Neuropathologic Substrates of Ischemic Vascular Dementia

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Abstract. Ischemic vascular dementia (IVD) is a relatively uncommon entity, in the course of which multiple ischemic brain lesions result in progressive cognitive and memory impairment. Ischemic brain lesions may also aggravate the neuropsychologic deficit of Alzheimer disease (AD). In this review we summarize our experience based upon autopsy examination of the central nervous system in 20 patients (age range 68–92 years) enrolled in a longitudinal investigation of structural, neurochemical, functional neuroimaging, and neuropsychologic components of IVD, especially dementia associated with cerebral microvascular disease. While cystic infarcts were present in the CNS of 5 patients, the most commonly observed neuropathologic abnormalities were lacunar infarcts and microinfarcts—both types of lesion were encountered in over half of patients’ brains. Evidence of (remote) hippocampal injury was found in 11/20 patients. Severe atherosclerosis and arterio/arteriolosclerosis were both associated with the occurrence of multiple lacunar infarcts. Pronounced cerebral amyloid angiopathy (CAA) was noted in a single patient, who also showed other microscopic changes of severe AD. While fairly unusual as a nosologic entity, IVD appears to correlate with widespread small ischemic lesions distributed throughout the CNS. We furthermore propose an approach to quantifying the burden of ischemic vascular and parenchymal disease that may be associated with a dementia syndrome. A brief review of neuropathologic features of vascular dementia (both familial and sporadic) is presented.

Key Words: Aging; Arteriosclerosis; Cerebral amyloid angiopathy; Cerebral ischemia; Cerebral microvessels; Vascular dementia.

INTRODUCTION

Alzheimer disease (AD) has, at least since the 1960s, become widely accepted as the most common etiology of presenile or senile dementia (1–5). In most memory clinic-based series, cerebrovascular disease is considered to be the cause of dementia in no more than 8%–10% of affected patients (6). While neuropathologic criteria for AD and other primary parenchymal dementias have, over recent decades, been debated, defined, and refined (7–10), morphologic substrates of dementia resulting from cerebrovascular disease remain controversial and confusing, in part because they are so variable from case to case (11–13). Furthermore, the pathogenesis of ischemic vascular dementia (IVD) is intimately intertwined with that of cerebrovascular disease itself. The burden of cerebrovascular disease in the elderly may worsen mild AD-related dementia or accelerate its progression, i.e. co-morbidity from AD and cerebrovascular disease (whether as ischemic infarcts or CNS parenchymal hemorrhage) is an expected complication of advancing age (14–16). Furthermore, since cerebrovascular disease is currently more readily prevented (by modification of risk factors) or treated than is AD, understanding its contribution to a “mixed dementia” may provide significant insights into decreasing the massive burden of cognitive decline in the elderly population.

This paper describes neuropathologic findings in 20 patients who were the first to undergo autopsy in a longitudinal clinicopathologic study of ischemic-vascular dementia (IVD) that has been ongoing in California since 1994. The emphasis of this study has been on subcortical IVD (SIVD). Specific questions related to these autopsies included: 1) Do patients labeled clinically as having IVD show significant AD neuropathologic change with only a minor pathological component of cerebrovascular disease? 2) Assuming IVD is a “true entity,” what are its morphologic substrates in terms of both (a) vascular disease, and (b) resultant brain injury—and how is this injury best assessed using morphologic tools? 3) What is the contribution of (ischemic) hippocampal injury to AD or IVD? 4) How might ischemic brain lesions associated with IVD realistically be quantified and their evaluation standardized, facilitating correlations between neurobehavioral, clinical, or neuroimaging variables and morphologically defined brain lesions?

We will use the observations made in this highly selected group of patients to discuss the broader literature pertinent to IVD and mixed parenchymal/vascular dementias. Portions of this data have previously been presented in abstract and summary form (17–19).
MATERIALS AND METHODS

Twenty autopsies constitute the basis for this neuropathologic investigation. All patients were followed as part of a longitudinal investigation of structural, chemical, and functional neuroimaging, neuropathological and morphologic substrates of dementia in subcortical ischemic vascular disease (SIVD). Results of some of these investigations have been published (20–22). Upon enrollment, all patients had been assigned to one of several diagnostic categories, based upon clinical evaluation and neuroimaging. These categories were defined by the presence of cognitive dysfunction (D = demented), CI = cognitively impaired, CN = cognitively normal) and lacunes, as follows: D = demented, D + L = demented with lacunar infarcts, CN + L = cognitively normal with lacunar infarcts, and CI + L = cognitively impaired with lacunar infarcts. Three additional patients followed as controls have also been studied at autopsy.

