



Predicting cerebral amyloid angiopathy-related intracerebral hemorrhages and other cerebrovascular disorders in Alzheimer's disease

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Cerebral amyloid angiopathy (CAA) of amyloid β -protein ($A\beta$) type is common in Alzheimer's disease (AD). $A\beta$ immunotherapies have been reported to induce CAA-related intracerebral hemorrhages (ICH) or vasogenic edema. For the purpose of developing a method to predict CAA-related ICH and other cerebrovascular disorders in AD, the biomarkers, and risk factors are reviewed. The biomarkers include (1) greater occipital uptake on amyloid positron emission tomography imaging and a decrease of cerebrospinal fluid $A\beta_{40}$ levels as markers suggestive of CAA, and (2) symptomatic lobar ICH, lobar microhemorrhages, focal subarachnoidal hemorrhages/superficial siderosis, cortical microinfarcts, and subacute encephalopathy (caused by CAA-related inflammation or angiitis) as imaging findings of CAA-related ICH and other disorders. The risk factors include (1) old age and AD, (2) CAA-related gene mutations and apolipoprotein E genotype as genetic factors, (3) thrombolytic, anti-coagulation, and anti-platelet therapies, hypertension, and minor head trauma as hemorrhage-inducing factors, and (4) anti-amyloid therapies. Positive findings for one or more biomarkers plus one or more risk factors would be associated with a significant risk of CAA-related ICH and other cerebrovascular disorders. To establish a method to predict future occurrence of CAA-related ICH and other cerebrovascular disorders in AD, prospective studies with a large number of AD patients are necessary, which will allow us to statistically evaluate to what extent each biomarker or risk factor would increase the risk. In addition, further studies with progress of technologies are necessary to more precisely detect CAA and CAA-related cerebrovascular disorders.

Keywords: cerebral amyloid angiopathy, Alzheimer's disease, intracerebral hemorrhage, cerebrovascular disorders, dementia, amyloid β -protein, biomarker, risk factor

INTRODUCTION

Cerebral amyloid angiopathy (CAA) is cerebrovascular amyloid deposition, and is classified into several types according to amyloid protein involved; among them, sporadic CAA of amyloid β -protein ($A\beta$) type is most commonly found in elderly individuals as well as in patients with Alzheimer's disease (AD; see review Yamada and Naiki, 2012).

Cerebral amyloid angiopathy is pathophysiologically related to both cerebrovascular disorders and dementia as shown in **Figure 1** (Yamada and Naiki, 2012). A subset of patients with AD spontaneously develop CAA-related intracerebral hemorrhages (ICH) and other cerebrovascular events, which may affect the clinical course of AD; furthermore, in clinical trials for AD, $A\beta$ immunotherapies induced CAA-related ICH and other vascular complications (Cordonnier and van der Flier, 2011). To develop a method to predict CAA-related ICH and other cerebrovascular events in AD, this article reviews the prevalence, clinical manifestations, biomarkers, and risk factors for CAA and CAA-related cerebrovascular disorders in patients with AD.

SPECTRUM OF CEREBRAL $A\beta$ AMYLOIDOSIS: CAA WITH OR WITHOUT AD

High prevalence of CAA in patients with AD as well as of cerebral parenchymal $A\beta$ deposition (senile plaques, SPs) in patients with CAA can be explained by the fact that AD and CAA represent two sides of a single condition, i.e., cerebral $A\beta$ amyloidosis. The length of $A\beta$ of SPs is mainly 42–43 residues ($A\beta_{42}$), while that of cerebrovascular $A\beta$ is mainly 39–40 residues ($A\beta_{40}$) (Prelli et al., 1988; Suzuki et al., 1994). Tissue levels of soluble $A\beta_{40}$ in the brain correlate with severity of CAA (Suzuki et al., 1994). In the process of vascular $A\beta$ deposition, $A\beta_{42}$ is initially deposited, and later $A\beta_{40}$ is massively accumulated (Shinkai et al., 1995). It has been indicated in both human and experimental studies that an increase of $A\beta_{40}$ to $A\beta_{42}$ ratio significantly shifts $A\beta$ deposition toward the cerebral vasculature, resulting in prominent CAA, as demonstrated in hereditary cerebral hemorrhage with amyloidosis-Dutch type (HCHWA-D) with a point mutation at codon 693 of the $A\beta$ precursor protein (APP) gene that causes a single amino acid substitution (Glu to Gln) at position 22 of $A\beta$, and the transgenic mouse model of this disease (Herzig et al., 2004). However,

determinants for the pattern of parenchymal or vascular amyloid deposition remain to be elucidated for sporadic cases of AD as well as CAA.

