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Pandemic of the aging society — sporadic cerebral small vessel disease

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Abstract

Age-related sporadic cerebral small vessel disease (CSVD) has gained increasing attention over the past decades because of its increasing prevalence associated with an aging population. The widespread application of and advances in brain magnetic resonance imaging in recent decades have significantly increased researchers' understanding in the *in vivo* evolution of CSVD, its impact upon the brain, its risk factors, and the mechanisms that explain the various clinical manifestation associated with sporadic CSVD. In this review, we aimed to provide an update on the pathophysiology, risk factors, biomarkers, and the determinants and spectrum of the clinical manifestation of sporadic CSVD.

Keywords: Cerebral small vessel disease; Clinical spectrum; Pathophysiology

Introduction

With an aging population, the prevalence of age-related sporadic cerebral small vessel disease (CSVD) will also increase. Community prevalence of confluent white matter hyperintensities (WMH), lacunes, and cerebral microbleeds varies from 28.4% to 38.5%, 8% to 31%, and 3.1% to 26.9%, respectively.[1-3] CSVD is commonly asymptomatic or it may associate with subtle changes in mental (eg, slower thinking, depressive mood, apathy) and/or motor functions (eg, slower gait). Such subtle changes are often accepted as part of the normal aging process.[4] CSVD may progress slowly (eg, over years to decades) and when a certain threshold has been reached or when some precipitating events (eg, pneumonia, hypotension) happen,[5] the CSVD may become "malignant" and manifest clinically in a more rapid manner, commonly presenting as stroke or stroke-like episodes, affecting single or multiple mental and bodily functions, resulting in dementia and disability. The first clinical manifestation of CSVD can even be a fatal event if it is an intracerebral hemorrhage (ICH). In most cases, once a disabling clinical state is reached, the chance of reversibility is minimal. In addition, since age is the most important risk factor for sporadic CSVD, it is often found in patients with other age-related brain diseases, for example, Alzheimer disease (AD), and is associated with worsening of the clinical condition of these patients. Of further note is that findings from recent studies suggested an etiological role of CSVD in AD as well.[6]

In this article, we aimed to review the pathology and pathophysiology, methods of *in vivo* detection, and clinical manifestation of sporadic CSVD. Cerebral amyloid angiopathy, other hereditary causes of CSVD, neuroimaging quantification of CSVD, and management of CSVD will be discussed in separate reviews of this issue. At the time of writing this article, the coronavirus 2019 (COVID-19) pandemic is posing a serious threat to the aging society around the world.[7] Since CSVD bears a resemblance to COVID-19 in that it also poses a serious threat to older people worldwide, sporadic CSVD may be considered as a pandemic of the aging society as well. More attention should indeed be paid in tackling sporadic CSVD.[8]

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Pathology and Pathophysiology

Anatomy

Cerebral small vessels refer to the intracranial perforating arteries that originate from the major cerebral large arteries of the Circle of Willis, the basilar/vertebral artery, and the superficial leptomeningeal pial vessels. The diameter of the perforating artery decreases as it courses its way into deeper brain regions and branches into smaller arteries or arterioles (<300 μm).[9] Arterioles connect with the network of capillaries (~5 μm), which then transform into venules. The perforating arteries, arterioles, capillaries, and venules are all considered cerebral small vessels. Of further note is that the capillaries only have a single-layered wall consisting of endothelial cells (ie, without smooth muscle cells), which are connected by tight junctions to form the blood-brain barrier (BBB) embedded by a thin basement membrane. The capillary is surrounded by pericytes, astrocytes, neurons, and extracellular components that jointly constitute the neurovascular units (NVU). The diffuse and dense capillary network can reach almost every single neuron in the brain.