Autopsy Procedures

Autopsies on all patients were carried out at either the Northern California (UC Davis) or Southern California (USC-Rancho Los Amigos National Rehabilitation Center) clinical sites in such a way as to minimize postmortem autolysis times. Tissues were subsequently reviewed independently at the Neuropathology Core for this project (UCLA Medical Center). In all cases, fixed brains were sliced coronally at 0.5 cm thickness using a rotary slicer, and then all slices were photographed using a digital camera. Areas of the brain blocked for histologic staining were recorded by photocopying the brain slice with an overlying slide, the latter used as an indicator of sites sampled. (A piece of cellophane was placed under the slice in order to prevent contamination of the photocopy machine.)

In both Northern and Southern California centers, extensive blocking of brains was routinely undertaken in order to ensure sampling of all grossly identifiable lesions, and multiple other regions of cortex, subcortical white matter, and deep central grey structures. The blocking protocol was based upon recommendations of the Consortium to Establish a Registry for Alzheimer disease (CERAD), to allow for Braak and Braak staging, and to optimize the likelihood of establishing the diagnosis of dementia with Lewy bodies (7, 8, 23, 24). Initial evaluation of tissue blocks has included routine (hematoxylin and eosin [H&E]), Congo red, and Bielschowsky staining of hippocampal, transentorhinal and multiple regions of neocortex, as well as sections immunostained using primary antibodies to Abeta protein, tau, ubiquitin and GFAP. Initial neuropathological sign-out of all cases was carried out at the local site, followed by independent re-review of the case at the UCLA Neuropathology Core. A consensus conference involving several of the authors (HVV, WGE, BWZ, HCC, and CZ) was held periodically to discuss neuropathologic findings in all cases and in order to arrive at a standard, consensus neuropathological evaluation and lesion score for each specimen.

All autopsy specimens were reviewed for the following features: 1) Presence and extent of AD lesions, including both diffuse and neuritic senile plaques (SPs), neurofibrillary tangles (NFTs), and cerebral amyloid angiopathy (CAA). 2) Presence of other parenchymal lesions that may indicate the presence of a non-AD dementia, e.g. Lewy body disease (LBD) (23, 24). 3) Severity and extent of atherosclerosis of the basal arteries, arteriosclerosis/lipohyalinosis (2, 25) of small parenchymal and meningeal arteries and arterioles, and CAA (see below). 4) Topography and extent of encephalomalacic lesions within brain parenchyma—arbitrarily classified as cystic infarcts (1 cm or larger in greatest dimension), lacunar infarcts (26–29) (cystic infarcts smaller than 1 cm in greatest dimension), and microinfarcts (by definition, lesions not visible on gross examination of the brain slices but apparent on subsequent microscopic review of the case). 5) Extent of any hippocampal lesions, including selective segmental regions of neuron loss and gliosis, micro- or cystic infarcts.

Severity of basal atherosclerosis was evaluated semiquantitatively on a scale of “0” (absent) to 4+ (occlusion of at least 1 basal artery). Widely used guidelines allowing for semiquantitative evaluation of arteriosclerosis/lipohyalinosis (AS/LH) do not, to the authors’ knowledge, exist, and therefore this was assessed semiquantitatively as being absent (“0”) to severe (3+) (good interobserver agreement on scoring of both atherosclerosis and AS/LH was noted at the time of each consensus conference). Severity of CAA was evaluated using the criteria of Vonsattel et al (30); presence or absence of CAA-associated microangiopathies (CAA-AM) (31–33)—a change usually identified only in patients with severe degrees of CAA—was documented. The presence of Charcot-Bouchard microaneurysms (34, 35), seen with severe degrees of both AS/LH and CAA, was noted.

For all cases, the presence and “stage” of AD alterations was evaluated using both CERAD criteria (9) and Braak and Braak staging (8) on appropriately stained sections. Vascular and brain parenchymal lesions were tabulated using a “work sheet” that takes into account types and topographic localization of encephalomalacia (see “Discussion” below). The final data presented were those that emerged after consensus conference evaluation of all cases.