Pathologically, CAA is commonly found in AD, with a prevalence of more than 80% (Yamada et al., 1987; Yamada, 2002). The prevalence and severity of CAA in AD are significantly higher compared with non-AD cases (Yamada, 2002). Actually, some of patients with AD are complicated with CAA-related cerebrovascular disorders as reviewed in the next section. On the other hand, a relatively small subset of patients with symptomatic CAA-related ICH present with dementia/AD at onset of ICH, suggesting vascular-dominant distribution of amyloid deposition in the brain (Cordonnier et al., 2010; Hirohata et al., 2010).

Thus, the severity of each of vascular and parenchymal amyloid deposition varies. The wide spectrum of cerebral A β amyloidosis is shown in **Figure 2**, including “AD with severe CAA,” “severe CAA without AD,” “AD with no or mild CAA,” and “no AD with

no or mild CAA.” Severe CAA with or without AD may be associated with CAA-related disorders. **Figure 3** shows the distribution of the severity of CAA in elderly individuals [age (mean \pm SD), 85.9 \pm 8.0 years] with and without AD from our autopsy series (Yamada, 2002). “No or mild CAA,” that would be clinically free of CAA-related cerebrovascular disorders, is found in 86% of non-AD elderly individuals, while in 66% of AD patients, which would explain that AD patients are associated with higher risk of CAA-related cerebrovascular disorders than non-AD elderly subjects.

Patients who initially have the onset of symptomatic CAA-related ICH without AD may increase parenchymal A β deposition during the clinical course, leading to development of AD (Hirohata et al., 2010). On the other hand, patients who initially have AD with no or mild CAA may increase vascular A β deposition during the clinical course, which might lead to development of CAA-related cerebrovascular disorders (**Figure 2**). The long time course after onset of AD may allow progression of vascular A β deposition, as observed in the kinetic study of CAA in a transgenic mouse model (Robbins et al., 2006).

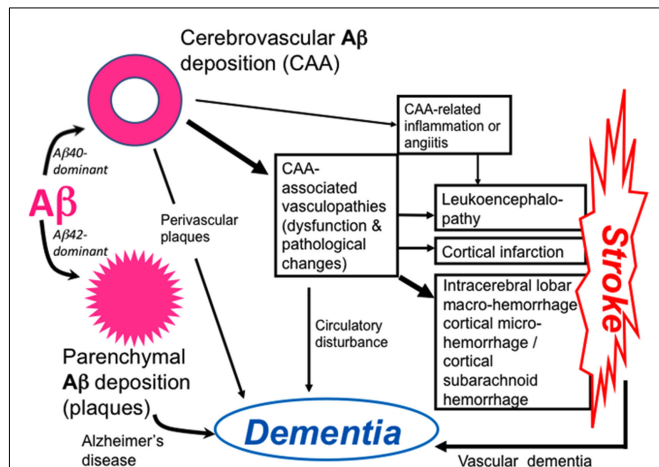


FIGURE 1 | Pathophysiology of cerebral amyloid angiopathy (CAA)-related disorders. A β shows parenchymal or vascular deposition, depending on dominance of A β 42 or A β 40, respectively, in elderly individuals and patients with Alzheimer's disease (AD). Cerebrovascular amyloid deposition, CAA, is related to stroke and dementia.

CAA-RELATED INTRACEREBRAL HEMORRHAGE AND OTHER CEREBROVASCULAR DISORDERS IN AD

INTRACEREBRAL HEMORRHAGE

Symptomatic ICH

Incidence of symptomatic CAA-related ICH in patients with AD (**Figure 4C**) has not been elucidated as yet, requiring further prospective studies. Prevalence of ICH (excluding microhemorrhages) among AD cases at autopsy was reported to be 5.6%, including both CAA-related and non-CAA-related ICH, in a large autopsy series (Attems et al., 2008); it is suggested that additional risk is important to develop symptomatic macrohemorrhages, even if AD patients have CAA or CAA-related microhemorrhages in the brain.