Small vessel changes

Autopsy studies relating to sporadic CSVD were mostly performed in those with dementia, stroke, or vascular risk factors (eg, hypertension), as well as in older people in general. Affected cerebral arterioles are characterized by loss of smooth muscle cells in the tunica media, subintimal deposits of fibrinoid and/or hyaline material, thickening of the vessel wall, resulting in stiffening of the vessels, weakening of the vessel wall, luminal narrowing, and sometimes, occlusion (ie, arteriosclerosis).[10,11] There may be a rupture of the vessel wall and microaneurysms (fusiform or saccular) may be found along the arterioles.[10] Excessive deposits of collagen may be found in the vessel wall of the venules (venous collagenosis), particularly around the periventricular regions, which are associated with luminal narrowing or occlusion of the venules. In addition, there may be a loss of capillary density.[12]

Brain parenchymal changes

Brain parenchymal changes around the affected small vessels commonly include a variable combination of the followings: Infarcts ("microinfarct" [<3 mm], "lacune" [3–15 mm]), hemorrhages ("microbleeds" [~200 μm to <10 mm] or ICH), enlarged perivascular space (ePVS), and white matter changes (WMC). The WMC are often patchy or confluent, symmetrically distributed, and located in periventricular regions, sparing the superficial subcortical association U-fibers. On magnetic resonance imaging (MRI) fluid-attenuated inversion recovery sequence, these WMC are described as WMH. There may be ventricular enlargement (secondary to atrophy of the white matter), which increases with the extent of periventricular WMC. On a microscopic level, WMC consist of varying degrees of the following changes: Swollen myelin sheaths or loss of myelin, loss of axons and oligodendrocytes, astrocytic gliosis, zones of rarefaction, or cavitation.[13]

Early hypothesis suggested that the arteriosclerotic occlusion leads to lacunar/microinfarcts, luminal narrowing leads to partial ischemia, resulting in WMC, while rupture of the vessel wall or microaneurysm results in microbleeds or ICH. Recent evidence suggests that endothelial dysfunctions, breakdown of the BBB with leakage of "toxic" blood products into the interstitial space, and disintegration of the NVU at the capillary level, together with a cascade of other pathological processes (eg, impaired vasodilatory response to ischemia, triggering of an inflammatory response, increased vascular pulsatility, impaired drainage of interstitial fluid and wastage, impaired cerebral autoregulation), may play more important roles in inducing the CSVD-related brain parenchymal changes (WMC, infarcts, ePVS, microbleeds).[14,15] With time, secondary loss of white matter (subcortical atrophy with dilated ventricles) and grey matter (cortical and/or subcortical grey matter) ensue, leading to overall shrinkage of the brain.[16] Recent works employing single-cell RNA sequencing of the aged brain revealed prominent aging-associated transcriptomic and functional changes especially at the capillary endothelium, implicating altered energy metabolism, immune/cytokine signaling, and neurovascular regulation processes.[6,17] Interestingly, our group further found that the expression changes of AD susceptibility genes appear especially prominent at the capillary endothelium, suggesting a possible etiological role of capillary endothelial dysfunction in AD.[4]

Note further that a microatheroma may also form at the proximal portion of the perforator, leading to vessel occlusion, resulting in lacunar infarct[11] [Figure 1]. In addition, an atheromatous disease affecting the parent major large artery may also block the orifice of the perforator, or a "junctional" plaque may extend into the orifice leading to blockage.[11,18] All these conditions can lead to lacunar infarcts, which are usually larger in size than infarcts associated with arteriosclerosis as described above.

Risk factors

Sporadic CSVD and its related brain pathological changes are believed to be related to an interplay of aging, vascular diseases or risk factors (in particular, hypertension and smoking), and genetic susceptibility.[19] Note that the association between high blood pressure and WMH decreases with increasing age, and may even reverse, in particular when cerebral autoregulation is impaired.[20] Diabetes was found to associate mainly with lacunes and association with other CSVD brain changes (eg, WMH) was less consistent.[19,21] Hyperlipidemia was possibly associated with microatheroma or atheromatous-related lacunar infarcts and not with arteriosclerosis-related lacunes.[22] Findings on its association between WMH were somehow conflicting.[19,23] Some but not all studies showed an association of homocysteinemia, sleep disturbance, and obesity with CSVD.[19] Recent studies have identified increasing genetic loci that can increase the susceptibility for developing sporadic CSVD, eg, HTRA1 (10q26), FOXC/FOXF2 (6p25), and COLA41/COL4A2 (13q34).[24] Genetic factors may determine why some subjects with similar risk factors (eg, hypertension) develop

