCHWA-F) types and in the different familial forms of Alzheimer disease (FAD).[3] Mutations in APP that cause haemorrhages are mostly located within the Aβ domain and involve substitutions of amino acids 21–23 of Aβ, whereas those responsible for FAD are most often located in APP next to but outside of Aβ. Enhanced Aβ accumulation within vessel walls causes cell loss and increasing propensity to rupture and obstruction with resultant haemorrhages and infarcts. In the Italian and Iowa families, CAAH is a common feature, along with dementia. In those FADs associated with presenilin-1 mutations, CAA has been reported to be more common if the presenilin-1 mutation is located beyond codon 200.[51]

Other hereditary CAAs

Hereditary cerebral haemorrhage with amyloid angiopathy of the Icelandic type (HCHWA-I, hereditary cystatin C amyloid angiopathy) is a rare autosomal dominant CAA associated with fatal brain haemorrhages in young and middle-aged normotensive adults.[52] In addition to the cerebral and meningeal arteries, ACys-amyloid is deposited in extracerebral tissues, including the skin.

Worster-Drought *et al*[53] originally described an autosomal dominant CAA with non-neuritic plaques and neurofibrillary tangle formation, clinically characterized by dementia, spastic tetraparesis and cerebellar ataxia with onset around the sixth decade. The disease was subsequently called familial British dementia (FBD) caused by the defective gene *BRI2*.[54] A mutation at another site on the same *BRI2* gene causes heredopathia ophthalmo-oto-encephalica.[29] This disorder, renamed familial Danish dementia (FDD), is characterized by cataracts and ocular haemorrhages in the third decade, followed by hearing problems and, in the fourth to fifth decades, cerebellar ataxia and dementia.

Although CAA in both FBD (with deposition of ABri) and FDD (with deposition of ADan) is severe, with concentric splitting and occlusion of affected vessels, ICH is rare. CAA also affects small arteries and arterioles in white matter as well as in systemic organs. In FDD, Aβ is sometimes co-deposited with ADan in both vessels and parenchyma. In both disorders, amyloid plaques, hyperphosphorylated tau-positive neurofibrillary tangles and neurites are also present in the brain parenchyma.

In gelsolin-related familial amyloidosis of the Finnish type,[55] the amyloid AGel is deposited systemically, particularly in the skin, peripheral nerves and cornea. Two mutations in the *GEL* gene on chromosome 9 cause AGel amyloidosis. Remarkably, CNS deposition of AGel is widespread in spinal, cerebral, and meningeal blood vessels, and extensive extravascular deposits are present in the dura, spinal nerve roots and sensory ganglia.[56]

Transthyretin-related and other CAAs

TTR CAA is caused by mutations in the transthyretin (TTR) gene, located on chromosome 18. Patients may suffer from dementia, cerebellar ataxia, motor dysfunction, and decreased vision and hearing. Currently >100 different mutations have been identified in TTR. Mutated TTR is prone to form amyloid fibrils. In addition to systemic ATTR deposition, common consequences of which include peripheral neuropathy and cardiomyopathy, nine mutations are associated with oculoleptomeningeal amyloidosis with prominent CAA of meningeal vessels.[57] Patients with the p.Val30Met mutation in TTR 4.4% exhibit retinal amyloidotic angiopathy[58], and there is early CNS involvement showing a topographic spread from leptomeninges to cortical vessels and finally involving deep vessels, although with early brainstem and spinal cord involvement.[59]

CAA in patients with prion disease usually results from vascular deposition of Aβ. CAA due to prion protein (PrP) deposition is rare and associated with stop mutations in *PRNP*. PrP amyloid (APrP) may be extensively deposited in parenchymal and leptomeningeal vessels and in the surrounding neuropil.[60]

Hereditary Non-Amyloid Angiopathies

Molecular genetic studies have identified several monogenic conditions characterised by SVD and predispose to ischaemic

and haemorrhagic strokes and diffuse white matter disease[61] (Table 2). CADASIL is the most common hereditary SVD. Other hereditary SVDs include cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL), the collagen type IV (COL4A1/A2)-related disorders, retinal vasculopathy with cerebral leukodystrophies (RVCLs), and cathepsin A related arteriopathy with strokes and leukoencephalopathy (CARASAL).[61] Although hereditary SVDs vary in phenotype, they demonstrate convergent effects of microangiopathy on cerebral grey and white matter, leading to cognitive impairment. Collectively, all these hereditary SVDs involve mutations in single genes, whose products are responsible for cell signalling or extracellular matrix development and maturation.[62](Table 2).

CADASIL as a Model SVD

Heterogeneity within the CADASIL phenotype is now increasingly recognised. Multiple small infarcts, detectable on T1-weighted MRI cause cognitive decline between 40 and 70 years of age, primarily in executive frontal lobe functions, followed by impairment of memory and other cognitive functions, leading to the development of a subcortical dementia in ~80% after 65 years of age. The characteristic neuropathological feature is non-atherosclerotic and non-amyloid arteriopathy,[63] affecting penetrating small and medium-sized arteries of the white matter but also leptomeningeal blood vessels. Large intracerebral haemorrhages are rare but cerebral microbleeds are often described to occur in subcortical structures.[64,65] The extracellular matrix (ECM) within the basal lamina is disrupted[16] and may accumulate other proteins (see below) with impact on IPAD. In accord with other SVDs, alterations in retinal microvessel are also apparent in CADASIL. Arteriolar narrowing is the most consistent change and can be revealed by fundoscopy and fluorescence angiography.[64] Autopsy shows thickened arterial walls with fibrosis, accumulation of eosinophilic material, pericyte degeneration and loss of smooth muscle cells in the central retinal artery and branches.[66] Other pathological features of note include severe astrocytopathy associated with white matter disease.[67]

One of the key pathological characteristics of CADASIL is the deposition of electron dense extracellular granular osmiophilic material (GOM), which contains extracellular domains of NOTCH3 (N3ECD).[16,63,68] Presence of GOM within dermal biopsies offers a means of *intra vitam* diagnosis and was reported to be completely congruent with genetic screening.[69] Immunohistochemical demonstration of N3ECD in skin arteries is also very useful in establishing diagnosis[70] provided clinical symptoms are consistent with the disease. Up to 280 distinct mutations within the 34 epidermal growth factor receptor (EGFr) domains of *NOTCH3* have been associated with CADASIL. The vast majority of these (~70%) are missense point mutations with most frequently occurring in exon 4 of the gene.[71] Almost all of the mutations result in either a substitution of a wild-type cysteine by another amino acid or *vice versa* in one of the 34 epidermal growth factor-like (EGF) repeats in N3ECD. Cysteine-sparing mutations, such as p.Asp80Gly, appear to cause CADASIL with a phenotype indistinguishable from cysteine mutations including aggregation properties of N3ECD.[72] Upon recent analysis of large exome databases involving global populations, the frequency of the archetypal cysteine altering *NOTCH3* (*NOTCH3*cys) mutations in the EGFr domains were found to be 100-fold higher than expected based on estimates of CADASIL prevalence[71]. Recent advances suggest individuals with a mutation located in EGFr domains 1-6 are predisposed to more severe classical phenotype including characteristic clinical and pathological features compared with those with a mutation in 7-34 domains[71,73].

The pathogenesis of CADASIL remains elusive. The uneven number of cysteine residues affects the formation of disulphide bridges and therefore changes the three-dimensional structure of the NOTCH3 receptor and consequently its functions.[74] The formation of abnormal disulphide bridges could affect receptor trafficking, processing, specificity for ligand binding and/or signal transduction. Most mutations in *NOTCH3* do not appreciably impair signal transduction activity, NOTCH3 processing, or signalling to CBF1/RBP-Jκ activation. It is more likely that the misfolded, non-degradable N3ECDs that accumulate within GOM[75] over the years affect the function of vascular smooth muscle cells and block the drainage routes.[76]

Proteomic studies of CSF, isolated cerebral vessels and cultivated vascular smooth muscle cells from CADASIL patients have provided various clues to the pathogenesis. Proteins involved in inflammatory responses (Factor B, serum amyloid P component, periostin),[77,78] protein degradation and folding, endoplasmic reticulum stress with activation of Rho kinase and unfolded protein response,[79,80] vascular functions (clusterin and endostatin),[81] extracellular matrix proteins (tissue inhibitor of metalloproteinases 3 and vitronectin),[82] and serine proteases (high-temperature requirement protein A1, HTRA1)[83] are evident that may or may not complex with N3ECD. Majority of the studies favour that mutant NOTCH3 induces gain of toxic involving misfolding or aggregation of proteins. Prolonged retention of mutant NOTCH3 aggregates in the endoplasmic reticulum decreases cell growth and increases sensitivity to other stresses.[84]

CARASIL

CARASIL was first described as Maeda syndrome.[85,86] CARASIL is characterised by severe non-amyloid arteriopathy, leukoencephalopathy and lacunar infarcts together with spinal anomalies and alopecia. As in CADASIL, the recurrent strokes lead to insidious deterioration with most subjects becoming

cognitively impaired in older age. Typical CARASIL is caused by mutations in the *HTRA1* gene, which encodes the serine protease. Both nonsense and missense as well as frameshift plus splicing site mutations have been reported in the *HTRA1* gene that causes typical CARASIL or HTRA-1 related SVD.[86] Heterozygous HTRA1-related SVD has a milder clinical presentation of CARASIL. Differing locations of mutations found in symptomatic carriers with mild disease and classical CARASIL suggests that distinct molecular mechanisms influence the development of SVD. Mutations result in haploinsufficiency or reduced HTRA1 protease activity (21%-50%) or loss of the protein.[85]

The arteriopathy is described by extensive loss of medial smooth muscle cells, intimal proliferation, and splitting of the internal elastic lamina with severe disruption of the ECM in the pial arteries, perforating arteries, and arterioles. CARASIL extends the spectrum of diseases associated with the dysregulation of transforming growth factor (TGF) to read transforming growth factor (TGF)-β signalling. It may also influence the metabolism of APP, which includes several HTRA1 cleavage sites. However, defective TGF-β signalling due to mutations in the TGF-β receptors leads to hereditary haemorrhagic telangiectasia, whereas activation of TGF-β signalling contributes to Marfan's syndrome and related disorders.[87] Dysregulation of the inhibition of signalling by TGF-β growth factors has also been linked to alopecia and spondylosis.