RESULTS

The 20 patients (not including the 3 controls) ranged in age from 68 to 92 yr, and included 7 females and 13

<table>
<thead>
<tr>
<th>Patient Category</th>
<th># of Patients</th>
<th>Mean Age (Year)</th>
<th># with Cyst Inf</th>
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<th>Micro- Hippo Inf</th>
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<tr>
<td>D</td>
<td>8</td>
<td>80.9 (5M/3F)</td>
<td>1</td>
<td>1</td>
<td>4</td>
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<tr>
<td>CI</td>
<td>1</td>
<td>76 (M)</td>
<td>0</td>
<td>0</td>
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<tr>
<td>CN + L</td>
<td>4</td>
<td>76.8 (3M/1F)</td>
<td>1</td>
<td>4</td>
<td>2</td>
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<tr>
<td>CN + L</td>
<td>2</td>
<td>77.5 (1M/1F)</td>
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Abbreviations: a, 2 patients in this category had diffuse Lewy body disease (Lewy body dementia). Categories are as follows: D = dementia; D + L = dementia + lacune(s); CI = cognitively impaired; CI + L = cognitively impaired with lacune(s); CN + L = cognitively normal + lacune(s); Cyst Inf = cystic infarct (1 cm maximal size), microinf = microinfarct (not grossly visible in cut brain slice), hippo inj = evidence of hippocampal injury (for details, see text); M = male; F = female.
ISCHEMIC VASCULAR DEMENTIA

Fig. 1. A: Bar graph summarizing age distribution of IVD study patients (not including controls) who were examined at autopsy. B: Graph summarizing frequency of different categories of destructive/encephalomalacic lesions among the 20 autopsy cases. Many brains showed more than 1 type of ischemic lesion. The bar indicated by “1 cm- infarcts” denotes lacunar infarcts.

males. Details of the patients studied, including the types of brain lesions observed, are presented in Table 1. Figure 1A shows the age distribution of study patients; the majority were in the eighth decade of life. Figure 1B summarizes the relative frequency of brain parenchymal lesions among the patients, emphasizing that (a) lacunar and microinfarcts were approximately 2.5 times as common as regions of cystic encephalomalacia, and (b) hippocampal injury or “scarring” of some form (details below) was seen in over half of all study patients. Of the 3 control patients (subjects with no cognitive impairment or lacunes), 2 males of age 80 and 87 yr, and one 74-yr-old
Fig. 2. Regions of cystic encephalomalacia. Photographs show coronal slices of brain oriented with either patient’s left cerebral hemisphere on left of the image (panels A–C) or transposed, i.e., right cerebral hemisphere on left of the image (panels D, E).

A: Coronal section of frontal lobes from fixed brain of a 68-yr-old man in the “D + L” clinical category, showing a large frontal lobe infarct (arrow) that straddles cortex and white matter. B, C: Two coronal brain slices from a 92-yr-old female in the “D + L” clinical category. Panel (B) shows a left medial frontal infarct (arrow), while Panel (C) shows a large right thalamic infarct (arrow) involving the lateral geniculate nucleus. D, E: Patient was a 71-yr-old male in the “CI + L” clinical category. A right hippocampal infarct involving subiculum, presubiculum and CA1 was found (arrow, D); the resultant trans-synaptic degeneration/atrophy of the right mammillary body is shown in panel (E).
Fig. 2. Continued.
female showed severe, though non-occlusive, atherosclerosis, while 2 had moderately severe AS/LH. Only 1 individual in this group had rare cortical microinfarcts; none of the 3 controls showed evidence of lacunar infarcts, cystic encephalomalacia or hippocampal scarring. One of the controls, an 80-yr-old man, died of a massive right cerebral hemispheric infarct. Two of the control patients had negligible AD lesions. However, 1 patient (an 87-yr-old man) had Braak and Braak stage V AD changes, even though clinical and neuropsychological evaluation had found him to be cognitively intact 6 months prior to death.