Microhemorrhages in AD

The frequencies of cerebral microhemorrhages on sensitive magnetic imaging (MRI), such as gradient-echo T2⁺, were reported

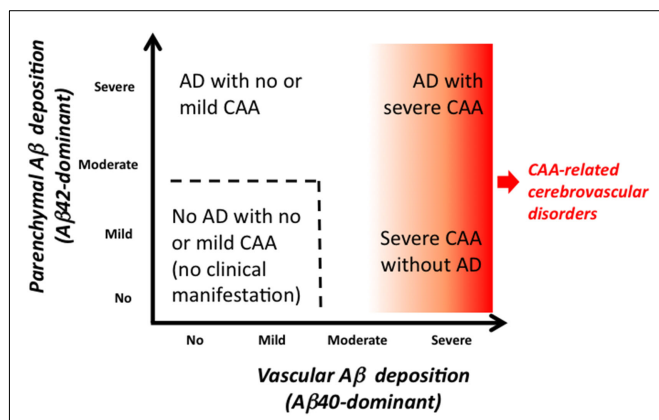


FIGURE 2 | The spectrum of cerebral A β amyloidosis.

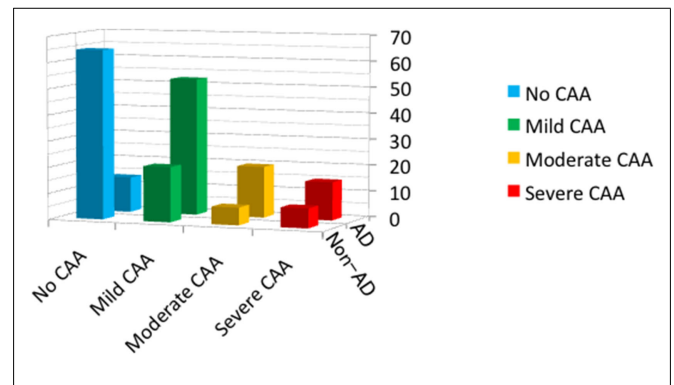


FIGURE 3 | The distribution of the severity of CAA in elderly individuals (n = 201; age, 85.9 \pm 8.0 years) with and without Alzheimer's disease (AD), based on an autopsy series including AD (n = 82; age, 86.1 \pm 7.9 years) and non-AD cases (n = 119; age, 85.7 \pm 8.0 years). Frequencies are shown in the percentages in each of the AD and non-AD group (The modified data from the previous report; Yamada, 2002).

to be 16.7–32%, which are higher than those in general population (5–6%) (Hanyu et al., 2003; Cordonnier et al., 2006, 2007; Nakata-Kudo et al., 2006; Pettersen et al., 2008); microhemorrhages in AD are frequently distributed in lobar distribution with more numbers compared with those in control subjects (Figure 4A). A recent study with amyloid positron emission tomography (PET) using ^{11}C -Pittsburgh compound B (PiB) reported high prevalence of lobar microhemorrhages in PiB-positive mild cognitive impairment (MCI) and healthy subjects as well as AD patients, indicating strong association of A β deposition with lobar microhemorrhages (Yates et al., 2011). Microhemorrhages were reported to preferentially occur in local regions of concentrated amyloid indicated by PiB retention (Dierksen et al., 2010).

CONVEXAL SUBARACHNOID HEMORRHAGE OR SUPERFICIAL SIDEROSIS

Superficial siderosis associated with CAA is detected on MRI in AD patients (Figure 4B) and was suggested to be a marker of CAA in AD (Feldman et al., 2008). It was reported that CAA was a frequent cause of convexal SAH, a subtype of non-aneurysmal subarachnoid bleeding, in patients over the age of 60 (Kumar et al., 2010). Superficial siderosis closely accompanied microhemorrhages in lobar locations, suggesting a close link between superficial siderosis and CAA (Vernooij et al., 2009b). Focal subarachnoid hemorrhages in conjunction with or without lobar microhemorrhages were reported to present with transient repetitive migraine auras or transient ischemic attack mimics (Izenberg et al., 2009).