Collagen type IV (COL4) Disorders

Recently several conditions akin to SVD features have been found to be associated with mutations in collagen IV (*COL4*) *A1* and *A2* genes.[88-90] Two previous conditions described in large German and Swedish families as subcortical angiopathic encephalopathy (SAE)[91] and hereditary multi-infarct dementia of the Swedish type[92] were originally thought to be CADASIL- like but are now classified as COL4 type disorders. Both these disorders are consistent with the clinical features of what is now coined as PADMAL for pontine autosomal dominant microangiopathy and leukoencephalopathy.[93] Neurological manifestations of *COL4A1* and *COL4A2* mutations may vary even within families.[94,95] Depending on the age of onset, affected individuals present with infantile hemiparesis, seizures, visual loss, dystonia, strokes, migraine, mental retardation, cognitive impairment and dementia. Single or recurrent ICH may occur in non–hypertensive young adults (foetus > adult) in the deep brain regions: spontaneously, subsequent to trauma or as a result of anticoagulant use (Table 2).

Autosomal dominant *COL4A1*-related disease with 100% penetrance has been described in European Caucasian families, with 100% penetrance. More than 50 mutations have been described in the coding region of *COL4A1/COLA2* that mostly involve glycine substitutions, some of which also cause ICH. Most glycine (gly) substitutions occur in the conserved Gly-X-Y motifs within the triple-helical collagenous domain. They also cause COL4-related ICH with an estimated ~20% penetrance.[96,97] In addition, 10 different mutations in the 3' UTR of *COL4A1* have been described[98,99] that all cause PADMAL-like syndrome and some develop ICH although the frequency is not known.

Arteriolar pathology is characterised by moderate to severe segmental loss of arteriolar myocytes, fibro-hyalinosis, intimal proliferation and microvascular degeneration often also involving the endothelium. *COL4A1* mutations are also associated with variable degrees of retinal arteriolar tortuosity, and abnormalities of endothelial basement membranes in the skin. Mutations in *COL4A1* and *A2* actually reduce expression perhaps weakening the vessel walls and giving way to bleeds. The mutation in 3' UTR of *COL4A1* disrupts miR-29 binding and increases COL4A1 protein expression.[13] Mutant COL4A1/COL4A2 chains accumulate in vascular smooth muscle cells and cause endoplasmic reticulum (ER) stress responses, as in CADASIL,[84] possibly leading to cytotoxicity.[100,101] Mutant COL4A1 accumulates may also disrupt TGF-β signalling[102] and cause abnormal angiogenesis underlying ICH development.

Retinal vasculopathies with cerebral leukodystrophy (RVCL)

Hereditary endotheliopathy with retinopathy, nephropathy and stroke (HERNS), cerebroretinal vasculopathy (CRV) and hereditary vascular retinopathy (HVR) were reported independently but linkage analysis demonstrated that they are allelic disorders or different phenotypes of same disease spectrum.[103] (Table 2). They cause progressive central visual impairment. Lesions occur in the pons, cerebellum and basal ganglia in addition to the frontal and parietal lobes, and consist of foci of coagulative necrosis with negligible inflammation. Whilst heterozygous mutations in *TREX1* cause RVCL, homozygous mutations in the same gene are linked to the typical autosomal recessive form of Aicardi-Goutières syndrome,[104] which manifests as a progressive encephalopathy of early onset, brain atrophy, demyelination, basal ganglia calcifications and chronic lymphocytic proliferation. It is unclear how the carboxyl truncating mutations in *TREX1* lead to the phenotype or pathogenesis of RVCL involving arteriolosclerosis but it seems obviously due to disruption of the predicted transmembrane domain with subsequent dissemination of TREX1 throughout the cell.[105]

Cathepsin A related arteriopathy with strokes and leukoencephalopathy (CARASAL)

CARASAL is a rare hereditary SVD affecting small cerebral arteries in adults due to mutations in the *cathepsin- A* (*CTSA*) gene found on chromosome 20q13.12. *CTSA* encodes for the serine carboxypeptidase cathepsin-A, a member of the peptidase S10 family, with various functions. Patients with

CARASAL exhibit adult-onset leukoencephalopathy with early onset clinical manifestations involving the brainstem. CARASAL is delineated from CADASIL and CARASIL but also from other SVDs with secondary leukoencephalopathies, such as granulomatous encephalitis, lymphoma, vasculitis, mitochondrial disorders and WMHs due to diabetes, hypertension, or smoking and also from primary leukoencephalopathies, such as GM1 gangliosidosis, Krabbe disease, or Tay-Sachs-disease.[106)]

It is predicted that mutations in cathepsin-A cause loss of several function(s) including dysregulation of the ECM. Cathepsin-A forms a complex with neuraminidase-1 and elastin binding protein, forming the elastin binding protein receptor. This receptor complex plays a role in the formation of elastic fibres, which are also a component of arterioles. CARASAL also belongs to a group of leukodystrophies with abnormalities in components of the neurovascular unit affecting tight junctions and astrocytic end-feet juxtaposed to endothelial cells.[107)]

Rarer vasulopathies and angiopathies

Other families with hereditary SVDs have been described that are not explained by any of the known gene defects. These include hereditary systemic angiopathy (HSA) in which the retinal microvessels undergo progressive occlusion leading to ischaemic retinopathy with subsequent optic disc atrophy and formation of capillary aneurysms. Pathological changes include foci of coagulative necrosis in the white matter with prominent perivascular inflammation, oedema, astrocytic gliosis. There is evidence of proliferation of microvessels, many with hyperplastic endothelium and severely thickened walls, and some showing fibrinoid necrosis or thrombosis.[108)]

Conclusion

In recent years, there have been several advances in the understanding of the pathophysiology of sporadic and familial SVDs. Parenchymal pathology attributed to SVD indicates that this is largely caused by arteriolar wall modifications due to age-related loss of cellular elements within vascular smooth muscle cells and disruption of the extracellular matrix within the basal lamina. Among the genetic forms of cerebral SVD, CADASIL remains the most aggressive type of arteriopathy. However, an overall theme in all these SVD type of disorders including monogenic causes indicates severe loss of vascular smooth muscle cells and dysregulation of the extracellular matrix or basal lamina with variable consequences on IPAD. Reducing SVD via vascular risk factors is a viable strategy to tackling the burden of dementia.

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Table 1

Spectrum of disorders with SVD pathology associated with cognitive impairment or dementia

Primary or Secondary Vascular Disorder(s)*	Common conditions	Vascular Distribution	Predominant Tissue changes	Form(s) of VCI- mild or major VCI (VaD) †
Arteriolosclerosis	Sporadic small vessel disease	Perforating and penetrating arteries, lenticulostriate arteries	Cortical infarcts, lacunar infarcts/lacunes, microinfarcts, WML	Small vessel dementia; subcortical ischaemic vascular dementia; strategic infarct dementia
	Hypertensive vasculopathy			Hypertensive encephalopathy with impairment; strategic infarct dementia
Non-atherosclerotic non-inflammatory vasculopathies	Arterial dissections (carotid, vertebral and intracranial), fibromuscular dysplasia, dolichoectatic basilar artery, large artery kinking and coiling, radiation induced angiopathy, moyamoya disease	Vertebral, basilar, Branches of MCA, mural haematoma perforating artery; SVD	No pattern of brain infarctions: haemodynamic, thromboembolic, or due to occlusion of a perforating artery. Subarachnoid haemorrhage; lacunar infarcts, PVS	Mild VCI
Vasculitides	Vasculitis (infectious and non-infectious); rheumatoid arthritis	Various cerebral and systemic vessels	White matter changes, SVD like lesions	Mild VCI
Amyloid angiopathies	Sporadic and Familial CAAs (Amyloid β, prion protein, cystatin C, transthyretin, gelsolin)	Leptomeninges, intracerebral arteries	Cortical microinfarcts, lacunar infarcts, WML	Mild and Major VCI (Independently affect cognition)
Monogenic stroke disorders	CADASIL, CARASIL, retinal vasculopathy with cerebral leukodystrophies (RVCLs), Moyamoya disease, Hereditary angiopathy, nephropathy, aneurysm and muscle cramps (HANAC)	Leptomeningeal arteries, intracerebral subcortical arteries	Lacunar infarcts/lacunes, microinfarcts, WML	Mild and Major VCI
Monogenic disorders involving stroke	Fabry disease, familial hemiplegic migraine, hereditary haemorrhagic telangiectasia, Vascular Ehlers-Danlos syndrome, Marfan syndrome, Psuedoxanthoma elasticum, Arterial tortuosity syndrome, Loeys-Dietz syndrome, polycystic kidney disease; Neurofibromatosis type 1 (von Ricklinghausen disease), Carney syndrome (Facial lentiginosis and myxoma)	Branching arteries	Cortical and subcortical infarcts, haemorrhagic infarcts	Mild and Major VCI
Metabolic disorders	Mitochondrial disorders (MELAS, MERRF, Leigh's disease, Myoclonic epilepsy with ragged red fibres), Menkes disease, Homocystinuria, Tangier's disease	Intracerebral small arteries, territorial arteries	Cortical and subcortical stroke-like lesions, microcystic cavitation, cortical petechial haemorrhages, gliosis, WML	Mild VCI

Data in Table modified from Kalaria et al,[109] and several original references.[8] Several disorders may also occur with other co-morbidities such as coronary artery disease, congestive heart failure, hypertension, diabetes, hyperlipidaemia, hypercoagulability, renal disease, atrial fibrillation and valvular heart disease. *Other miscellaneous causes of stroke including mechanical, invention induced or rare genetic syndromes such as trauma, iatrogenic, decompression sickness, air or fat embolism, transplantation and Werner's syndrome can lead to cognitive impairment. † VCI determined when two or more cognitive domains are affected per minimal harmonisation guidelines or minor VCI.[110] Abbreviations: CAA, cerebral amyloid angiopathy; CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; CARASIL; cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy; ICH, intracerebral haemorrhage; MCA, middle cerebral artery; MELAS, Mitochondrial Myopathy, Encephalopathy, Lactic Acidosis and Stroke-like Episodes; MERRF, PCA, posterior cerebral artery; PVS, perivascular spaces; SLE, systemic lupus erythematosus; SVD, small vessel disease; VaD, vascular dementia; VCD, vascular cognitive disorder; WML, white matter lesion.