Cystic (1 cm + size) Infarcts
These were found in 5 patients, and were multiple in all but one. In most cases, they were seen as typical regions of cystic encephalomalacia (Fig. 2) affecting both cortex and white matter, while in 1 individual the infarcts involved primarily white matter. In 1 patient with multiple lesions, they were predominantly in a watershed/borderzone distribution. Two of the 4 patients who manifested large cystic infarcts had occlusive (by our definition, 4+) basal atherosclerosis, and all but 1 showed severe cerebral atheromatous disease, usually with evidence of complicated atheroma (calcification of the plaque, focal intimal ulceration) on histologic sections. In rare patients with severe basal atheroma, even leptomeningeal arteries were affected by intimal fibromuscular hyperplasia, i.e. “microatheroma” (Fig. 3). The patient with predominantly white matter infarcts showed relatively mild basal atherosclerosis but severe cerebral arteriosclerosis/arteriolosclerosis.

Lacunar Infarcts
Lacunar Infarcts (26–29) were found in 12 patients, including all 5 of the individuals who had cystic encephalomalacia. All except 1 had been in a clinical category that included the “L” (lacunar infarct) designation during life, and all but 2 showed either dementia or cognitive impairment (“D” and “CI” categories, respectively). One of the 2 patients with lacunes, but judged to be cognitively normal, showed lacunar infarcts only in the basal ganglia andpons. Lacunar infarcts were widely distributed throughout the brain, including within deep grey matter and subcortical white matter, and frequently also involved cortex. Figure 4 summarizes graphically the relative severity of atherosclerosis and arteriosclerosis among the patients who showed lacunar infarcts.

Microinfarcts
These were as prevalent as lacunar infarcts among the 20 brains examined, and were always multiple and widespread within the brain, involving both cortical and white matter structures. Though usually seen quite readily on routine hematoxylin and eosin-stained sections (Fig. 5), they become especially prominent, and their number easily recognizable, on sections immunostained with primary antibodies to glial fibrillary acidic protein (GFAP) (Fig. 6).

Hippocampal Injury
A common finding among the brains examined (seen in 11/20 patients) was some manner of hippocampal injury, though its neuropathologic substrate was extremely variable. Within this category, we have included lesions that range from cystic encephalomalacia (Fig. 2D) to well-defined regions of segmental hippocampal scarring (e.g. selective, severe neuron loss in the CA1 segment or prosubiculum associated with pronounced gliosis) that resemble hippocampal sclerosis, seen as a common neuropathologic substrate in patients with temporal lobe epilepsy (36).
Fig. 4. Bar graphs showing relationship between severity of atherosclerosis (A) or arteriosclerosis (B) and number of patients with lacunar infarcts (ordinate in each graph). In each graph, the full length of the bar represents total number of brains with that severity of atherosclerosis or AS/LH, while shaded portion of the bar represents number of patients with lacunes. Atherosclerosis and AS/LH were assessed semiquantitatively (see text).

Microvascular Disease

The 2 most common microangiopathies associated with aging are arteriosclerosis (arteriolosclerosis), sometimes also referred to as lipohyalinosis (AS/LH), and CAA (37). AS/LH was of variable severity among the brains examined, but some degree of this microangiopathy (Fig. 7) was noted in 15/20 cases. In severe cases of AS/LH, partial or complete thrombosis of affected arteries was rarely noted (Fig. 8). Charcot-Bouchard type microaneurysms were prominent in 1 patient with very severe
Fig. 5. Cerebral microinfarcts. (All images are from H&E-stained sections). A: Characteristic wedge-shaped indentation of pia and underlying cortex, suggestive of an adjacent glial scar. Arrow indicates a meningeal artery with "double barrel" lumen, suggestive of previous occlusion with recanalization. (Magnification: ×25) B: Similar focus to that shown in (A). Note linear scar (arrows) extending beneath the pial indentation, through the cortical ribbon. (Magnification: ×25). (Panels (A, B) are from brain of an 80-yr-old demented man.) C: Microfocus of cystic encephalomalacia in deep cortex, near the cortex-white matter junction, is filled with histiocytes and surrounded by astrocytes. White matter is at left, cortex at right of the micrograph. Patient was a 78-yr-old female with lacunar infaracts and microinfarcts. (Magnification: ×65). D: Section from brain of a 77-yr-old male with multiple cerebral microinfarcts. Upper arrows indicate deep boundary of a cortical infarct, while lower arrows show preserved overlying molecular layer of the cortex. (Magnification: ×65).