WHITE MATTER LESIONS

Although white matter lesions or hyperintensities detected by MRI are found in AD, MCI, and healthy elderly subjects as well as CAA, CAA-related perfusion impairments result in progressive damage of white matter and cognitive impairment (Smith et al., 2004; Chen et al., 2006; Yoshita et al., 2006; Viswanathan et al., 2008). Patients with CAA-related ICH showed occipital dominant white matter hyperintensities on MRI, compatible with predilection of CAA pathology for posterior brain regions (Zhu et al., 2012).

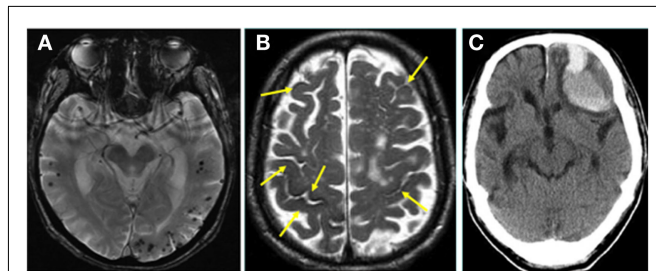


FIGURE 4 | (A) Cerebral microhemorrhages with lobar distribution in a patient with Alzheimer's disease (AD) on gradient-echo T2* imaging. **(B,C)** A patient with AD had presented with multiple, old focal subarachnoid hemorrhages (superficial siderosis; arrows) on T2-weighted MRI at the time of the diagnosis of AD **(B)**. The patient later developed a large intracerebral hemorrhage in the left frontal lobe as shown on CT **(C)**, probably related to CAA (by courtesy of Dr. Toshiya Fukui, Showa University).

MICROINFARCTS

Cerebral amyloid angiopathy was revealed to be an important risk factor for microinfarcts restricted to the watershed cortical zones in AD, suggesting a role of cerebral hypoperfusion in the pathogenesis of cortical microinfarcts (Suter et al., 2002).

CONTRIBUTION OF CAA TO DEMENTIA IN AD

Patients with AD and severe CAA may have mixed dementia of AD and CAA-related vascular cognitive impairment, and there may be occasionally “a vascular variant of AD” in which most of A β plaques are formed around CAA (Yamada et al., 1997a). CAA had deleterious effects on cognition even after controlling for age and AD pathology, and CAA was associated with white matter abnormalities and cognitive impairment (Greenberg et al., 2004). It was reported that moderate-to-very severe CAA, but not mild-to-moderate CAA, is associated with lower performance in specific cognitive domains, most notably perceptual speed, separately from the effect of AD pathology (Arvanitakis et al., 2011). Multiple microhemorrhages in AD were reported with worse cognitive function and higher abnormalities of cerebrospinal fluid (CSF) markers (Goos et al., 2009).

CAA-RELATED INFLAMMATION

A subset of patients with CAA present with CAA-associated vascular inflammation or angiitis showing subacute encephalopathy characterized by cognitive symptoms, seizure, headaches, and focal neurological deficits with white matter lesions on MRI (Eng et al., 2004; Oh et al., 2004; Scolding et al., 2005; Kinnecom et al., 2007). In the clinical course all patients with CAA-related inflammation presented with subacute cognitive impairment, but not with AD-like slowly progressive dementia (Kinnecom et al., 2007). Parenchymal A β load in CAA-related angiitis was significantly lower than in AD (Scolding et al., 2005).

CAA-RELATED CEREBROVASCULAR DISORDERS INDUCED BY A β IMMUNOTHERAPIES IN AD

Recent clinical as well as experimental studies with A β immunotherapies for AD have demonstrated that CAA has important implications for the future of anti-amyloid therapies. Experimental studies with AD model mice indicated that A β immunotherapies can induce CAA-related cerebral hemorrhage, although long-term A β immunotherapies could decrease CAA (Pfeifer et al., 2002; Wilcock et al., 2004, 2007; Racke et al., 2005; Prada et al., 2007; Schroeter et al., 2008).

In clinical trials with A β 42 immunization for AD (AN1792, Elan), immunized patients showed significantly higher levels of CAA and cortical microhemorrhages and microvascular lesions compared with unimmunized AD controls, although the longest living had virtually complete absence of both plaques and CAA (Boche et al., 2008). A CAA-related macrohemorrhage was reported in an AD patient in the phase 2a AN1792 trial (Orgogozo et al., 2003). The findings suggest that A β immunization results in solubilization of plaque A β 42, which flows out of the brain parenchyma via the perivascular pathway, causing an increase of CAA and CAA-related hemorrhages. Eventually, this flow also results in A β clearance from the cerebral vasculature.