Table 2

Molecular genetics and pathology of cerebral arteriopathies

Disorder	Onset Age (yrs.) ‡	Gene (mutations)	Protein	Protein type/cellular abnormalities	Proposed dysfunction(s)
CADASIL (most common); Autosomal dominant)	20-60	*NOTCH3 (dominant >280)*	NOTCH3	Transmembrane cell signalling receptor; SMC loss; ECM changes	Aberrant cell-cell signalling, activates unfolded protein response and impaired gene transcription (NICD)
CARASIL Autosomal récessive	20-30	*HTRA1 (>50 in symptomatic carriers or typical CARASIL)*	HTRA1	Serine protease; ECM dysregulation	Promotes serine-protease-mediated cell death, suppresses TGFβ expression
COL4A1 and COL42- related disorders / PADMAL*	14-50	*COL4A1; COL4A2 (dominant in coding regions; 3' UTR in COL4A1)*	COL4A1 and A2	Collagen IV, α1 and α2 chains; ECM disruption	Weakening of vascular BM; ER stress responses.
RVCL disorders: HERNS (Chinese descent); CRV (cerebroretinal vasculopathy); HVR (hereditary vascular retinopathy)	30-50	*TREX1 (dominant)*	TREX1	3'→5'-prime exonuclease DNase III	Disruption of cell death mechanisms, impaired DNA degradation and repair
CARASAL	20-40	*CTSA (dominant)*	Cathepsin-A	Lysosomal peptidase complexes with β -galactosidase, neuraminidase; predicted ECM dysregulation	ER stress response; disruption of multi-enzyme complexes in lysosomes
Hereditary small vessel disease of the brain (SVDB) †	36-52	*Not known*	-	-	Unknown functions

* *COL4A1* and *A2* gene disorders consist of 5 major phenotypes:[111] (1) perinatal haemorrhage with porencephaly, (2) hereditary infantile hemiparesis, retinal arteriolar tortuosity and leukoencephalopathy (HIHRATL)[112], (3) SVD with Axenfeld-Rieger anomaly (anterior segment dysgenesis of the eye), (4) hereditary angiopathy with nephropathy, aneurysms and muscle cramps (HANAC) and (5) PADMAL,[93] which also incorporates subcortical angiopathic leukoencephalopathy and hereditary multi-infarct dementia of the Swedish type.[91,92] † Several other disorders prominently characterised by leukoencephalopathy and cognitive impairment are described in isolated families. ‡ Age of onset signifies when first cerebrovascular event or gait disturbance due to spasticity was recorded. Abbreviations: BM, basement membrane; CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; CARASAL, cathepsin A related arteriopathy with strokes and leukoencephalopathy; CARASIL, cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy; ECM, extracellular matrix; NICD, Notch intracellular domain; PADMAL, pontine autosomal dominant microangiopathy and leukoencephalopathy; RVCL, autosomal dominant retinal vasculopathy with cerebral leukodystrophy.

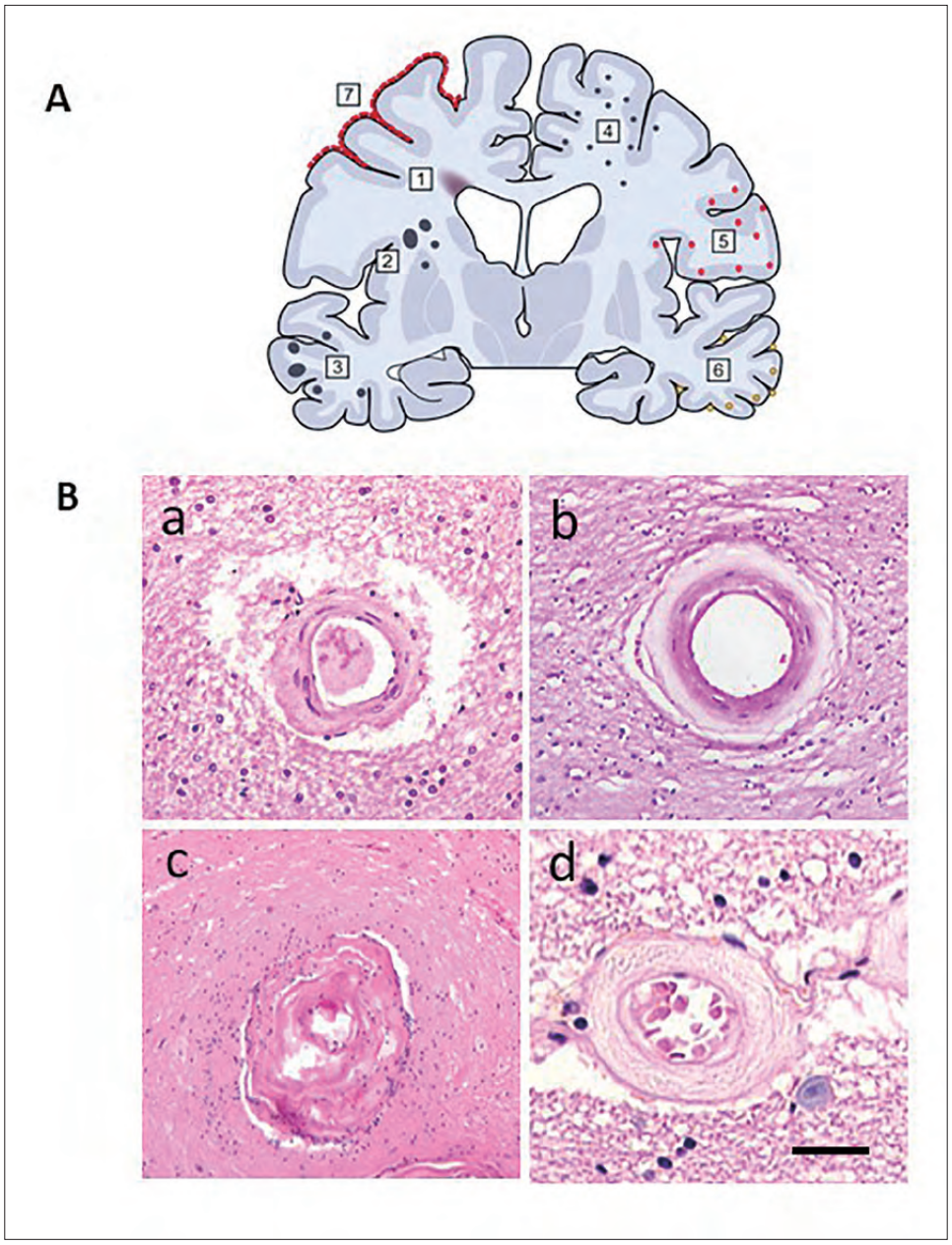

Figure 1

Schematic of a coronal brain section showing different types of cerebral SVD pathology. Modified from Kalaria and Sepulveda-Falla.[3] Numbers in boxes [1-7] correspond 1) perivascular and deep WM attenuation, 2) lacunar infarcts (<1.5cm), 3) WM infarcts (1-2 cm), 4) microinfarcts (<0.5 cm), 5) lobar or deep microbleeds or haemosiderin, 6) CAA or CAA related ICH, 7) superficial siderosis and 8) perivascular spaces. Increased perivascular spacing occurs because of reduction in arterial vascular tone and failure of IPAD[113]. The WM changes ensues due to a chronic hypoxic state and decline in oligodendrocytes[114,115]. White arrows in panels show location of key lesion(s). B, Microscopic images of cerebral arterioles showing gradual changes a, some loss of SMC; b and c, degrees of fibrinoid necrosis and d, hyalinosis or glassy like appearance of vessel wall. Abbreviations: ICH, intracerebral haemorrhage; SVD, small vessel disease; WM, white matter. Magnification bar: 100 μm.

Young Investigator Award (review article)

The deleterious effects of Alzheimer's disease pathology on skeletal muscle

Hikari Takeshita, PhD[1,2)]

1) Department of Geriatric and General Medicine, Osaka University Graduate School of Medicine, Suita, Osaka, Japan
2) Department of Medical Science Technology, Faculty of Medical Science Technology, Morinomiya University of Medical Sciences, Osaka, Osaka, Japan

Abstract:

Cognitive dysfunction and skeletal muscle dysfunction tend to coexist, and the combined condition of MCI and physical frailty is defined as cognitive frailty. In this review, to understand the pathomechanism of skeletal muscle dysfunction in Alzheimer's disease (AD), the most common cause of cognitive impairment, we first describe the physiological functions of Aβ peptide, the causative factor of AD, and its precursor, APP, in skeletal muscle. Next, the mechanism of skeletal muscle dysfunction associated with AD is discussed based on the findings of inclusion body myositis, which shows pathological conditions similar to AD, such as the accumulation of Aβ42. Then, recent findings on the effects of skeletal muscle secretory peptides on AD pathology will be presented and the physiological significance of the brain-skeletal muscle connection will be discussed. Finally, we will present our experimental results on the skeletal muscle phenotype of AD mouse models and discuss the effects of Alzheimer's disease causative factors on skeletal muscle.

Key Words: Cognitive frailty, Alzheimer's disease, Muscle atrophy

Correspondence to:

Department of Geriatric and General Medicine, Osaka University Graduate School of Medicine
2-2 Yamadaoka, Suita, 565-0871, Japan.
E-mail: takeshita@geriat.med.osaka-u.ac.jp

Introduction

The relationship between physical and cognitive function has been explored in many clinical studies, and the coexistence of physical and cognitive decline has been identified as an emerging risk. In 2013, the International Academy on Nutrition and Aging (IANA) and the International Association of Gerontology and Geriatrics (IAGG) defined cognitive frailty (CF), as the coexistence of physical frailty and mild cognitive impairment, MCI (defined as Clinical Dementia Rating = 0.5). In addition, CF was defined as the absence of dementia, such as Alzheimer's disease (AD)[1)]. The definition of CF has drawn attention not only to the existence of common pathophysiological mechanisms in dementia and physical weakness, but also to the possibility that skeletal muscle dysfunction may occur before cognitive impairment manifests.