(3+) AS/LH. CAA of some degree was found in only 5/15 cases, and in 4 of those was only mild to moderate in severity (by Vonsattel criteria, see ref. 30). One unusual patient in the “D” category (i.e. demented) showed extremely severe and widespread CAA, including evidence of secondary microvascular injury, CAA-AM including microaneurysm formation (Fig. 9). Of interest, this 84-yr-old female showed a relative absence of large or small destructive parenchymal lesions in the brain, and was thought to have Braak and Braak stage V/VI Alzheimer disease changes at autopsy.

Alzheimer Disease Changes and Other Abnormalities

By Braak and Braak staging, only 5/20 patients showed stage IV or greater disease, including the aforementioned 84-yr-old woman with marked CAA throughout the brain. Eight patients showed negligible “Alzheimerization” even within the transentorhinal and hippocampal cortices, i.e. they were stage 0/I by Braak and Braak criteria. Braak and Braak staging and CERAD evaluation of brains sometimes led to discordant results, probably because of different emphasis on neurofibrillary tangles and neuritic senile plaques in the 2 grading schema (8, 9). Two patients, both males (ages 78 and 79 yr) in the “D” category, showed the (unexpected) neuropathologic finding of widespread diffuse Lewy body disease. One individual, a 75-yr-old male in the “CI + L” category, showed the presence of classic demyelinating plaques of multiple sclerosis, in addition to multiple lacunar infarcts.

DISCUSSION

Though it is now regarded as a much less common etiology for dementia than AD, multi-infarct dementia...
Fig. 6. GFAP immunostaining is especially useful for demonstrating regions of cortical gliosis/microinfarcts, which may be relatively inconspicuous on H&E staining. Section is from same brain as illustrated in Figure 5D. Note the rim of GFAP-immunoreactive cells surrounding a small area of encephalomalacia. (Magnification: ×25).

Fig. 7. The spectrum of AS/LH. Panels (A–D) are from brain of a 79-yr-old male, panel (E) from that of a 68-yr-old man, both with dementia and lacunar infarcts. A: Note hyaline arteriosclerosis and dense adventitial fibrosis (arrows) of basal ganglionic arteries. B: Hyalinization and ectasia of another artery. C: Hyaline thickening and ectasia of parenchymal arteries showing pronounced AS/LH. Arrow indicates a cluster of adventitial lymphoid cells, while arrowhead indicates foamy macrophages in the vessel wall. D: Charcot-Bouchard microaneurysm. Note dilated, tortuous arterial wall segment with abundant surrounding old hemorrhage in the form of hemosiderin and hematoidin. E: Onionskin-type thickening of a parenchymal arteriole. (All panels from H&E-stained sections, Magnifications: A, B, ×65; C, E ×130; D, ×40).
Fig. 8. AS/LH involving leptomeningeal arteries, with partial (A) or complete (B) thrombosis of affected vessels (both panels). Patient was a 79-yr-old male with dementia and lacunes. Note rim of hematoidin around artery shown in panel (B). (Both panels H&E, Magnification: ×65).

Fig. 9. Severe CAA in a patient who also fulfilled neuropathologic criteria for AD. A: Section immunostained with anti-Abeta shows prominent labeling of both leptomeningeal and parenchymal arterioles, as well as subpial Abeta immunoreactivity. (Magnification: ×65). B: Cortical capillaries in several loci were also immunolabeled with anti-Abeta, as shown in this micrograph. (Magnification: ×65). C: Secondary microangiogiopathies found in this brain included frequent microaneurysm formation. Note a Charcot-Bouchard type microaneurysm (arrow) in the subarachnoid space, apparently in continuity with an amyloid-laden arteriole in underlying cerebral cortex (arrowheads). (H&E stain, magnification: ×85).
has been recognized as a nosologic entity for decades, a
time during which its neuropathologic substrate(s) have
been the subject of considerable debate (38–42). In recent
years, several groups have attempted to facilitate research
into dementia associated with cerebrovascular disease by
defining clinical criteria by which it may be diagnosed
(43–46). Relatively few follow-up autopsy studies, how-
ever, have attempted to reconcile clinical diagnostic cri-
teria and clinical or neuroimaging observations with nec-
ropsy findings among patients with suspected ischemic
vascular dementia (IVD) or (more specifically) SIVD.
Clinical likelihood of vascular dementia is greater when
patients have the following features: abrupt onset, step-
wise progression, emotional incontinence, or a history of
hypertension or strokes (43). The report of the NINDS-
AIREN International Workshop on vascular dementia
emphasized the heterogeneity of vascular dementia syn-
dromes and their neuropathologic subtypes, variability of
the clinical course of IVD (including static, remitting or
progressive variants), the importance of establishing a
temporal relationship between stroke and dementia onset
for a secure diagnosis of IVD, and the value of both high
resolution CNS imaging studies and detailed neuropsy-
chological patient evaluation in distinguishing IVD from
parenchymal dementias such as AD (44).