In the AN1792 trial, 6% of patients treated with the AN1792 suffered meningoencephalitis (Orgogozo et al., 2003) and there was

perivascular infiltration of lymphocytes around vessels with CAA (Nicoll et al., 2003). In a phase 2 trial of bapineuzumab, a humanized monoclonal anti-A β antibody, vasogenic edema occurred in 9.7% of patients, suggesting a vascular permeability change of CAA-laden vessels (Salloway et al., 2009). Vasogenic edema was found only in 2 of 2762 patients with AD at baseline of clinical trials for AD; this indicates that naturally occurring vasogenic edema is a very rare event in untreated patients with AD, though one case of vasogenic edema was presumably related to CAA-related angiitis (Carlson et al., 2011).

MARKERS FOR CAA AND CAA-RELATED CEREBROVASCULAR DISORDERS IN AD

IMAGING MARKERS

CT/MRI

Although cranial CT is available for symptomatic CAA-related ICH (macrohemorrhages), MRI is useful to detect small hemorrhagic lesions (lobar microhemorrhages and focal subarachnoid hemorrhages), and ischemic lesions (various white matter lesions and microinfarcts) as discussed above. Sensitive MR imagings, such as gradient-echo T2* imaging and susceptibility-weighted images (SWI), are particularly useful to detect microhemorrhagic lesions (Nandigam et al., 2009). Although subacute, silent cortical, or subcortical infarctions were recognized on diffusion-weighted images (DWI) in patients with CAA (Kimberly et al., 2009), cortical microinfarcts observed in neuropathological studies are often undetected on MRI because of their limited size (Brundel et al., 2012). Introduction of ultra-high strength clinical MR scanners with a higher spatial resolution may make their detection possible.

Amyloid-PET

In amyloid imaging with a PET ligand, PiB, it was reported that PiB binding was moderately increased in most patients with probable CAA-related ICH and that the occipital uptake was greater in CAA-related ICH compared with AD (Johnson et al., 2007; Ly et al., 2010). In an autopsy-confirmed case, PiB-PET could detect CAA as the dominant source of signal (Bacskaï et al., 2007). Microhemorrhages are found to be associated with PiB retention (Dierksen et al., 2010; Yates et al., 2011).

BIOCHEMICAL MARKERS

Cerebrospinal fluid markers are useful for the diagnosis of AD; the CSF findings in AD are characterized by a decrease of A β 42 levels, an increase of the ratio of A β 40 to A β 42, and an increase of total and phosphorylated tau protein. A significant decrease of CSF A β 40 as well as A β 42 was reported in patients with probable CAA, suggesting the trapping of A β 40 as well as A β 42 in the cerebral vasculature (Verbeek et al., 2009). Plasma A β 40 levels were reported to be associated with extent of white matter hyperintensity in AD, MCI, or CAA (Gurol et al., 2006).

RISK FACTORS FOR CAA AND CAA-RELATED CEREBROVASCULAR DISORDERS IN AD

In addition to old age and AD, both genetic and non-genetic risk factors have been reported for CAA and CAA-related cerebrovascular disorders.

GENETIC RISK FACTORS

Besides hereditary cases of AD/CAA-associated with mutations of the A β PP or presenilin genes (see review Yamada and Naiki, 2012), the ApoE gene (*ApoE*) has been reported to be risk for sporadic CAA as well as AD; the ϵ 4 allele for CAA itself, and the ϵ 2 allele for CAA-related ICH (Greenberg et al., 1995; Premkumar et al., 1996; Nicoll et al., 1997). Carriers of the *ApoE* ϵ 2 or ϵ 4 allele, particularly, of the *ApoE* ϵ 2/ ϵ 4 genotype were associated with early recurrence of lobar ICH in patients who survived a lobar ICH (O'Donnell et al., 2000). The *ApoE* ϵ 4 allele constituted a risk factor for capillary CAA (CAA-Type 1) (Thal et al., 2002) and CAA-related inflammation (Kinnecom et al., 2007). The presence of CAA in head injured cases was significantly associated with the *ApoE* ϵ 4 allele, suggesting an interaction between gene and environment in development of CAA (Leclercq et al., 2005). Another CAA-related gene reported by more than one research group is transforming growth factor (TGF)- β 1 (TGF- β 1) (Hamaguchi et al., 2005; Peila et al., 2007).