Cross-sectional studies have reported an association between physical and cognitive function, and cohort studies have showed both that cognitive decline was associated with the risk of physical decline[2)] and that the rate of concomitant cognitive impairment increased with the severity of physical frailty[3, 4)].

On the other hand, CF is reported to have a higher rate of progression to vascular dementia than AD[5, 6)], but prospective cohort studies have reported that the risk of developing AD is higher when there is a decline in physical function, such as muscle weakness or reduced ability to walk[7, 8)].

In addition, it has been reported that AD is associated with weight loss of more than 5% of normal weight[9)] and that weight loss begins gradually more than 10 years before the diagnosis of AD and accelerates especially 2-3 years before the onset of the disease[10, 11)]. Furthermore, muscle mass loss is observed from the early stages of AD and continues to decline as the disease progresses[12, 13)]. And, it has also been reported that balance functions such as the Functional Reach Test and one-leg stand time decline early in AD patients, and that walking ability and muscle strength decline with the progression of cognitive impairment[14)].

Thus, it has been suggested that loss of muscle mass and physical disability in AD may occur before the manifestation of dementia, and it has been hypothesized that skeletal muscle symptoms in AD patients are a manifestation of latent neurological deficits in patients who do not meet diagnostic criteria for dementia[15, 16, 17)].

Although there are many clinical studies on AD and skeletal muscle disorders, the pathophysiological mechanisms of why skeletal muscle disorders occur in AD and whether skeletal muscle disorders exacerbate the pathophysiology of AD are still unclear. In this review, we will first discuss the physiological role of AD pathogenic factors in skeletal muscle, inclusion body

myositis (IBM), a skeletal muscle disease very similar to AD pathology, and the effects of skeletal muscle atrophy on AD pathology, followed by the results of our brief validation experiments using AD model mice and the resulting discussion.

Physiological Function of APP in Skeletal Muscle

In the brains of AD patients, senile plaques and neurofibrillary tangles occur in large numbers, and brain atrophy results from the associated neuronal cell death. Senile plaques are caused by the extracellular deposition of amyloid beta protein (Aβ), which is produced by the cleavage of amyloid precursor protein (APP), and neurofibrillary tangles are caused by the accumulation of phosphorylated tau protein in neurons. APP is a ubiquitous protein that is widely expressed in vivo outside the brain[18], and in skeletal muscle, APP has been identified at the neuromuscular junction[19]. APP expression increases during neuronal differentiation and is highest during the formation of synaptic connections[20, 21, 22, 23]. And, overexpression of human wild-type APP in mice increases presynaptic terminals[24], and increased APP mRNA expression has been reported in regenerating human muscle fibers from patients with neuromuscular diseases, suggesting that APP is important for synapse formation and maintenance in vivo[25] . Conversely, it has been reported that mice lacking APP have decreased body weight and reduced locomotor activity and forelimb grip strength compared to wild-type controls[26, 27]. Thus, APP expression is also essential in skeletal muscle to maintain and improve skeletal muscle function due to its ability to form synapses at the neuromuscular junction.

Similar to APP, β-site APP cleaving enzyme 1 (BACE1) and BACE2[28], the enzymes of β-secretase, and presenilins 1 and 2 (PS1 and PS2), the catalytic subunits of γ-secretase, have been found to be expressed in skeletal muscle[29]. In addition, Aβ accumulation and phosphorylated tau have been reported in peripheral tissues of AD patients, including skin and skeletal muscle[30, 31, 32]. Regarding the presence of Aβ peptide in skeletal muscle, quantification of Aβ40 and Aβ42 peptide levels in temporalis muscle of AD patients and controls showed that Aβ 40 tended to be higher in AD patients than in controls, but not significantly, while Aβ42 was significantly higher in AD patients than in controls[30].

Next, we discuss the effects of Aβ peptide accumulation in skeletal muscle on skeletal muscle morphology and function, as suggested by studies of the pathogenesis of inclusion body myositis.

Skeletal muscle diseases with similar pathophysiology and symptoms to AD

In the skeletal muscle diseases inclusion body myositis (IBM), polymyositis, and dermatomyositis, APP deposition and hyperphosphorylated tau are known to be present in skeletal muscle. Inclusion myositis is the most common age-related muscle disease in the elderly and is characterized by weakness of proximal and distal skeletal muscles[33, 34]. Histopathologically, the presence of atrophic myofibers, fringe vacuoles, and a variety of proteins including ubiquitin, Aβ protein, emerin, lamin A/C, valocin-containing protein (VCP), histones, 43 kDa TAR DNA binding protein (TDP-43), and p62 have been reported in skeletal muscle with IBM[33, 35, 36]. The similarity of these pathologic findings to neurodegenerative diseases such as AD and amyotrophic lateral sclerosis (ALS) is controversial, but the relationship between these diseases and IBM is not well understood[37].

To investigate the influence of Aβ peptide accumulation on skeletal muscle, Sugarman et al. and Kitazawa et al. generated MCK-APP mice, an IBM mouse model in which a human Swedish APP mutation is overexpressed in skeletal muscle under the regulation of the muscle creatine kinase (MCK) promoter[38], and MCK-APP/PS1 mice, double transgenic mice in which a mutation in the presenilin-1 (PS1) gene associated with familial AD was added to MCK-APP mice[39]. MCK-APP and MCK-APP/PS1 mice are models with increased production of Aβ40 and Aβ42, respectively, in skeletal muscle. MCK-APP/PS1 mice showed increased accumulation of phosphorylated tau compared to MCK-APP mice and exhibited histopathologic features similar to IBM, including a central core, intracellular accumulation of Aβ peptide, and increased inflammation around affected muscle fibers. Physical function was also more severely affected in MCK-APP/PS1 mice and developed at an earlier age[39]. These results suggest that Aβ42 accumulation in skeletal muscle, as in the brain, induces tau phosphorylation and induces cellular damage.

On the other hand, p62, which is abundant in IBM muscle fibers, is known to be deposited with neurofibrillary tangles in AD and Parkinson's disease. Recently, p62 has been reported to function as an autophagy receptor protein, and autophagy pathways involving p62 are known to selectively degrade tau oligomers[40]. Deletion of p62 in a mouse model of AD (tau transgenic mouse: PS19 model) has been reported to increase the accumulation of tau oligomers in the hippocampus, leading to brain atrophy and increased inflammation[41]. Thus, in inclusion body myositis, as in AD, autophagy defects are thought to be one of the mechanisms of pathogenesis.

Impact of Skeletal Muscle NEP Expression in the Pathogenesis of IBM and AD

Neprilysin (NEP), a peptidase, efficiently degrades bioactive peptides such as cardioprotective BNP, antihypertensive bradykinin, and Aβ peptides. Regarding the physiological function of NEP in skeletal muscle, it has been reported that its expression is enhanced during skeletal muscle differentiation using primary human myoblasts and that NEP expression correlates with the degree of myofiber regeneration using IBM muscle biopsy samples, suggesting an important role in

skeletal muscle regeneration[42]. In addition, studies using muscle biopsy samples from IBM patients showed that NEP protein expression was significantly increased compared to skeletal muscle from normal controls, and in particular, NEP protein was highly enriched in abnormal fibers with Aβ peptides[42]. This is thought to be a compensatory response to A β peptides accumulation. Interestingly, NEP gene transfer into skeletal muscle is also attracting attention as a new treatment for AD. It has been reported that introduction of an adeno-associated virus (AAV) expressing the mouse NEP gene into the hindlimb muscles of 3X-Tg-AD mice, a mouse model of AD, and overexpression of NEP in the muscles reduced brain soluble Aβ peptide levels and amyloid deposition[43]. Similar results have been observed using other techniques and AD mouse model. Introducing human NEP plasmid into the skeletal muscle of APP/PS1 mice, a mouse model of AD, using ultrasound combined with microbubbles, significantly reduced brain Aβ peptide levels after one month[44]. These results indicate that peripheral expression of NEP has a direct effect on the brain and demonstrate the efficacy of inducing NEP expression in muscle for the prevention and treatment of AD.

Effects of Skeletal Muscle Secreted Substances on the Brain

Physical inactivity has been cited as a factor strongly associated with the development of AD[45], and there are several hypotheses about the mechanism by which exercise is effective in preventing AD. In this regard, it has recently been reported that brain-derived neurotrophic factor (BDNF), whose secretion is stimulated by exercise, is associated with brain volume[46]. Irisin released into the blood from skeletal muscle during exercise, is cleaved from fibronectin type III domain-containing protein 5 (FNDC5), a transmembrane precursor protein expressed in muscle under the control of PGC-1α. FNDC5/irisin is known to stimulate the expression of brain-derived neurotrophic factor (BDNF) in the hippocampus, and reduced levels of FNDC5/irisin have been reported in the hippocampus and cerebrospinal fluid in AD patients and in AD mouse models[47].

On the other hand, Nagase et al. examined the effects of skeletal muscle atrophy on cognitive function in 5XFAD mice, a mouse model of AD[48]. By inducing muscle atrophy in 12-week-old 5XFAD mice by immobilizing their hind limbs in a cast prior to the onset of memory impairment, memory performance was normal in mice without induced muscle atrophy, but memory deficits developed in mice with muscle atrophy. A comprehensive study of molecules secreted by atrophied skeletal muscle showed that hemopexin, a glycoprotein that binds free heme in the blood, is particularly elevated, and the amount of hemopexin is increased in skeletal muscle, blood, and the hippocampus of the brain in mice with muscle atrophy[48]. In addition, continuous administration of hemopexin directly into the ventricles of younger, 6-7 week old AD model mice for 2 weeks resulted in memory impairment, suggesting that skeletal muscle atrophy may increase the synthesis and secretion of hemopexin from muscle and promote cognitive dysfunction in AD model mice.

Skeletal Muscle Phenotype of APP23 Mice

To investigate the effects of AD pathology on skeletal muscle, we evaluated skeletal muscle morphology and strength in APP23 mice, a mouse model of AD, and compared them to wild-type mice. APP23 mice are transgenic for APP with a Swedish mutation in the Thy-1 promoter, and the formation of intracerebral amyloid plaques and cognitive dysfunction usually appear around 6 to 12 months of age.

