MRI features of Binswanger's disease predict prognosis and associated pathology

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Abstract

Objective: To identify the prevalence of MRI features of Binswanger’s disease (BD), specifically MRI with diffuse white matter lesions and scattered multiple lacunes (BD-MRI), and to describe neurological features and pathological outcomes of a community-based cohort study. Methods: Of 697 participants (all 75 years old), 503 completed neurological examinations at baseline and were followed-up every 30 months thereafter with MRIs, the mini-mental state examination (MMSE) and the Unified Parkinson Disease Rating Scale-Motor Section (UPDRSM). Data from participants with BD-MRI were compared with those from participants with predominant white matter lesions (WML-MRI), scattered multiple lacunes (ML-MRI), or normal MRIs. Results: Fourteen BD-MRI patients (2.8%) were detected at baseline. The mean MMSE scores in the BD-MRI, WML-MRI, ML-MRI, and normal MRIs groups were 26.4, 28.2, 28.4, and 28.5, respectively, and the mean UPDRSM scores were 9.1, 1.3, 3.1, and 1.7, respectively. At the 30-month follow-up, mortality rates in the normal MRIs, WML-MRI and ML-MRI were 4%, 9.1%, and 22.2%, respectively, and follow-up MRIs were available for 80%, 82%, and 61% of the participants, respectively. In the BD-MRI, however, five patients were deceased, and only five follow-up individual MRIs were available (33.3%). Autopsies were performed on six of eight BD-MRI brains, and these brains fulfilled the pathological criteria for BD independent of Alzheimer disease pathology. All these six individuals also showed systemic atherosclerosis and renal arterio-arteriolosclerosis. Interpretation: The BD-MRI participants had poor prognoses and showed pure BD pathology with advanced systemic vascular disease. BD-MRI appears to be a predictor of vascular neurocognitive impairment.

Introduction

Vascular dementia (VaD) is the second most common cause of dementia after Alzheimer’s disease (AD). VaD is classified into subcortical VaD, cortical VaD, and strategic single infarct dementias.1,2 VaD comprises heterogeneous vascular pathologies that have been classically linked to small vessel and large vessel diseases.3 Cerebrovascular diseases underlying VaD comprise the majority of small vessel diseases, and the rest being large vessel diseases.4 Binswanger’s disease (BD), a major subtype of subcortical VaD, is caused by hypertensive lipo- and fibrohyalinosis

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of cerebral small vessels, and it leads to widespread diffuse white matter lesions (WML) and scattered multiple lacunes.\(^5\)\(^-\)\(^8\) The cognitive and clinical features of the BD defined the impairment of attention, volition and executive function as well as the impairment of memory and emotions. Evidence of focal cerebrovascular disease and subcortical cerebral dysfunction (for example, vascular parkinsonism, pseudobulbar palsy or a history of incontinence secondary to a spastic bladder) is also associated.\(^5\)\(^-\)\(^7\)

In a long-term follow-up study of our hypertensive patients with lacunar infarct, concomitant diffuse WML were independent predictors for subsequent development of dementia, while multiple lacunes were independent predictors for vascular events.\(^9\) However, it remains unknown whether BD, multiple lacunar state, and diffuse WML are merely a disease process or different categories of small vessel disease, and whether their clinical profiles and brain pathologies are sufficient for vascular neurocognitive impairment.

This study aims to identify the prevalence of MRI features of BD, specifically diffuse WML and scattered multiple lacunes (BD-MRI), to compare the BD-MRI findings with the MRI finding of predominant WML (WML-MRI) and predominant lacunar state with a scattering of more than five lacunes (ML-MRI), and to describe the differences in the clinicopathological features and long-term outcomes between these three subtypes in a community-based birth cohort investigation (The Vienna Trans-Danube Aging Study).\(^10\) In this study, we performed the major cognitive and neurological examinations at baseline and at follow-ups every 30 months thereafter. Pathological outcomes were followed for up to 90 months using the pathological diagnostic criteria for BD.