The variability of neuropathologic findings among the
20 patients in our study who have come to autopsy further
highlights the heterogeneity of the neuropathologic sub-
strates of IVD. However, several important observations
emerge despite this variability. Clearly, cognitive impair-
ment and dementia can occur purely as a function of ce-
rebrovascular disease, in the relative absence of signifi-
cant AD brain changes. Not surprisingly, lacunar infarcts
and microinfarcts affecting many regions of the brain are,
in this series, a much more common substrate of IVD
than are large regions of cystic encephalomalacia, though
the latter were a significant factor in the morbidity of 5
patients. In most individuals, both lacunar infarcts and
microinfarcts were found in the same brains—perhaps
not unexpected, since they are distinguished only by their
size and visibility to the naked eye. The spectrum of vas-
cular disease associated with IVD involved both large
basal arteries and smaller cerebral arteries and arterioles;
the former were affected by severe, usually complicated
atherosclerosis, the latter by AS/LH and, less commonly,
CAA. The 1 patient who showed severe CAA with as-
associated microangiopathies fulfilled neuropathologic cri-
teria for AD and had remarkably little in the way of brain
parenchymal injury despite the burden of microvascular
abnormalities. Although patients had been selected for
inclusion in the study because of suspected subcortical
ischemic vascular disease and obvious subcortical ische-
mic vascular lesions (lacunes) on magnetic resonance im-
aging, the underlying cerebrovascular abnormality was
often a combination of small and larger artery disease,
with frequent resultant damage in neocortical structures.

Hippocampal abnormalities were frequent and pro-
nounced in over half of the patients we have studied.
Because assessment of hippocampal pathology was based
upon only a small number of sections from this structure
in each case, there is reason to believe that more thorough
examination of it (e.g. using subserial sections) may yield
evidence for even more frequent lesions. Indeed, a com-
ponent of our ongoing studies emphasizes morphometric
abnormalities of the hippocampus in IVD vs AD patients
and age-matched controls (47). Dickson et al (48) have
found hippocampal sclerosis in 16% of autopsy brains
from patients over 80 yr of age, and in 26% of those
from patients with dementia. The incidence of hippocam-
pal injury was over 50% in our highly selected patients.
A study examining the effect of cerebrovascular disease
and Parkinson disease on AD alterations in the hippo-
campus (49) has found that additional vascular disease
augmented the accumulation of hyperphosphorylated tau
in the CA1 region of hippocampus in cases of mild AD,
but reduced the extent of paired helical filament forma-
tion (in hippocampal CA2/3 and CA4 regions) in cases
with severe AD pathology.

The variability of clinicopathologic substrates of IVD
has been emphasized by others. Hulette et al, in a detailed
study of 6 male patients who had experienced a “non-
stepwise” slowly progressive dementia, found evidence
of variably severe atherosclerosis with occlusion of large
arteries in half of the patients, and resultant large cystic
cerebral infarcts in 5 of 6 individuals. Lacunar infarcts
were noted in only 2 patients, and CAA in one (11).
Others have highlighted the relative importance of mi-
crovascular disease in IVD. Esiri et al (50) compared
autopsy brain specimens from 24 elderly demented
patients with cerebrovascular disease, 19 nondemented
subjects with cerebrovascular disease, and 18 nondemented
individuals without vascular disease. They found that
microvascular disease, manifest as subcortical white matter
damage and micro-infarction, correlated with a history of
dementia. CAA was also noted more frequently in the
IVD group than in controls.