In male APP23 mice and wild-type littermates, we evaluated skeletal muscle function and cognitive function at 3 months of age. The grip strength test we developed was used to assess skeletal muscle function[49], and the passive avoidance test and open field test were used to assess cognitive function. Then, as factors related to both muscle strength and cognitive function, glucose tolerance was assessed by the ipGTT test and voluntary locomotion was assessed by placing a running wheel in the cage over a 3-day period. After these experiments, skeletal muscle was harvested for histologic evaluation. As a result, grip strength, body weight, and some skeletal muscle weights of APP23 mice were lower than those of wild-type mice (Fig.1 A, B). The cross-sectional area of gastrocnemius muscle fibers was also significantly smaller in APP23 mice than in wild-type mice (Fig.1 C). There were also no significant differences between APP23 and wild-type mice in food intake or assessment of glucose tolerance using the ipGTT test. Results of cognitive function tests using the passive avoidance test and the open field test showed no significant differences between APP23 mice and wild-type mice. However, APP23 mice showed significantly more voluntary movements than wild-type mice during the three days of free activity as measured by the running wheel (Fig.2). These findings suggest that skeletal muscle dysfunction is already apparent in APP23 mice at the early stage of cognitive dysfunction. In addition, the results of the ipGTT test suggest that this skeletal muscle dysfunction is independent of glucose intolerance.

Furthermore, although APP23 mice showed increased voluntary exercise, skeletal muscle function and skeletal muscle mass were rather decreased, suggesting that the process of exercise-induced muscle hypertrophy is impaired in APP23 mice.

In addition, APP23 mice are known as a model for overexpression of mutant APP specifically in the central nervous system, but we confirmed gene expression of mutant APP in skeletal muscle. A recent study reported that brain Aβ 42 affects skeletal muscle, as a model in which Aβ42 was injected into the dorsal hippocampus of rats also showed reduced muscle strength and skeletal muscle mass[50].

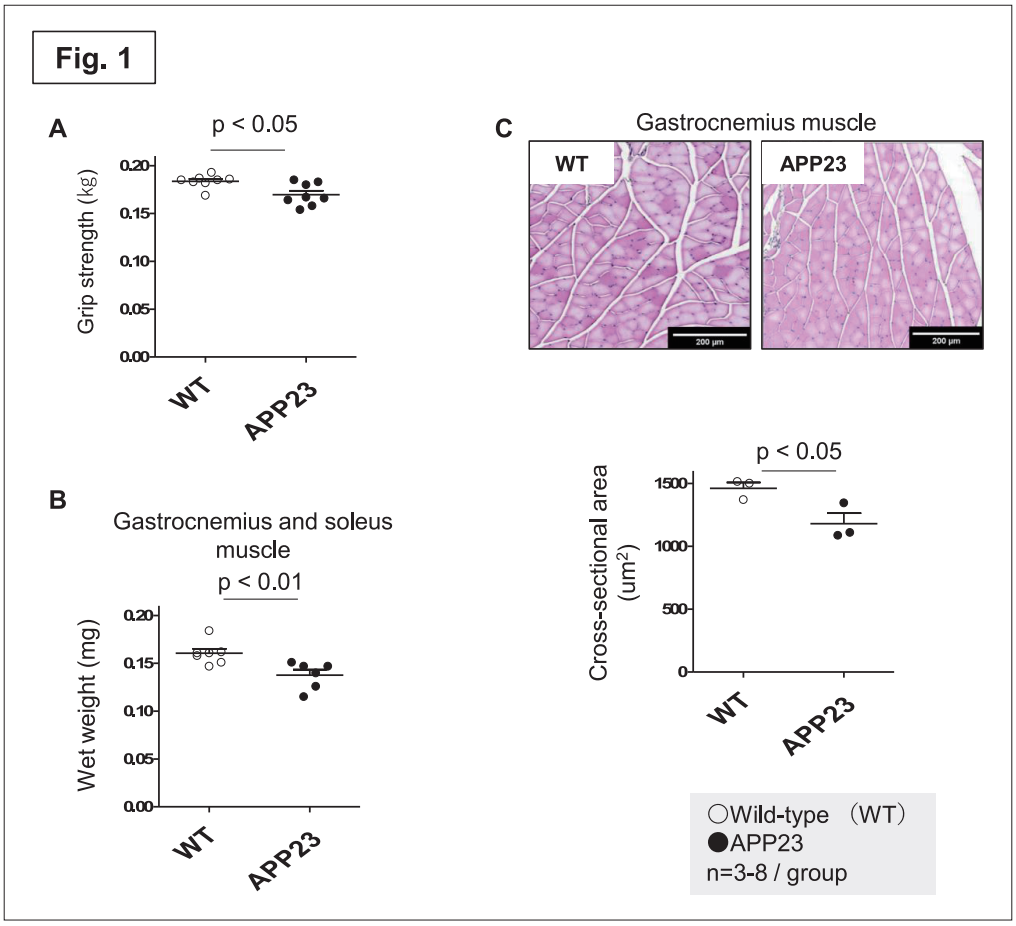

Figure 1

Comparison of muscle strength (A), wet weight of gastrocnemius and soleus muscles (B), and myofiber cross-sectional area of gastrocnemius muscle (C) in APP23 and wild-type mice.
WT, Wild-type

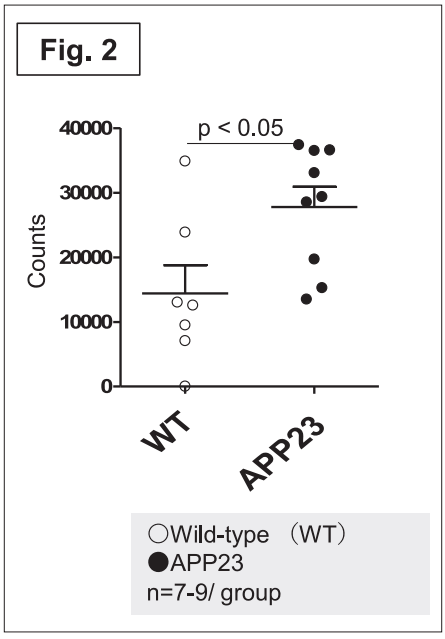

Figure 2

Comparison of voluntary locomotor activity between APP23 and wild-type mice over three days.
Assessed by the number of revolutions of the running wheel.

Therefore, it is possible that the skeletal muscle impairment in APP23 mice is also dependent on the presence of Aβ42, but more detailed studies are needed.

Discussion and Conclusion

This review first discussed the possibility that skeletal muscle dysfunction precedes cognitive dysfunction, based on findings from several clinical trials and the definition of cognitive frailty. Next, the negative effects of AD pathogenic factors, such as Aβ peptide, on skeletal muscle were discussed based on findings from IBM's pathophysiology studies. This series of discussions assumes that AD pathogenic factors such as Aβ42 affect skeletal muscle even before AD pathology becomes apparent. However, the only reports of Aβ peptide quantification in skeletal muscle are studies using temporalis muscle, and little is known about the detailed phenotype of skeletal muscle in AD patients. This is due to the invasive nature of muscle biopsy, which makes it difficult to obtain a muscle biopsy sample unless there is an obvious skeletal muscle disease. For this reason, it is and will remain nearly impossible to test for skeletal muscle Aβ peptide in human muscle biopsy samples prior to the MCI stage. Therefore, it is necessary to further verify the fluctuation of Aβ peptide in skeletal muscle before cognitive dysfunction becomes apparent using experimental animal methods, and this will be our future study topic.

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Case report

A case of Moyamoya disease with Graves' disease presenting clinical and radiological improvement only after treatment for hyperthyroidism

Ryo Sasaki MD, PhD[1)]; Masafumi Hiramatsu MD, PhD[2)]; Toru Yamashita MD, PhD[1)]

1) Department of Neurology, Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama University, Japan.
2) Department of Neurosurgery, Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama University, Japan.

Abstract:

Graves' disease, an autoimmune thyroid disease that results in hyperthyroidism, is rarely complicated by progressive stenosis or the occlusion of proximal intracranial arteries. The combination of these two pathologies was classically categorized as "quasi-Moyamoya disease", but the revised diagnostic criteria for Moyamoya disease established a new disease concept of "Moyamoya disease with Graves' disease", for which an appropriate treatment is still unclear. In the present case, a 35-year-old woman showed transient hemiparesis and poor concentration. After serum analysis and brain imaging, she was diagnosed as having Moyamoya disease with Graves' disease. Her symptoms and radiological findings improved dramatically after medical treatment for Graves' disease without any other interventions. The present case represents a valuable reference for selecting treatment steps for this rare disease with a unique pathophysiology.

Key Words: Moyamoya disease, Graves' disease, hyperthyroidism, TIA, cognitive impairment

Abbreviations used: A/E, all extremities; CSF, cerebral spinal fluid; DSA, digital subtraction angiography; FLAIR, fluid-attenuated inversion recovery; HDS-R, Hasegawa dementia scale-revised; ICA, internal carotid artery; ^{123}I-IMP-SPECT, ^{123}I-N-isopropyl-p-iodoamphetamine single photon emission computed tomography, MCA, median cerebral artery; MMSE, mini-mental state examination; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; TIA, transient ischemic attack; TPO, thyroid peroxidase; TSH, thyroid stimulating hormone.

Address correspondence and reprint requests to:

Dr. Toru Yamashita

Department of Neurology, Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama University, 2-5-1 Shikata-cho, Kita-ku, Okayama 700-8558, Japan.