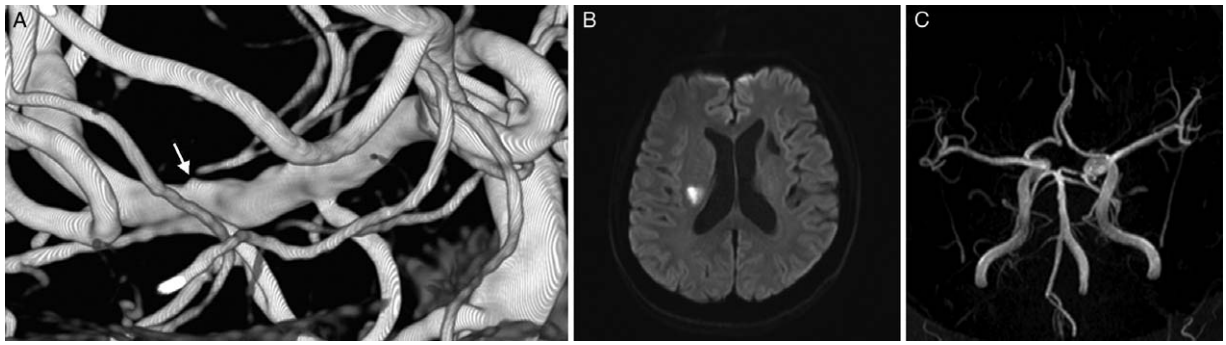

Figure 1: Three-dimensional rotational angiography (3DRA) of the right middle cerebral artery showing steno-occlusion of the perforator ostium (A, white arrow) possibly causing an acute infarct in the right corona radiata as illustrated by the MR diffusion-weighted imaging (B). Of note, the time-of-flight MR angiogram did not reveal any significant intracranial atherosclerotic disease (C). MR: Magnetic resonance.

sporadic CSVD while others develop large artery atherosclerosis. In addition, in the first population study comparing the prevalence of CSVD between Chinese (Shanghai) and Caucasians (Australia), we found that Chinese had a higher prevalence of moderate-to-severe WMH (38.5%) than that in Caucasians (28.4%) even adjusted to age and vascular risk factors. Whether there are certain genetic and/or environmental factors account for the higher prevalence of WMH in Chinese over Caucasians requires further investigation.[2]

In Vivo Detection

Given the small size of the small vessel, *in vivo* direct visualization of CSVD in humans using conventional MR angiopathy (with or without contrast) is difficult. The 7.0-Tesla MR angiopathy (with or without contrast) or three-dimensional rotational angiography [Figure 2] may provide better visualization on the morphology of the perforators/arterioles.[25] MR susceptibility-weighted imaging can visualize deep medullary small veins[26]; however, further studies are needed to clarify its additional value on top of conventional imaging markers in the study of CSVD.

Other means of obtaining a more direct assessment of cerebral small vessel measures include the use of transcranial Doppler ultrasound (TCD) and retinal imaging. The pulsatility index (PI) of the middle cerebral artery as derived from TCD reflects vascular resistance of small vessels and higher PI was found to associate with MRI markers of CSVD[27] as well as with the level of cognitive performance.[28] In addition, imaging the retinal arterioles and venules may also reflect changes of the cerebral small vessel because the retina and its vessels share similar anatomical and physiological properties with the brain.[29] Past studies have shown a significant association between measures of retinal vessels calibers and network parameters with CSVD imaging markers.[30] We recently showed that a retinal imaging analysis powered with machine learning technology achieved good performance in detecting CSVD in the community.[31]

To date, *in vivo* assessment on the presence and severity of CSVD are conventionally done by assessing the related brain parenchymal changes using brain MRI (or computed tomography [CT]). The STandards for ReportIng Vascular changes on nEuroimaging describes the MRI characteristic on different MRI sequences of several types of CSVD-related brain parenchymal damages as described in the above section: Recent small subcortical infarct, lacune of presumed vascular origin, WMH, PVS, cerebral microbleeds, spontaneous ICH, and brain atrophy.[32] In addition, using 3T MRI (as well as 7 T), studies also showed that cortical cerebral microinfarcts (~1–5 mm) could be visualized.[33] CT is overall less sensitive than MRI in picking up most of the CSVD-related changes, except for ICH. Majority of studies conducted over the last few decades aiming to understand the clinical impact of CSVD used MRI (or CT).