**Methods**

**VITA study**

The Vienna Trans-Danube Aging Study (The VITA study) is a prospective cohort study of aging and dementia since 2000 organized by the Ludwig Boltzmann Institute of Aging Research and Danube Hospital. It was approved by the appropriate ethics committee. The participants were all 75-year-old inhabitants of the 21st and 22nd districts of Vienna, an area on the east shore of the Danube River. A total of 1920 individuals (765 males and 1155 females) who were born between May 1925 and June 1926 were identified; the birth data were extracted from official voting registries. At baseline, we investigated 697 inhabitants who agreed to participate, of whom 503 completed extensive neurological examinations, including MRI, the minimal state examination (MMSE), trail-making tests A and B, the Unified Parkinson Disease Rating Scale-Motor Section (UPDRSM), the Alzheimer’s Criteria test from the National Institute of Neurological and Communicative Disorders and Stroke, and the Alzheimer’s Disease and Related Disorders Association (ADRDA criteria). The data from participants with BD-MRI were compared with those from individuals with other small vessel disease subtypes (either WML-MRI or ML-MRI) and from individuals with normal MRI. The term “small vessel diseases” encompasses a range of features that are visible on brain imaging, including lacunar infarcts, ischemic WML, microbleeds, and enlarged perivascular spaces.\(^4\) MMSE, trail-making tests A and B, and UPDRSM and ADRDA criteria were performed after 30 and 60 months of follow-up and were compared with baseline data. The prognoses in each small vessel disease groups and in the AD and normal MRIs groups were also evaluated after 30, 60, and 90 months of follow-up.

**Neuroradiological assessment**

The MRI scan was performed using a 1.0-T unit (Siemens Impact Expert; Siemens Medical Systems, Inc., South Iselin, NJ) with a circular polarized skull coil. The following sequences were obtained: transverse proton density and T2-weighted Turbo Spin Echo, and coronary T1-weighted gradient echo sequence. The images were independently assessed by two experienced neurologists (I. A. and Y. S.). The severity of WML on MRI was evaluated from grade 0 to 4 as follows: 0, absent; 1, punctuate; 2, early confluent; 3, confluent; and 4, diffuse.\(^11\),\(^12\) The severity of the lacunar state was rated from grade 0 to 3 as follows: 0, zero lacuna; 1, one to two lacunes; 2, three to four lacunes; and 3, more than five lacunes.\(^7\),\(^8\) The MRI criteria for BD-MRI were defined as diffuse WML with a severity score of 3 or 4 with a scattering of multiple lacunes (more than five). The MRI criteria for ML-MRI were defined as a scattering of lacunar infarcts (more than five) and WMLs with a severity score of 0 or 1. The criteria for WML-MRI were defined as predominant WML with a severity score of 3 or 4 and a severity of lacunar state from 0 or 1. AD patients were diagnosed based on interview assessments and NINCDS ADRDA scores of typical of probable AD.\(^13\) For these small vessel disease groups and AD, we performed longitudinal neuroradiological examinations at baseline and at follow-ups every 30 months thereafter.