Tel: 81-86-235-7365, Fax: 81-86-235-7368

Email: pwag680v@okayama-u.ac.jp

Introduction

Moyamoya disease is a progressive cerebrovascular disease that is characterized by severe stenosis/occlusion of the proximal median cerebral artery (MCA) or distal end of the internal carotid artery (ICA), with the formation of collateral vessels that look like puffs of cigarette smoke (Suzuki et al. 1969). Patients with Moyamoya disease present variable symptoms such as ischemic stroke/transient ischemic attack (TIA), intracranial hemorrhages, seizures, headaches, and cognitive or psychiatric changes (Scott et al, 2009). Graves' disease, an autoimmune thyroid disease caused by autoantibodies of the thyroid stimulating hormone receptor, is rarely complicated by Moyamoya disease. Graves' disease with intracranial artery stenosis was classically categorized as "quasi-Moyamoya disease", with this disease group having certain causative complications typical of Moyamoya disease. However, it was recently discovered that elevated anti-thyroid peroxidase antibody and hyperthyroidism were more frequent in adults than had previously been expected, so the diagnostic criteria of Moyamoya disease were modified, thereby establishing the disease concept of "Moyamoya disease with Graves' disease" rather than quasi-Moyamoya disease (Kuroda et al., 2021). The standard medical treatment options for Moyamoya disease include antiplatelet agents and surgical revascularization. Although both treatments were reported to be effective for symptomatic Moyamoya disease patients without complications, the appropriate treatment for Moyamoya disease with Graves' disease was unclear.

In this report, we present a 35-year-old woman diagnosed as having Moyamoya disease with Graves' disease showing transient hemiparesis and poor concentration. Her symptoms and radiological findings improved dramatically after medical treatment for Graves' disease.

Case report

A 35-year-old woman showed poor concentration, numbness in her right hand, and transient weakness in her right limb, so she visited a local hospital. A general examination revealed hyperreflexia in all extremities (A/E) without muscle weakness. Blood tests showed elevated levels of free thyroxine (fT4, 3.43 ng/dl, normal 0.75-1.45 ng/dl) and anti-thyroid peroxidase (TPO) antibody (540 IU/ml, normal < 16 IU/ml) and decreased levels of thyroid stimulating hormone (TSH, undetectable). Magnetic resonance imaging (MRI) of her brain showed no brain infarction and magnetic resonance angiography (MRA) showed bilateral MCA stenosis (data not shown). She was referred to our hospital and was admitted for a closer examination (Fig. 1).

She was 155.5 cm tall and weighed 48.9 kg. Her blood pressure was 152/84 mmHg and her heart rate was 95 beats/minute. She had no medical or family history or past use of medication. After admission, she claimed poor concentration and general fatigue all day. A neurological examination revealed a slightly drowsy state but showed a normal score in the mini-mental state examination (MMSE, 30/30) and Hasegawa dementia scale-revised (HDS-R, 29/30), normal muscle power, generally hyperreflexia in A/E without pathological reflex, and a standard sensory system without any other abnormal findings. Serum analysis showed continuously elevated fT4 (4.79 ng/dl, normal 0.75-1.45 ng/dl), free triiodothyronine (fT3, 15.20 pg/ml, normal 2.30-4.00 pg/ml), thyroglobulin (Tb) (127.82 ng/mL, normal 3.71-35.12 ng/mL), anti-TPO antibody (998.5 IU/mL, normal upper limit 3.3 IU/mL), and anti-TSH receptor antibody (7.53 IU/l, normal upper limit 2.00 IU/L). Serum level of TSH remained undetectable. A cerebral spinal fluid (CSF) study showed normal pressure, normal cell count (1/μl, monocyte 100%), and a normal level of protein (38 mg/dl, normal 10-40 mg/dl).

A whole body CT showed no evident features of malignancy. A brain MRI showed leptomeningeal high signal intensity ("Ivy sign") in the frontal and parietal lobe on fluid-attenuated inversion recovery (FLAIR) images (Fig. 2A, B). An MRA revealed bilateral proximal MCA stenosis (Fig. 2C, arrowheads) with the poor depiction of distal MCA. A ^{123}I-N-isopropyl-p-iodoamphetamine single photon emission computed tomography (^{123}I-IMP-SPECT) image showed low accumulation in the bilateral frontal lobe (Fig. 2D, arrowheads), parietal lobe, and occipital lobe.

She was diagnosed with Moyamoya disease with Graves' disease. Cerebral angiography, which may provide detailed vessel information, was abandoned because the iodine contrast media could potentially worsen her thyroid function. We planned to treat Graves' disease first to normalize her condition, and then perform angiography or transcatheter intervention. We started by administering 20 mg of potassium iodide followed by 15 mg of thiamazole. After the start of

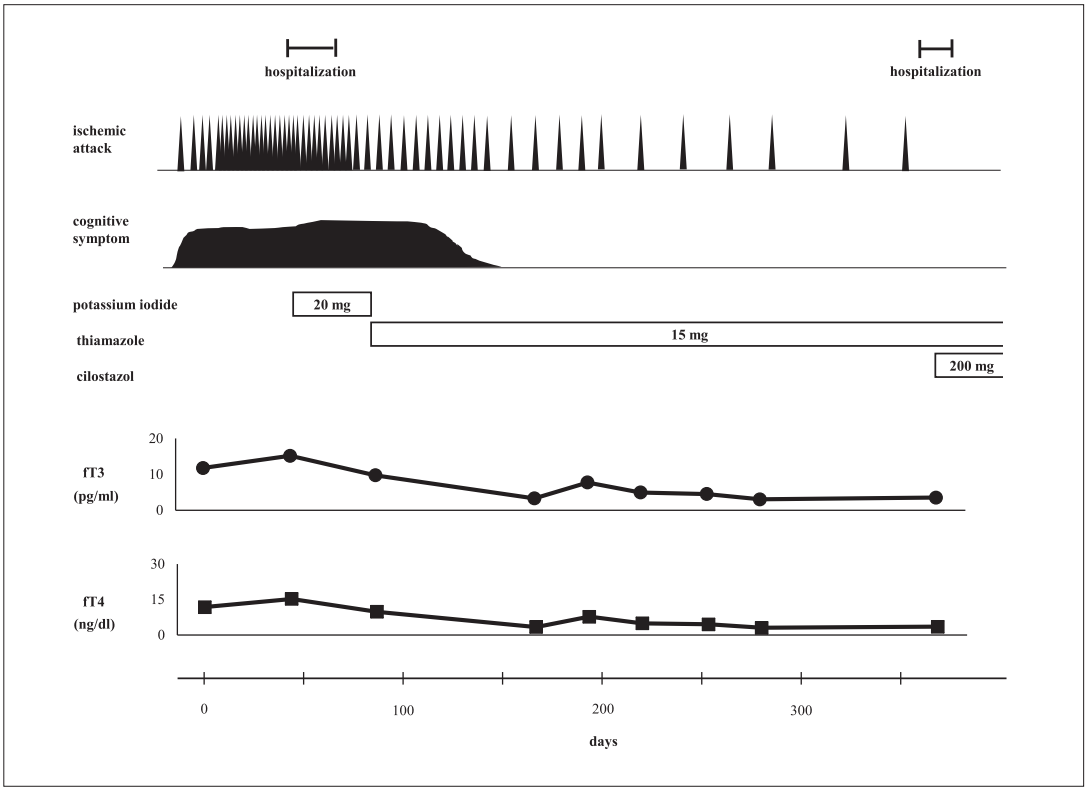

Fig. 1)

Clinical course of the present case: The ischemic attack and cognitive symptoms with hyperthyroidism improved dramatically after the administration of potassium iodide and thiamazole and completely disappeared after induction of cilostazol.

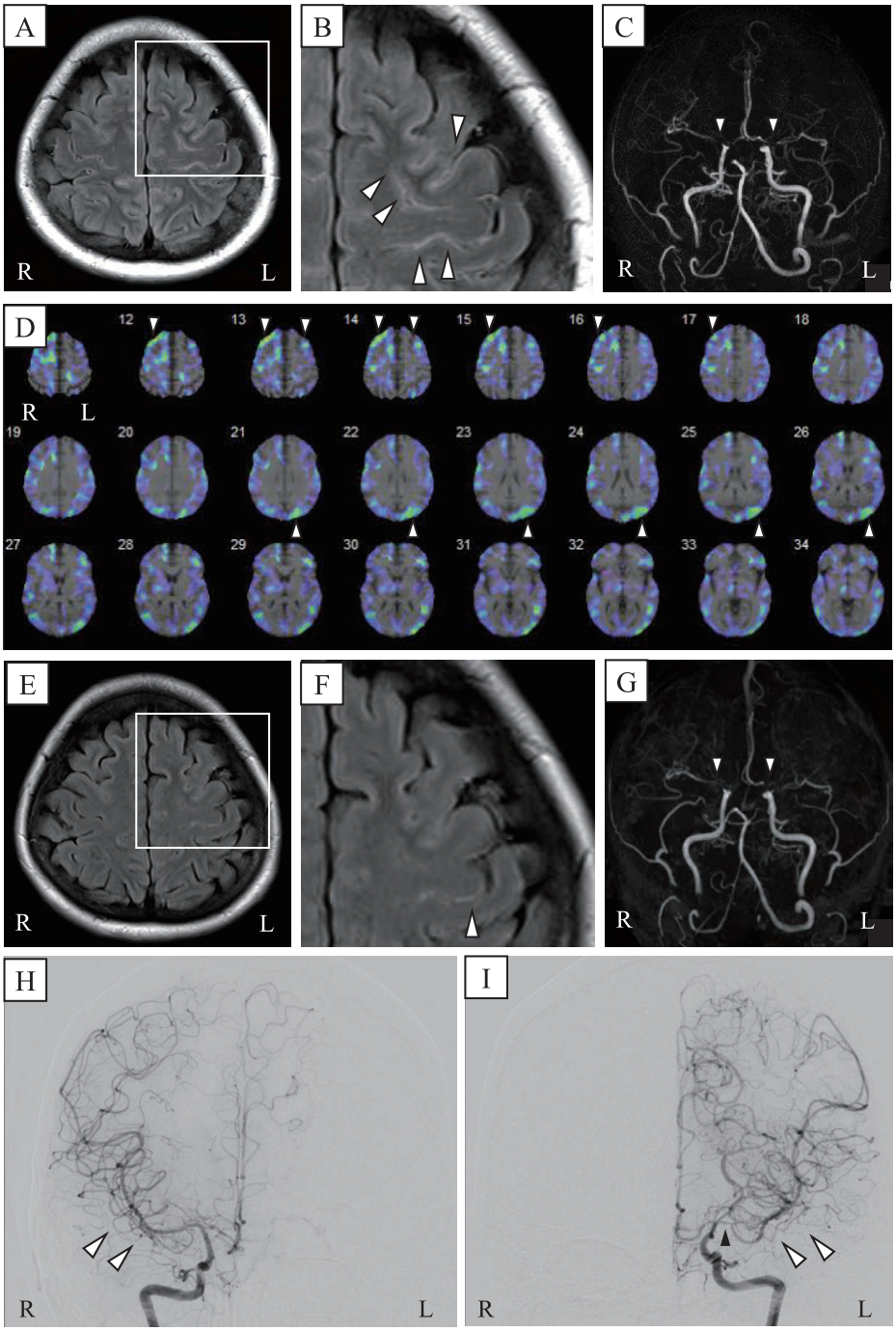

Fig. 2)