In addition, CAA was reported to be associated with other gene polymorphisms, including the presenilin 1 (PS1), α 1-antichymotrypsin (ACT), neprilysin, low-density lipoprotein-receptor related protein (LRP-1), and angiotensin-converting enzyme (ACE) genes (Yamada et al., 1997b, 1998, 2003; Yamada, 2002, 2004; Christoforidis et al., 2005; Thal et al., 2010; Domingues-Montanari et al., 2011). A recent study reported that a CR1 gene polymorphism, reported to increase risk for AD, was also associated with risk of CAA-ICH as well as CAA (Biffi et al., 2012).

NON-GENETIC RISK FACTORS

Hypertension

Lowering of blood pressure reduced risk of CAA-related ICH, suggesting that high blood pressure could be a factor inducing ICH in patients with CAA (Arima et al., 2010).

Thrombolytic, anti-coagulation, and anti-platelet therapies

There is increasing evidence that CAA could be a risk factor for ICH in thrombolytic therapies for acute myocardial infarction, pulmonary embolism, or ischemic stroke, and for ICH in warfarin therapies (Rosand et al., 2000; McCarron and Nicoll, 2004). The use of anti-platelet drugs such as aspirin was related to the presence of microbleeds, and to strictly lobar microhemorrhages suggestive of CAA (Vernooij et al., 2009a). In a systematic review of clinical trials with aspirin in AD, ICH was found in 3.2% of the aspirin group, while, in 0% of the control group, suggesting that aspirin use in AD might pose an increased risk of ICH; a possible explanation for an increased risk of ICH could be CAA in AD (Thoonsen et al., 2010).

Anti-amyloid therapies

As discussed above, clinical trials with A β immunotherapies for AD could induce CAA-related ICH and microvascular lesions (Orgogozo et al., 2003; Boche et al., 2008), inflammation around CAA (Nicoll et al., 2003), and vasogenic edema related probably to vascular permeability changes of CAA-laden vessels (Salloway et al., 2009). These findings in the A β immunotherapies (Nicoll et al., 2003; Orgogozo et al., 2003; Boche et al., 2008; Salloway et al., 2009) suggest that, generally, anti-amyloid therapies with the removal effects of parenchymal A β may be complicated

with CAA-related cerebrovascular disorders, because solubilized parenchymal A β would flow via the perivascular pathway and may deposit on vascular walls resulting in an increase of CAA and CAA-related cerebrovascular disorders; in addition, in the case of A β immunotherapies, inflammatory, or permeability changes may be also induced in vessels with CAA by immune reactions with vascular A β .

PREDICTING CAA-RELATED INTRACEREBRAL HEMORRHAGE AND OTHER CEREBROVASCULAR DISORDERS IN AD

Biomarker findings and risk factors for CAA and CAA-related ICH and other cerebrovascular disorders are summarized in **Table 1**. In the table, CAA-related white matter hyperintensities are not included as a biomarker, because they are common findings in elderly subjects and AD patients with small vessel diseases including both CAA and non-CAA. As for CAA-related ICH, the Boston criteria were proposed for the diagnosis (Knudsen et al., 2001). When a given person presents with one or more biomarkers plus one or more risk factors, we need to be careful about future development of CAA-related ICH and other cerebrovascular disorders, and should avoid additional risk factors if they are avoidable (**Table 1**).

Alzheimer's disease is a definite risk factor for CAA. When a patient with AD presents with positive findings for one or more biomarkers with additional risk factors such as anti-amyloid therapies, the patient would be associated with higher risk of CAA-related ICH and other cerebrovascular disorders compared with AD patients with no positive biomarkers or additional risk factors. However, the reported data for AD were based on cross-sectional or retrospective studies; prospective studies of CAA-related ICH and other cerebrovascular disorders with a large number of AD patients are necessary to establish a method to predict them in AD. Such studies will allow us to statistically evaluate to what extent each biomarker or risk factor would increase the risk of future development of CAA-related ICH and other cerebrovascular disorders in AD patients.