**Neuropathological assessment**

Six BD-MRI brains were available for autopsy study during the 90 months of follow-up and were evaluated based on diagnostic criteria for BD pathology (Akiguchi & Budka).\(^14\),
and AD pathology (Braak & Braak, Consortium to estab-
lish a registry for Alzheimer’s disease [CERAD] and
NIA-Reagan criteria15–16). The following pathological
diagnostic procedures and staging criteria were used for
BD brains.
1 Stainings: (A) always done: (1) hematoxylin–eosin and
Kluver-Barrera stains, (2) Elastica van Gieson
stain, and (3) Bielschowsky stain. (B) Optionally done: (1) HLA-
DR or CD68 immunohistochemistry for activated
microglia, (2) amyloid precursor protein (APP)-immuno-
histochemistry for axonal damage, and (3) amyloid
staining (Congo Red or Aβ to exclude amyloid vascul-
opathy).
2 Diagnostic items: (A) subcortical and periventricular white
matter rarefaction, stages, 0 = none, 1 = mild/focal,
2 = moderate/focal, 3 = severe/fronto-parietal, 4 = diffuse.
Supporting features (if all are present = raise one stage),
1 = clusters of HLA-DR/CD68-positive microglia, 2 =
clusters of APP-positive axons, and 3 = Strategic fiber bun-
dle lesions17 (capsular genu/anterior thalamic peduncle or
temporal stem). (B) Multiple lacunes: stages 0 = none,
1 = 1–2 lacunes in total, 2 = 3–4 lacunes, 3 = 5 or more
lacunes. Supporting features (if all are present = raise one
stage), 1 = clusters of HLA-DR/CD68-positive microglia
around the perivascular space, 2 = Clusters of APP-positi-
ve axons around perivasular space, and 3 = incomplete
lacunes/micro-infarcts.8,18 (C) Small/large vessel diseases
(lipo- and fibro-hyalinosis in medullary arteries and ath-
ersclerosis in basal brain arteries), stages, 0 = none,
1 = mild, 2 = moderate, 3 = severe.
3 Excluded items: (A) chronic major arterial occlusion.
(B) Other causes of ischemic diffuse WM diseases (e.g.,
cerebral amyloid angiopathy, cerebral autosomal domi-
nant arteriopathy with subcortical infarct and leukoen-
ccephalopathy, etc.).
4 Staging criteria: (A) pathological staging criteria for
definitive BD required stage 3 for small/large vessel dis-
eases, and either stage 4 for white matter rarefaction
with more than stage 2 for multiple lacunes or stage 3
for both white matter rarefaction and multiple lacunes.
Probable BD required stages 3 or 4 for white matter
rarefaction with multiple lacunes stages 1 or 2 (Fig. 1).
(B) The staging criteria used for the lacunar state
and ischemic leukoencephalopathy are also shown in
Figure 1.

Statistical analysis
The differences in the UPDRSM and MMSE scores and
mortality rates between the small vessel disease groups
and normal MRIs were analyzed using ANOVA with mul-
tiple comparisons. A P < 0.05 was considered to be statis-
tically significant.

Results
Baseline studies and outcome after
30 months of follow-up
Table 1 shows prevalence, baseline major cognitive and
neurological studies and mortality rate after 30 months
follow-up in participants with BD-MRI and related small-
vessel diseases. Fourteen patients with BD-MRI (2.8%),
20 with WML-MRI (4.0%), 23 with ML-MRI (4.6%), and
112 with normal MRIs (22.3%) were detected at baseline.
Two observers (I. A. and Y. S.) reviewed the MRI record-
ings using a set of independent images from all partici-
pants of this study blinded to their clinical information.
Inter-observer agreements for MRI diagnosis of BD-MRI
between two observers from 57 participants with three
small vessel disease groups were 91.2%.

The mean MMSE in the BD-MRI, WML-MRI, ML-
MRI, and normal MRIs groups were 26.6, 28.1, 28.2, and
28.6, respectively, and the mean UPDRSM scores were
8.9, 1.3, 4.4, and 1.9, respectively. The mean trail-making
test A and B in the BD-MRI, WML-MRI, ML-MRI, and
normal MRIs groups were 62.2 and 219.8 sec, 51.2 and
192.6 sec, 64.9 and 175.1 sec, and 48.3 and 159.4 sec,
respectively. MMSE scores in BD-MRI group were signifi-
cantly lower compared with those in the normal MRIs,
WML-MRI, and ML-MRI groups (P < 0.05). The UP-
DRSM score in the BD-MRI group was significantly
higher compared with those in the normal MRIs and
WML-MRI groups (P < 0.05). Longer mean performance
time in trail-making test A and B were also prominent
features of BD-MRI as well as other small vessel disease
groups compared to normal MRIs, however, there were
no significant differences between these groups. The fre-
quency of gait disturbance in the BD-MRI group was

Figure 1. Staging and pathological diagnostic criteria for BD, lacunar
state, and ischemic leukoencephalopathy (Akiguchi & Budka). BD,
Binswanger’s disease.
greatest (38.5%) in the small vessel diseases and normal MRIs groups.