A brain magnetic resonance imaging (MRI) showing leptomeningeal high signal intensity ("Ivy sign") on fluid-attenuated inversion recovery (FLAIR) (A) especially in the frontal lobe (B, arrowheads). A magnetic resonance angiography (MRA) image showing bilateral proximal MCA stenosis (C, arrowheads). A ^{123}I-N-isopropyl-p-iodoamphetamine single photon emission computed tomography (^{123}I-IMP-SPECT) image revealed hypoperfusion in the bilateral frontal lobe and left occipital lobe (D, arrowheads). A brain MRI at 352 days after the first symptom showing improved leptomeningeal high signal intensity (E, F) without a significant improvement of MRA finding of bilateral proximal MCA stenosis (G, arrowheads). A digital subtraction angiography (DSA) image showing bilateral MCA (left > right) stenosis with an abnormal vascular network ("moyamoya vessels") (H, I, arrowheads).

treatment, fT3 and fT4 gradually decreased to a normal range, and her cognitive symptom (poor concentration) disappeared 2 months after the start of this treatment. In addition, the frequency of transient muscle weakness in the right upper and lower extremities decreased to about once a month (Fig. 1).

At 352 days after the first symptom appeared, she was admitted to our hospital's neurosurgery department for reassessment. A brain MRI showed an improvement of leptomeningeal high signal intensity (Fig. 2E, F, arrowhead). The MRA finding of bilateral proximal MCA stenosis did not improve significantly (Fig. 2G, arrowheads). A digital subtraction angiography (DSA) showed bilateral MCA stenosis (left > right, Fig 2I, black arrowhead) with an abnormal vascular network ("Moyamoya vessels") (Fig 2H, 2I, arrowheads). After adding 200 mg of cilostazol medical treatment, her motor and cognitive symptoms completely disappeared (Fig. 1).

Discussion

A typical symptom of Moyamoya disease, transient hemiparalysis, was observed in the present case, but neuropsychiatric symptoms such as poor concentration or general fatigue are relatively rare (Hiruma et al., 2022). Cognitive symptoms may occur in Moyamoya disease patients regardless of the coexistence of cerebral infarctions (Karzmark et al., 2012). Long-term hypoperfusion in specific brain regions can cause related neurocognitive dysfunction leading to progressive cognitive decline without ischemic stroke (Nakamizo et al., 2018). In the present case, our therapeutic intervention at an early stage may have prevented long-term severe cortical hypoperfusion potentially leading to the progression of cognitive decline. We speculate a relationship between vascular stenosis and psychiatric symptoms since hemiparesis and cognitive symptoms started almost simultaneously. However, we cannot exclude the possibility that psychiatric symptoms were presented merely due to hyperthyroidism, as was previously reported (Fukao et al., 2020).

In patients with Graves' disease, a detailed examination by angiography with iodine contrast cannot be performed because it may increase the risk of thyrotoxic crisis (van der Molen et al., 2004), so MRA has become the main tool to evaluate arterial stenosis and the development of collateral vessels. In the present case, although the MRA findings did not change significantly, the "Ivy sign", which indicates dilated blood vessels on the surface of the brain, almost disappeared, suggesting improved blood flow in the middle cerebral artery (Fig. 2B, 2F). Regarding treatment for such patients, a small number of cases showed an improvement of symptoms only with a treatment for hyperthyroidism (Ishigami et al., 2014; Sasaki et al., 2006) although their clinical and radiological outcomes varied. In Moyamoya disease with Graves' disease, vascular stenosis due to Moyamoya disease is caused by neointimal hyperplasia, disruption of the internal elastic lamina, and medial attenuation (Fox et al., 2021). In addition, increased thyroid hormones may cause progressive vascular narrowing through a rise in vascular sensitivity to the sympathetic nervous system (Liu et al., 1994).

The present case clearly demonstrates that treatment of hyperthyroidism should be considered before antithrombotic drugs or surgical therapy for Moyamoya disease with Graves' disease. To achieve a successful and minimally invasive treatment, staged management is recommended. This includes diagnosis of Ivy sign by MRA, initial treatment for hyperthyroidism, a detailed examination by angiography with iodine contrast media after normalization of the thyroid function, and consideration of antiplatelet agents if stenosis still persists. The present case represents a valuable reference for appropriate treatment steps for this rare disease with a unique pathophysiology.

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Greetings from the President of the Japanese Society for Vascular Cognitive Impairment

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

It is my great honor to administrate the Japanese Society for Vascular Cognitive Impairment as the 4th president. This society has been developing with great support of the former presidents, members of each committee, academic members, and secretariats. This society was initially established as the Japan Vas-Cog Study Group in April 2010, and has been renamed to the Japanese Society for Vascular Cognitive Impairment also known as the Vas-Cog Japan in October 2014. As of December 2022, the number of academic members is 209, and it is composed of 68 councilors, 22 directors, 3 advisors and 2 auditors. I sincerely thank all colleagues for their effort to raise awareness of the Vas-Cog Japan.

Since COVID-19 pandemic began, all of social, educational, cultural and academic activities were restricted. The mRNA vaccines and the novel medicines for the SARS-CoV-2 could reduce the number of patients with severe symptoms, however, COVID-19 is still big threat, and repeating to increase and decrease the number of patients. After struggling against the SARS-CoV-2 for three years, introduction of so-called "new-lifestyle" and treatment/prevention options could gradually reverse our academic activities. Due to COVID-19 pandemic, the Vas-Cog Japan 2020 meeting was suspended, and the Vas-Cog Japan 2021 meeting was totally held online. Finally, we could hold the Vas-Cog Japan 2022 meeting and gather in Tokyo as hybrid style. The number of participants was 101 on site and 98 on the web. I was very pleased to be able to discuss face to face at the meeting. I greatly appreciate co-presidents Drs. Kazuo Kitagawa and Koichi Kozaki for their tremendous contribution to conduct the meeting. Theme of the 2022 meeting was "cerebral small vessel disease and cognitive impairment, frailty, sarcopenia". All of sessions such as special and educational lectures, symposiums and others were fascinating, and we discussed an important relationship between cerebral small vessel disease and frailty/sarcopenia. General oral presentations including those received young investigator's award were on the cutting edge, and contributed to provide useful scientific information for participants.

The purposes of academic activities of this society include to study the vascular factors related to the occurrence and progression of various types of dementia, and integration of researchers in the basic and clinical fields to promote research activities. In addition, doctors and researchers in the fields such as neurology, cardiology, geriatrics, psychiatry, and neurosurgery carry out activities from a wide range of perspectives beyond their specialties. We are developing unique activities that are not recognized in other academic societies.

According to the efforts of editorial board members, the Vas-Cog Journal has been resized larger since an issue of year 2022 than the previous one. Contents of the journal were refined and its visibility was improved. Further investigations are being promoted by the journal editorial board to publish our papers in PubMed Central (PMC) in the near future.

Recent results of clinical trials of anti-amyloid beta antibody therapies on Alzheimer's disease patients at the early stage revealed promising effect to reduce amyloid beta-deposition in the brain and improve cognitive function. However, it is still difficult to treat patients with dementia at the advanced stage. The Vas-Cog Japan society is focusing on elucidation of the pathophysiology of dementia, especially from the aspect of vascular risk factors. We will also try to establish effective preventive and therapeutic interventions, which in turn will lead to great social contributions. I think that the activities of this society fit well with the academic needs of specialists and professionals in many fields. We sincerely look forward to your participation.

Reports of the Vas-Cog Japan 2022

Department of Neurology, Tokyo Women's Medical University

Kazuo Kitagawa MD, PhD

Department of Geriatric Medicine, Kyorin University School of Medicine

Koichi Kozaki MD, PhD

The Vas-Cog Japan 2022 was held on August 6th, 2022 (Saturday) at Osaki Bright Core Hall and also on the WEB. The hall is about 10 minutes-walk from Osaki station across Meguro River, very popular and famous in the cherry blossom season. The society meeting was either postponed or held on the WEB due to COVID-19 pandemic these three years. This year's meeting was held on site and face-to-face, first since after 2019. A total of 224 researchers participated in the meeting, and hot discussions were exchanged.

The theme of this year's meeting was "Cerebral small vessel disease and cognitive impairment, frailty and sarcopenia". We are happy to meet many researchers in the field of neurology, geriatric medicine, cardiology, metabolic diseases and pharmacology, who are involved in these topics. Plenary lectures were "Cerebral small vessel disease: bridge from cerebral vessel disease and dementia" by Kazuo Kitagawa, and "Frailty and dementia in the elderly" by Koichi Kozaki, two conference chairs. We had two education programs by professors Ikeda and Hanyu, two YIA sessions, and four symposiums. As a sponsored seminar, we had two lunch and two afternoon seminars. Furthermore, we held education seminars for occupational health physicians. We hope all the participants really enjoyed our program.

We would like to express our deep appreciation for the participation and all the support to the meeting.

Welcome to Vas-Cog Japan 2023
Theme: Innovation in vascular cognitive impairment research

Congress Chairperson of the 13th Annual Meeting of the Japanese Society for Vascular Cognitive Impairment (Vas-Cog Japan)
Professor, Department of Neurology, The Jikei University School of Medicine

Masahiko Suzuki MD, PhD

It gives me great pleasure to welcome you to the 13th annual meeting of Vas-Cog Japan in a hybrid format.

This annual meeting will be held on August 5th, 2023, at Roppongi Academy Hills, Tokyo, which is located on the 49th floor of Roppongi Hills Mori Tower with a panoramic view of Tokyo.