There are certain brain changes that are associated with CSVD but may not be captured by pathological studies or conventional MRI sequences or CT, these include diffusion tensor imaging (DTI) (fractional anisotropy, mean diffusivity, peak weak of skeletonized mean diffusivity) and functional MRI, which reflect white matter microstructural changes and brain network connectivity changes, respectively.[4,34] In addition, the BBB leakage and neuroinflammation can also be captured by dynamic contrast-enhanced MRI[35] and translocator protein positron emission tomography (PET) imaging, respectively.[36]

Apart from neuroimaging, there are also potential cerebrospinal fluid (CSF)-based (or even blood-based) biomarkers that may reflect the key pathophysiological processes of CSVD, namely, BBB leakage, breakdown of white matter myelinated fibers, extracellular matrix, and neuroinflammation. These biomarkers may include elevated CSF/blood albumin ratio, altered matrix metalloproteinases, neurofilaments, vascular endothelial growth factor (eg, placenta growth factor), C-reactive protein, and interleukin-6.[37]

One must note that majority of the above imaging biomarkers are not specific for sporadic CSVD. On MRI, recent small subcortical infarct or acute microinfarcts can be due to embolism from more proximal arteries (eg, atherosclerosis) or the heart.[33,38] Old lacunes seen on MRI may be related to previous microbleeds, rather than to infarct. WMH on MRI can have multiple etiologies, including inflammation, neurodegeneration,

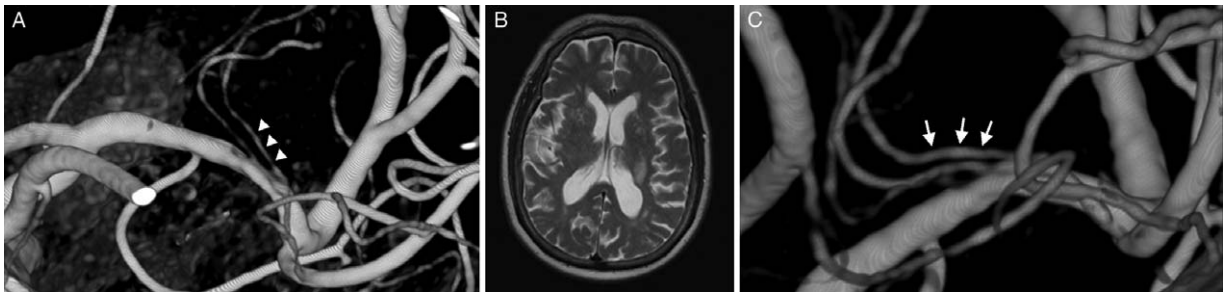

Figure 2: Three-dimensional rotational angiography (3DRA) of the left middle cerebral artery showing possible perforator stenosis (A, white arrowheads) in a patient with white matter hyperintensities in T2 MRI (B). (C) Follow-up 3DRA showed possible regression in perforator stenosis (white arrows) after 1 year of intensive medical therapy. MRI: Magnetic resonance imaging.

edematous changes, or small infarcts. Other types of CSVD, such as cerebral amyloid angiopathy or hereditary types, can have imaging features similar to that of sporadic CSVD. In Asia, since WMH involving the anterior temporal lobe is not common for CADASIL and the mean age of presentation approaches 60 years of age, differentiating between sporadic CSVD and CADASIL may sometimes be challenging.[39] Any "atypical" features (eg, young-onset, history of migraine, familial, presence of left ventricular hypertrophy, tremor, peripheral neuropathy) associated with CSVD-like MRI features should prompt investigation for causes other than sporadic CSVD, which may be hereditary or non-vascular in nature.[40]

Clinical Manifestations

Clinical manifestation of sporadic CSVD is heterogeneous because it varies with the site, severity, and types of CSVD lesions. Moreover, the temporal evolution may also have a varying combination of following patterns, for example, acute or slow progressive decline, plateau, and recovery.