After 30 months of follow-up, mortality rates in the WML-MRI, ML-MRI, and normal MRIs groups were 9.1%, 22.2%, and 4%, respectively, and follow-up MRIs were available for 82%, 61%, and 80% of individuals, respectively. In the BD-MRI group, five patients were deceased (33.3%), and only five follow-up MRIs were available, for which all MRI features shows deteriorating WML scores and lacunar states. The mortality rate was significantly higher in the BD-MRI group compared with those in the WML-MRI and normal MRIs groups (P < 0.05).

Assessments after 30 and 60 months and mortality rate at 90 months

Table 2 shows UPDRSIII, MMSE, and ADRDA criteria at baseline and after 30 and 60 months of follow-up in BD-MRI participants. UPDRSIII gait and total performance scores worsened for all BD-MRI individuals during follow-up. MMSE scores worsened or could not be examined in six of eight BD-MRI participants.

Eight of 14 BD-MRI patients (57.1%), nine of 18 AD patients (50%) and six of 23 ML-MRI patients (26.1%) were deceased by the 90-months follow-up. Only two deaths occurred in the WML-MRI (10%), and 11 of 75 (14.7%) patients died in the control groups. The mortality rate in the BD-MRI group was significantly higher compared with those of the normal MRIs, WML-MRI, and ML-MRI groups (P < 0.05).

Thus both the 30-month and 90-month prognoses for the BD-MRI group were extremely poor. The 90-month prognoses for other small vessel disease categories (i.e., WML-MRI, and ML-MRI), were not as poor, and those of the AD group were also poor, second to the BD-MRI group.

Table 1. Prevalence, baseline studies and mortality rate in BD-MRI and related small-vessel diseases.

| Prevalence at baseline | UPDRSSMS | MMSE | Gait disturbance | Mortality rate at 30 months |
|------------------------|----------|------|------------------|---------------------------|
| Normal MRIs            | 112 (22.3%) | 1.87 ± 2.74 | 28.6 ± 1.17 | 5.1% | 4% |
| BD-MRI                 | 14 (2.8%) | 8.92 ± 0.3* | 26.6 ± 2.40** | 38.5%** | 33.3%* |
| ML-MRI                 | 23 (4.6%) | 4.36 ± 7.47 | 28.2 ± 1.50 | 13.6% | 22.2% |
| WML-MRI               | 20 (4.0%) | 1.25 ± 2.07 | 28.1 ± 1.41 | 10.0% | 9.1% |

Statistically significant compared with normal MRIs and WML-MRI groups (*P < 0.05), and compared with normal MRIs, WML-MRI, and ML-MRI groups (**P < 0.05), respectively.

Table 2. Baseline and 30- or 60-months follow-ups and autopsy results in BD-MRI participants.