The theme of this meeting is "Innovation in Vascular Cognitive Impairment Research", which includes both basic and clinical research to facilitate further development in the field.

In addition, pre-symposium to Vas-Cog 2023 in Gothenburg will be jointly held with the tremendous support from both Dr. Ihara (Director, National Cerebral and Cardiovascular Center) and Prof. Mizuno (Kyoto Prefectural University)

Although the COVID-19 pandemic situation still holds uncertainty, I hope that you will enjoy the wonderful view of Tokyo from this facility and this opportunity to interact with fellow scholars to exchange wisdom and inspire innovation in the field.

Congress Vice-chairperson of the 13th Annual Meeting of the Japanese Society for Vascular Cognitive Impairment (Vas-Cog Japan)
Professor, Department of Neurology, Tokyo Medical University

Hiroo Terashi MD, PhD

I will be the Vice-chairperson of the 13th Annual Meeting of Vas-Cog Japan (on Saturday, August 5, 2023, at Roppongi Hills Mori Tower), which will be presided over by Professor Masahiko Suzuki of the Jikei University School of Medicine. The theme of the Meeting is "Innovation in Vascular Cognitive Impairment Research." We hope that clinicians and researchers from various fields will actively interact with one another, and that the Meeting will serve as a venue for sharing creative research information. The Meeting will be held in a hybrid format. However, if the situation permits, we would like a large number of people to attend the Meeting at the venue. We look forward to seeing you in Tokyo.

Meeting report of Vas-Cog Asia 11 from Kaohsiung

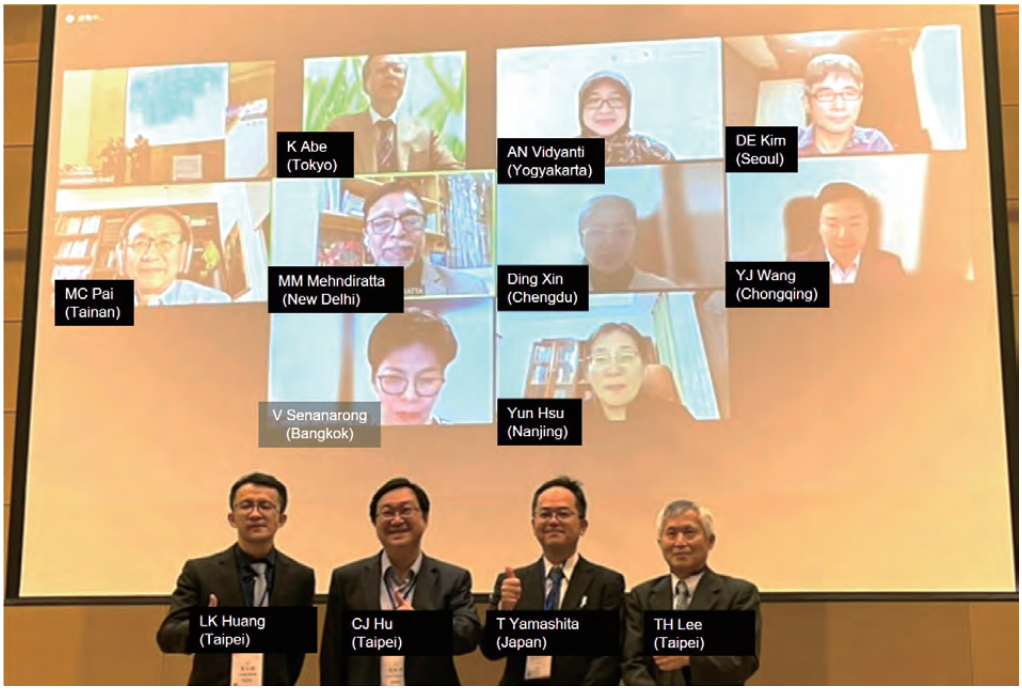
Toru Yamashita MD, PhD
General Secretary of Vas-Cog Asia

I would like to report the great success of Vas-Cog Asia 11, which was held at Kaohsiung (Taiwan) on November 26th (2022) always jointing with Asia-Pacific Stroke Conference (APSC) based on the great supports by Professors Byung-Woo Yoon (APSO president, Seoul) and Ku-Chou Chang (APSC2022 Chair, Taiwan). Regulations against COVID-19 were relaxed for entry into Taiwan, allowing entry without a quarantine period with only a self-check antigen test, and local participation was realized. During the conference period, the local elections in Taiwan were held, and I could feel the excitement in the city.

At Vas-Cog Asia, around 50 researchers from various countries including Japan, India, Taiwan, Korea, China, Thailand, and Indonesia gathered locally or on the web to discuss the latest topics in dementia related to cerebrovascular disorders, as shown below photo. Among others, there was a report that PDGFRα in spinal fluid is useful as a marker of blood-brain barrier damage in patients with Alzheimer's disease, which led to much discussion. In the evening, a reception was held to allow researchers to communicate with each other while taking care to avoid infections. We are reminded of the importance of researchers actually meeting each other, reporting on their recent activities, and interacting with each other.

Next Vas-Cog Asia 12 is going to be held in Hong Kong (2023) under direction of our President Tsong-Hai Lee (Taipei). All of you are welcome to actively join these forthcoming Vas-Cog meetings to present and discuss on vascular factors of all type dementia.

December 19, 2022



Reports of Vas-Cog Japan Council Meeting

Kenjiro Ono, MD, PhD
Department of Neurology, Kanazawa University
Graduate School of Medical Sciences

The 13th board and council meeting of the Japanese Society for Vascular Cognitive Impairment was held together with 21 members onsite, 33 members on the WEB, on the 6th of August 2022. The representative director and committee members reported the topics shown below and all proceedings were approved by members.

[Membership]

204 regular members (As of June 22, 2022)

[Report from each committee leader]

* The leader of board for the ARIKATA, Dr. Ryuichi Morishita
  A committee has been held, and it was reported that there was an opinion that we are proceeding from PMC publication toward becoming an academic organization, and that we should apply for additional applications to the Japanese Society of Anti-Aging Medicine as regarding the credits of other academic societies,. It was decided to proceed with the specialist system as an issue for future consideration.

* The leader of board for increasing membership and public relations, Dr. Kazuo Kitagawa
  A committee reported that this society may invite doctors who are active in other academic societies to join as symposium speakers, and encourage young doctors to join from the facilities of executives such as directors and councilors in order to increase the number of members. In addition, regarding the links between academic societies, if a director of our society is a director of another academic society, we may explain that we would like you to work on the links with other academic society.

* The chief editor of the academic magazine, Dr. Toshiki Mizuno
  From the 8th issue onwards, the chairman and special lecturers submitted their manuscripts, and we were able to enrich the content, but the increase in the number of pages increased the publication costs. From issue 9 onwards, it was reported that the cover only was in color and the middle pages were in black and white to reduce costs, and that all members of the committee were making efforts to collect advertisements in line with the publication costs.

* The leader of board for finance, Dr. Kenjiro Ono
  A committee meeting was held, and it was discussed that an increase in the number of members is necessary for the financial soundness of the society. Among them, there are many neurologists, so it was proposed to invite other fields such as neurosurgeons to join this society and to create a specialist system.

* The leader of board for COI, Dr. Masahiko Suzuki
  Although the committee did not hold a meeting this year, it was reported that a committee meeting would be held to prepare the English version of the COI report.

[Plans for future meetings]

1. The 14th Meeting (5th of August 2023)
   Roppongi Academyhills
   Chairmen: Dr. Masahiko Suzuki
2. Refer to the last page for subsequent schedules.

Editor's Note

Masayuki Satoh, MD, PhD
Professor
Department of Dementia and Neuropsychology,
Advanced Institute of Industrial Technology,
Tokyo Metropolitan Public University Corporation

This volume includes very interesting articles. Using quantitative amyloid PET analysis, Dr, Kasahara reported that more severe cerebrovascular disease (CVD) findings are associated with milder amyloid-β (Aβ) accumulation in patients with Alzheimer's disease (AD). Simultaneous presence of Aβ and CVD pathologies has been shown to significantly accelerate the onset of clinical dementia and cognitive decline. Professor Kalaria explained, in his excellent review, the relationship between findings of magnetic resonance imaging (MRI) and small vessel disease (SVD). Cerebral vessels undergo loss of smooth muscle cells and disruption of the extracellular matrix within basement membranes with consequences on interstitial fluid drainage. The distribution and quantity of SVD pathology involving both parenchymal lesions and arteriopathy vary with age, gender, vascular risk factors and genetically determined disorders. SVD is part and parcel of almost all types of dementias. Dr. Takeshita showed the pathomechanism of skeletal muscle dysfunction in AD. The author described the physiological functions of Aβ peptide, the causative factor of AD, and its precursor, APP, in skeletal muscle. Then, the mechanism of skeletal muscle dysfunction associated with AD is discussed based on the findings of inclusion body myositis, which shows pathological conditions. Dr. Sasaki reported a case of Moyamoya disease with Graves' disease, who complicated by progressive stenosis or occlusion of proximal intracranial arteries. The symptoms and radiological findings improved dramatically after medical treatment for Graves' disease without any other interventions. As shown in this volume, too, the present investigation of dementia is carried out mainly about Aβ.

Last year, the effectiveness of a new anti-amyloid antibody drug, namely the *Lecanemab*, was reported. The therapy of the AD is supposed to enter the new stage. But, besides the high cost of the drug, the anti-amyloid therapy to AD has the essential problem which should have been resolved. The Nun study by professor Snowdon had revealed that the dementia did not always occur even if the pathological process of the Amyloid cascade reached the final stage. Some persons had suffered from the dementia with almost normal brain pathology, and others had been cognitively normal though their brain pathology showed very severe Amyloid deposition. This fact means that, in order to occur the AD, another factor is necessary except the Amyloid deposition. But we have not known what this factor is. We can say that the essential and important problem remains unsolved for the realization of the disease-modifying therapy to the AD.

The past and future annual meeting of Vas-Cog Japan

The 1 st 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 (Tokyo)	Chairman : Masahiko Suzuki
The 14th Meeting : August, 2024 (Gifu)	Chairman : Takayoshi Shimohata
The 15th Meeting : August, 2025 (planned)	Chairman : Kazuma Sugie

- to be continued -