Stroke

Sporadic CSVD commonly presents as stroke (a lacunar stroke or deep ICH) or transient ischemic attack (TIA). If the acute lesion is small, the associated symptoms can be very mild, non-specific, and/or transient (ie, TIA), and are often ignored by patients or relatives, for example, transient dizziness, gait disturbance, or confusion. A small acute lesion on the diffusion-weighted imaging sequence on MRI may be visible if such an investigation can be arranged shortly after the occurrence of these transient symptoms.[41]

For more severe episode requiring medical attention, a clinical syndrome that is associated with an acute small subcortical infarct may include the following: Pure motor or sensory stroke (eg, internal capsule), ataxic hemiparesis/dysarthria-clumsy hand syndrome (eg, pons, internal capsule), hemiballismus/chorea/athetosis (eg, subthalamus, basal ganglia), vertigo (eg, cerebellum), Parkinsonism (eg, substantia nigra). The cognitive decline of the "subcortical" type may also happen immediately after a stroke if the lesion involves a cognitive relevant site (ie, "strategic" infarct cognitive impairment/dementia). Using assumption-free analyses (multivariate lesion-symptom mapping), the CU-STRIDE (The Chinese University of Hong Kong-Stroke Registry Investigating Cognitive Decline) study recently showed that subcortical infarct involving left caudate and pallidum, left hemispheric white matter tracts (anterior internal capsule, anterior corona radiata, external capsule, posterior thalamic radiation), and corpus callosum were "strategic" sites associated with cognitive impairment.[42] In our previous cohort of CSVD-related stroke, more than half of the patients (52%) experienced subjective cognitive complaints after the index lacunar stroke, around a third (34.7%) had residual mild cognitive impairment, and 13.3% had dementia.[43] More importantly, functional outcome was mainly associated with a measure of executive function in this cohort, while performance on tests that lack executive measure (ie, Alzheimer Disease Assessment Scale — Cognitive Subscale or mini-mental state examination) had no association with functional outcome in this cohort.[43]

Among the various CSVD lesions, the presence of cerebral microbleeds is associated with the highest risk of ICH.[44] We have shown that the risk of ICH (as well as mortality) increases significantly with the number of microbleeds.[45] Overall, the presence of subclinical CSVD increases the risk of stroke (first or recurrent) and mortality.[46,47] Our previous CSVD-related stroke cohort showed that although the first-year mortality was very low (5.3%), the 5-year cumulative mortality of CSVD-related stroke increased to 21%, which was similar to the long-term mortality observed in stroke associated with intracranial atherosclerotic diseases.[47] A greater burden of CSVD (eg, high WMH volume) predicted mortality in the long term.[47]

Cognitive impairment

Even in the absence of overt stroke, sporadic CSVD can associate with varying severity of cognitive impairment, from subtle impairment to frank dementia. Cognitive impairment is probably the commonest manifestation of sporadic CSVD. Using DTI MRI, the CU-RISK (The Chinese University of Hong Kong — Risk Index for Subclinical Brain Lesions in Hong Kong) community study showed that CSVD probably accounts for at least partially to the subtle cognitive decline that is related to aging.[4] The

cognitive impairment associated with CSVD is typically of the "subcortical" type, which is characterized by slow processing speed, executive dysfunction, and reduced attention span (often mixed with some degree of apathy, depression, or slow motion), as the frontal-subcortical circuits that are responsible for these cognitive domains are disrupted by the subcortically located CSVD lesions.[4,48] Of further note is that the memory or recall problem associated with CSVD commonly shows an improvement with cueing and the subject performs better on recognition task than on free recall. Hence, cognitive assessment for CSVD should incorporate tests that are sensitive to processing speed, executive function, and/or attention (eg, digit symbol modalities test, digit span, verbal fluency, trail making test, abstraction) and memory task should include delayed recall with cueing or recognition task.[49-51]

In general, the association between CSVD and severity of cognitive impairment is associated with the following factors[8]: (1) Severity of CSVD, which is manifested by increasing WMH extent, number of lacunes, cerebral microbleeds, or cortical microinfarcts, types of CSVD markers, disruption of white matter microstructural integrity (ie, DTI measures), and BBB leakage[1,48,52-56]; (2) Site of CSVD involvement (eg, WMH involving corpus callosum, corona radiata, posterior and left anterior thalamic radiation, forceps minor; strategically located infarcts as described in the sections above)[42,57,58]; (3) Disruption of brain network connectivity[59]; (4) Concurrent severity of regional or global brain atrophy (eg, cortical or frontal gray matter atrophy)[60]; and (5) The concurrent presence of other dementing pathologies (eg, AD).[61,62] Similar factors also increase the risk of a more rapid cognitive decline.[33,35,63-67]