| Case/sex | Outcome | UPDRS gait | UPDRS motor | MMSE | ADRDA | Autopsy (1)\(^1\) Macroscopic findings | Autopsy (2)\(^2\) BD pathology | Autopsy (3) AD pathology |
|----------|---------|------------|-------------|------|-------|--------------------------------------|-----------------------------|--------------------------|
| 1F BL/N/D | --/-- | --/-- | --/-- | 28/0 | 0/0 | Acute basilar thrombosis, SA, RAS, ren-artery infarction | None |
| 2M BL/D | 2 | 27 | 29 | 0 | | 25/0 | 1/0 | 1/0 | Pneumonia, AHF, SA, RAS, contracted kidney |
| 3F BL/N/N | --/-- | --/-- | --/-- | 25/0 | 1/0 | | |
| 4F BL/N/N | 0/0 | 0/0 | 0/0 | 29/0 | 0/0 | | |
| 5F BL/D | 1 | 17 | 21 | 1 | No brain |
| 6F BL/N/N | --/-- | 8/0 | 27/25/24 | 0/0 | | |
| 7M BL/D | 0 | 7 | 26 | 0 | No brain |
| 8M BL/D | 2 | 30 | 24 | 0 | | |
| 9M BL/N/N\(^3\) | 0/0 | 2/0 | 26/0 | 0/0 | | | |
| 10F BL/N/D | 1/0 | 7/0 | 29/0 | 0/0 | | | |
| 11F BL/F/F | 0/0 | 2/5/8 | 27/27/28 | 0/0 | | | |
| 12F BL/F/F | 0/0 | 0/0 | 29/30/30 | 0/0 | | | |
| 13F BL/F/N | 0/0 | 0/0 | 4/23/0 | 25/27/0 | 0/1 | | |
| 14M BL/D | 0 | 3 | 29 | 0 | | | |

BL, baseline; F, followed up/tested; N, not tested (home visit, telephone interview, or refusal), D, died.
\(^1\)SA, systemic atherosclerosis; RAS, renal arterio-arteriolosclerosis, AHF, acute heart failure, CS, coronary sclerosis.
\(^2\)W3, L3, V3, white matter rarefaction: stage 3, lacunar state: stage 3, and small/large vessel diseases: stage 3.
\(^3\)Died between the 60- and 90-months follow-ups.
\(^4\)Associated AGD Stage III and mild Lewy-body pathology.
Autopsy findings

Autopsies were performed on six of eight BD-MRI brains. All these six individuals showed systemic atherosclerosis, renal arterio-arteriolosclerosis and renovascular or cardiovascular lesions. All six brains fulfilled the diagnostic criteria for BD: three of six brains, pure BD pathology; two brains, BD pathology with low-intermediate likelihood AD pathology; one brain, both latter pathologies with argyrophilic grain disease. The autopsy summaries for the six BD-MRI (case numbers 1, 2, 8, 9, 10, and 14) and MRIs at baseline and pathological findings of the three BD-MRI brains with pure BD pathology (case numbers 1, 2, and 14) are shown in Table 2, Figures 2 and 3.

Discussion

BD is characterized pathologically by a combination of diffuse WML and lacunar infarcts in the basal ganglia and white matter. The vascular mechanisms underlying BD and subcortical VaD are likely chronic cerebral ischemia caused by both hypertensive lipohyalinotic small artery disease/arteriolar-capillary fibrohyalinosis6,8,19 and intracranial arterial dolichoectasia/dilatative arteriopathy,20 which may ultimately cause multiple lacunes in the basal ganglia and the white matter and diffuse WML by altering glia and axons.8,21 In BD brains, we previously demonstrated that cerebrovascular WML were associated with compromised axonal transport and blood–brain barrier...
function, regressive changes in astroglia, frequent infiltra-
tion of T lymphocytes, and activated microglia.\(^8\),\(^{22}\) How-
evertheless, the prognoses and pathological outcomes of MRI
features of BD such as diffuse WML with multiple lacun-
es have not yet been revealed.