FUTURE DIRECTIONS

In addition to the prospective studies with AD patients, further studies with progress of technologies are necessary to more precisely detect CAA and CAA-related cerebrovascular disorders. Currently, sensitive MRI, such as gradient-echo T2* and SWI, is widely used to detect hemorrhages with a characteristic distribution of CAA for the clinical diagnosis of CAA-related hemorrhages. However, CAA may not present with hemorrhagic lesions, but with other clinical features, such as dementia. Imaging techniques such as PiB-PET have been used to directly image cerebral amyloid deposits. However, such PET tracers are unable to distinguish A β from other amyloid proteins, or to distinguish CAA from amyloid plaques, though the greater uptake in the occipital lobe may be suggestive of CAA (Bacskai et al., 2007; Johnson et al., 2007; Ly et al., 2010). More CAA-specific imaging is required. It was reported that clinical field-strength MRI could directly visualize amyloid plaques, as demonstrated in animal models (Ronald et al., 2009). Postmortem detection of A β deposition in CAA as well as AD with 7.0 T MRI was reported (van Rooden et al., 2009). Further progress in high resolution MRI may enable direct visualization of CAA. Regarding amyloid-PET, resolution of amyloid deposits on PET

Table 1 | Biomarker findings and risk factors for cerebral amyloid angiopathy (CAA) and CAA-related intracerebral hemorrhages (ICH) and other cerebrovascular disorders.

BIOMARKERS
<p>a. Biomarkers suggestive of CAA:</p> <ul style="list-style-type: none"> Amyloid imaging with greater occipital uptake Cerebrospinal fluid markers with a decrease of Aβ40 levels <p>b. Biomarkers suggestive of CAA-related ICH and other cerebrovascular disorders:</p> <ul style="list-style-type: none"> Symptomatic lobar intracerebral hemorrhages on CT/MRI Microhemorrhages in lobar cortical–subcortical regions on MRI* Convexal, non-aneurysmal subarachnoid hemorrhages, or superficial siderosis on MRI* Cortical microinfarcts on MRI** Subacute leukoencephalopathy compatible with CAA-related inflammation or angiitis on MRI
RISK FACTORS
<p>a. General factors:</p> <ul style="list-style-type: none"> Old age Alzheimer's disease <p>b. Genetic factors:</p> <ul style="list-style-type: none"> CAA-related gene mutations in familial cases*** Apolipoprotein E gene in sporadic cases: ϵ4 for CAA and ϵ2 for hemorrhage <p>c. Non-genetic factors to induce CAA-related hemorrhages:</p> <ul style="list-style-type: none"> Thrombolytic, anti-coagulation, and anti-platelet therapies Hypertension Minor head trauma <p>d. Anti-amyloid therapies</p>

Gradient-echo T2 or susceptibility-weighted images are recommended to detect microhemorrhages or focal superficial siderosis.

**Future development of MRI scanners with a higher spatial resolution is necessary to detect cortical microinfarcts.

***Some mutations in the A β PP and presenilin genes are associated with severe CAA (see a review Yamada and Naiki, 2012).

imaging would not be enough to distinguish CAA from amyloid plaques, requiring a new tracer, or technique to identify vascular amyloid.

As for biochemical markers, we need to establish the values of plasma as well as CSF markers for CAA. Blood and brain/CSF levels of A β influence each other through transport across the blood–brain barrier, from brain to blood and from blood to brain, using LRP-1 and receptor for advanced glycation end products (RAGE), respectively (Bell and Zlokovic, 2009). The integrity of blood vessels is disrupted in CAA (Bell and Zlokovic, 2009). Changes of plasma as well as CSF levels of A β 40 and A β 42 need to be investigated in a longitudinal study of patients with CAA to further clarify their value.

Finally, it is required to establish methods for prevention of CAA and CAA-related cerebrovascular disorders. Some hemorrhage-inducing factors are controllable or avoidable, including hypertension and use of thrombolytic/anti-coagulation/anti-platelet therapies (Rosand et al., 2000; McCarron and Nicoll, 2004; Trouillas and von Kummer, 2006; Vernooij et al., 2009a; Arima et al., 2010). We need future strategies for protection of vessel walls against amyloid-related vascular damage

such as toxicity of A β oligomers, A β -induced oxidative stress, and inflammation.

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