One must note that cognition in CSVD can decline in a progressive manner even in the absence of concurrent AD pathology or overt stroke.[62,65] Using *in vivo* Pittsburgh Compound B PET, the VITATOPS-MRI substudy showed that the cognitive decline of the majority (90%) of severe CSVD patients occurred in the absence of significant amyloid burden.[65] Based on our previous randomized controlled study where we recruited CSVD patients with dementia (ie, subcortical vascular dementia), 30% did not have any history of stroke despite their neuroimaging revealed high burden of WMH and lacunes.[68]

In the context of stroke, the CU-STRIDE study showed that the presence of severe subclinical CSVD (eg, severe WMH) increases the likelihood of early onset dementia after stroke.[62] Note further that CU-STRIDE also showed that engagement of healthy lifestyle pre-stroke (intellectual and physical exercise) was associated with reduced risk of early onset dementia after stroke, suggesting that good cognitive reserve may protect the individual from developing dementia after a vascular injury.[69] While for patients who survive stroke without early onset dementia, severe CSVD (eg, severe WMH, multiple lacunes) also increases the risk of delayed-onset dementia.[64]

In the context of AD, the presence of CSVD also increases the risk of clinical manifestation of dementia in subjects with AD pathology[70] and in the presence of cerebrovascular lesions, less burden of AD pathology is required to induce a dementia syndrome.[71] In those with mild cognitive impairment, it increases the risk of conversion to AD with dementia.[72-74] In patients with AD dementia, CSVD is associated with worse cognitive performance and more rapid cognitive decline.[75,76] Indeed, pathological studies showed that CSVD is highly prevalent in patients with AD, and mixed dementia (ie, cerebrovascular disease plus AD) rather than pure AD or vascular dementia, is the commonest type of dementia in older people.[77,78] In addition, as mentioned earlier, recent work from our group[6] and other clinical studies have suggested a causative role of CSVD in AD.[79-81] However, other studies failed to find such an association.[82,83] Overall, population studies showed that the presence of CSVD increases the risk of incident vascular or Alzheimer dementia.[46,63,84]

Others

Apathy and depression are the two most commonly observed behavioral disturbances in patients with CSVD because these behaviors are mediated by frontal-subcortical regions.[85-87] Impact of these behavioral disturbances could not be underestimated as studies found that it is associated with increased disability and mortality in stroke patients.[88-90] Our group also found that the risk of suicide was mediated by apathy, further highlighting the clinical relevance of these behavioral issues in patients with stroke/CSVD.[91] Other behavioral problems that are commonly seen in AD with dementia may also occur in CSVD with dementia, including emotional lability, disinhibition, agitation, aberrant motor behavior, and sleep disturbance. We previously reported that CSVD lesion (eg, microbleeds) when located in the pons might be associated with emotional lability, highlighting the role of the brainstem in mediating emotional lability as well.[92] Note, however, that psychotic symptoms (ie, delusion, hallucination) are less common in CSVD with dementia relative to AD with dementia because regions responsible for psychotic symptoms (parieto-occipital regions) are in general less affected by CSVD.[87]

Other clinical manifestations associated with CSVD include parkinsonism and urinary incontinence.[93,94] Again, frontal subcortical tracts are also responsible for these motor and sphincter functions. The Parkinsonism associated with CSVD typically involves the lower body (eg, small step gait, slow speed, freezing, postural instability), and resting tremor is less often present in CSVD-related Parkinsonism when compared with idiopathic Parkinson disease (PD). In addition, there is usually minimal or no response to levodopa in CSVD-related Parkinsonism. In a situation where differentiation between idiopathic PD and CSVD-related Parkinsonism is required, dopamine transporter imaging (eg, dopamine transporter single-photon emission computerized tomography) may help.[93] As for urinary incontinence, it usually presents at a more advanced stage of the disease.[13,95]

With more diffuse and advanced CSVD, bilateral corticobulbar tracts may be damaged, leading to the development

of pseudobulbar palsy (dysarthria, dysphagia, reduced facial, and tongue movements). Overall, a full-blown severe CSVD syndrome may include impairment in multiple mental and bodily functions, leading to functional decline and mortality (ie, Binswanger's disease).[13] Common causes of death may include stroke (in particular ICH), coronary heart disease, and pneumonia.[46,47]

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Conflicts of interest

None.

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