Subcortical VaD and BD have long been considered
rare; however, because of the relatively high prevalence of
VaD and its treatable causes, such as nocturnal hyperten-
sion and chronic kidney disease, increasing attention has
been paid to subcortical VaD/BD not only in Europe and
Japan, but also in North America.\(^{1,6,8,23-27}\) In our cohort
study of 75-year-old individuals, the prevalence of BD-
MRI was 2.8%, which was two-thirds the rate of probable
AD based on ADRSA criteria (4.0%). Thus, our study, in
agreement with data from Japan,\(^{23,24}\) confirms a quite
high prevalence of BD features on MRI in a Western
community. However, there is considerable disagreement
on the epidemiology and prevalence of VaD and subcorti-
cal VaD/BD. In clinical studies, the prevalence of VaD
ranges from 4.5% to 39%, and in Western memory clinic-
and population-based series, the mean are between 8%
and 15.8%, with standardized incidence rates of between
0.1 and 2.68, which increase with age.\(^{28,29}\) VaD composes
heterogeneous vascular pathologies that have been classi-
ically linked to small vessel and large vessel diseases.\(^3,4\)
It has recently been proposed that patients with subcortical
VaD/BD, the majority of which arises from small vessel
disease, represent a highly prevalent 57.4% of VaD in autops-
y series from demented elderly individuals in Aus-
tria and 51.3% of VaD in Japan,\(^{23,24}\) and comprise a rela-
tively homogeneous group.\(^8,24\)

In addition, the prognosis for BD-MRI in our study
was extremely poor, based on the high, one-third mortal-
ity rate by 30 months, and the low, one-third follow-up
MRI study rate, for which all MRI features deteriorated at
the 30-months follow up. More than half of BD-MRI par-
ticipants were deceased by the 90-months follow-up. Frisoni et al. also noted that ~30% of patients in a memory clinic with mild cognitive impairment of the vascular type died during the follow-up period at an aver-
age of 33 months. However, less information was pre-
tended to enable identification of the clinical course and pathological outcome.\(^{30}\) Melkas et al. showed that in
an ischemic stroke cohort with ultra-long (12-year) follow-
ups, acute index stroke attributable to cerebral small
vessel disease was associated with worsened long-term
survival and a higher risk of cardiac death than other stroke subtypes due to large vessel diseases.\(^2\) Limitations,
however, were imposed by the authors’ use of a risk-fac-
tor based stroke classification and a selection bias of only
using hospitalized patients.\(^3\) It is clear that small vessel
diseases tend to slip through conventional stroke classifi-
cations, particularly in early stages of illness, because these
diseases occur incidentally and without overt manifesta-
tions. Thus, a longitudinal epidemiological cohort study
is required to attempts to clarify the true clinical profile
and outcome of cerebral small vessel diseases. In subcorti-
cal VaD/BD patients, concomitant chronic kidney disease,
 systemic vascular disease, cardiac insufficiency, and a hy-
percoagulation state may further accelerate their poor
prognosis.\(^8,26,31,32\)

The neuropsychological assessment used during this
study are very limited, however, BD-MRI individuals
showed significantly lower MMSE as well as higher UP-
DRSM scores compared with those suffering from other
small vessel diseases and controls. BD-MRI also showed
longer performance time in trail-making tests, which cor-
respond to deteriorated executive function in cognitive
domains. In contrast to recently refined pathological cri-
eria used for the diagnosis of AD and other degenerative
dementias, no validated pathological criteria for the VaD
brain have been established thus far.\(^{28}\) Because of the high
variability in pathological findings and the multi-factorial
pathogeneses,\(^33,34\) it is difficult to establish generally
accepted morphologic schemes for quantifying vascular
brain injury in VaD.\(^28\) Thus, we focused on pathological
staging and criteria for BD brains that are assumed to
show relatively homogenous small vessel disease
pathology. In proposing a new pathological staging for
BD-related cerebral small vessel disease, we refer to the
following publications: (1) the grading scheme for small
vessel disease\(^{35}\); (2) the scoring system for small vessel-
associated disease\(^{36}\); and (3) the cerebrovascular disease
pathology-scoring system.\(^{37}\) Briefly, scoring systems in (1)
and (2) consider whether pathology of the perivascular
space exists. Gliosis, perivascular pallor, hyaline thick-
ing, nerve fiber loss, and multiple lacunes must also be
evaluated. The scoring system in (3) quantifies hippocam-
pal sclerosis rather than pathology of the perivascular
space.

The functional anatomy and pathophysiological basis
of impaired cognitive function of the following items in
BD brains must also be considered in pathological diag-
nostic criteria. Impairment of attention, volition and
executive function are of paramount importance. The
underlying associated structures are the ascending reticu-
lar formation including anterior thalamic peduncle/capsu-
lar genu,\(^15\) nonspecific and specific thalamic nuclei and
the frontal subcortical circuits.\(^38,39\) These structures are
primarily involved in diffuse frontal/parietal WM raref-
tions because of hypertensive small vessel disease/chronic
cerebral hypoperfusion and small infarcts in the thalamus
and the related fiber bundle lesions.\(^17,39\) Impairment of
memory and emotions may also be reflected in evalua-
tion of BD pathology. The underlying associated struc-
tures include the limbic system (hippocampal complex,
amygdala, and temporal stem), the anterior and dorsomedial thalamic nuclei and other structures in the Papez and the basolateral limbic circuits. These structures are primarily involved in lacunes, branch atheromatous diseases, hippocampal sclerosis, and fiber bundle lesions related to these structures. Macro-pathological involvements in these structures and micro-cellular pathologies because of hypertensive small vessel diseases and chronic hypoperfusion (including microinfarcts, perivascular space pathologies, axonal damage, and immune-inflammatory responses) are essential for estimating pathological diagnosis scores.

Our recent in vivo neuroimaging studies revealed several possible measures for discrimination between AD and BD brains such as different topographic patterns of brain atrophy in voxel-based morphometry, absolute quantification of N-acetylaspartate in proton magnetic resonance spectroscopy, and different profile of hippocampal metabolites measured by proton magnetic resonance spectroscopy. In this prospective cohort study, we confirm the existence of “pure” BD pathology, and all six BD-MRI brains available for autopsy fulfilled our pathological diagnostic criteria for BD (three of six brains, pure BD pathology; two brains, BD pathology with low-intermediate likelihood of AD pathology; one brain, both BD and AD pathologies with argyrophilic grain disease). Moreover, all these six individuals showed systemic atherosclerosis, renal arterio-arteriolosclerosis and renovascular or cardiovascular lesions. Jellinger et al. observed 12.3% “pure” VaD (because of cerebrovascular disease without other concomitant pathologies; neuritic Braak stages 1.2–1.6) in 1700 retrospective hospital-based autopsy cases of demented elderly individuals in Austria. In the Honolulu Asia Aging Study, Launer et al. also stressed that the burden of vascular lesions and AD-type lesions are independent, and are consistent with an additive effect of the two lesion types on cognitive impairment. However, MRI used to acquire baseline and follow-up data in this study was a 1.0 T, which is not the gold-standard for imaging research and is associated with a very low signal-to-noise image. Further study will be necessary to clarify the significance of MRI-based markers of small vessel diseases in prognosis and pathological outcome of VaD using higher field strength (3 T or 7 T).

In summary, we compared the clinical profiles of BD-MRI cases with diffuse WML and multiple lacunes, participants with predominant WML and those with predominant lacunar state. These three MRI subtypes of cerebral small vessel diseases showed different clinical features at baseline and in the prognoses at long-term follow-up. Prognosis of BD-MRI is highly poor and showed corresponding BD pathology independent of AD pathology, and advanced systemic vascular disease at autopsy.

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Author Contributions
Dr Ichiro Akiguchi – Study concept and design, acquisition of data and analysis and interpretation. Dr Yoshitomo Shirakashi – Acquisition of data. Dr Herbert Budka – Study supervision. Dr Adelheid Woerther – Acquisition of data. Dr Toshiyuki Watanabe – Analysis and interpretation. Dr Akihiko Shiino – Analysis and interpretation. Dr Yasumasa Yamamoto – Analysis and interpretation. Dr Yasuhiro Kawamoto – Analysis and interpretation. Dr Susanne Jungwirth – Acquisition of data. Dr Wolfgang Krampla – Acquisition of data. Dr Peter Fischer – Study supervision.

Conflict of Interest
None declared.

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