Several studies have addressed accuracy of the clinical
diagnosis of both AD and IVD when affected patients are
examined at autopsy (51–55). There is general agreement
that evidence of ischemic CNS lesions is common, even
when patients have been labeled clinically as having a
relatively “pure” AD. Small ischemic brain lesions that
contribute to dementia may not have produced a clinici-
ally apparent stroke syndrome (56). As well, patients
with the clinical diagnosis of IVD who come to autopsy
often show evidence of negligible vascular disease, but
instead have AD changes (52); this information is of ob-
vious importance in the design of clinical therapeutic tri-
als for patients who are judged (on the basis of clinical

A. Multifocal/Diffuse Disease:
1. Multiple atherosclerotic/watershed infarcts (large artery/borderzone territories)
2. Anti-PL-related ischemia
3. “Granular atrophy” of cortex (multifocal cortical microinfarcts)
4. Multiple lacunar infarcts (due to microvascular disease or microatheroma)
5.Binswanger subcortical leukoencephalopathy (BSLE) [? linked to#4]
6. CADASIL (Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy)
7. Angiitis (PCNSA, granulomatous angiitis; some cases linked to CAA)
8. Cerebral amyloid angiopathy (CAA) +/- infarcts, hemorrhages (AD variant?)—Familial forms including Dutch, Icelandic, British
9. Miscellaneous angiopathies (FMD, Moyamoya)
10. Cortical laminar necrosis (post-cardiac arrest, hypotension)
11. Extreme dilatation/enlargement of brain parenchymal perivascular spaces

B. Focal Disease/Strategically Placed Infarcts:
1. Mesial temporal (including hippocampal) infarcts/ischemia/sclerosis
2. Caudate and thalamic infarcts (especially DM nucleus, bilateral damage)
3. Fronto-cingulate infarcts (ACA territory)
4. Angular gyrus infarct (dominant cerebral hemisphere)

Abbreviations: Anti-PL = anti-phospholipid; PCNSA = primary angiitis/arthritis of the central nervous system; FMD = fibromuscular dysplasia; ACA = anterior cerebral artery; DM = dorsomedial.

examination and neuroimaging) to have IVD. Several groups have found that significant cerebrovascular disease with brain parenchymal injury may increase the cognitive and neurobehavioral abnormalities of patients with Alzheimer lesions. Snowdon et al (15) observed that among 61 participants in the Nun study who met neuropathologic criteria for AD, the women who had sustained brain infarcts—especially lacunes in the basal ganglia, thalamus, or deep white matter—had poorer cognitive function and a higher prevalence of dementia than those without infarcts. Furthermore, fewer AD neuropathologic lesions seemed to cause dementia in Nuns with lacunar infarcts than in those without. The Oxford group has noted that, for a given level of cognitive deficit in a patient, significantly less AD pathologic change is present in the brain when cerebral infarcts are also found (16).

Though the 2 key components of IVD from a neuropathologic perspective are cerebral vascular disease and brain parenchymal injury associated with it (13), realistic evaluation of the morphologic substrates of IVD must obviously take into account numerous other dynamic neurobiologic phenomena. Wallerian, retrograde and trans-synaptic degeneration obviously occur in any patient who experiences a significant burden of ischemic brain lesions (57). In our patients with widespread lacunar and/or microinfarcts, white matter pallor and gliosis were suspected to be the result of Wallerian degeneration in most cases. The example of unilateral mammillary body atrophy consequent to a hippocampal infarct (Fig. 2D, E) is a dramatic example of trans-synaptic degeneration involving limbic circuits. New immunohistochemical approaches to quantifying white matter damage are evolving. For example, beta amyloid precursor protein is found to be overexpressed in many types of ischemic or traumatic brain injury found in both animal models and humans, and may thus be a surrogate marker for axonal injury (58–62). A recently developed, affinity purified polyclonal antibody against the C-terminus of the neuropeptide tyrosine (NPY) Y1-receptor protein appears to mark degenerating fibers in the CNS (63). Finally, the cells that react to ischemia and injury in the brain—primarily microglia/macrophages and astrocytes—may show unique proliferative patterns (in response to ischemic injury) or secrete distinctive molecules that result in cognitive and neurobehavioral impairment, not just focal neurologic damage (64–67). In kainic acid lesions of the adult rat hippocampus, for instance, microglial expression of class I MHC antigen appears to be a sensitive marker of axonal degeneration distant from areas of actual nerve cell death, while induction of microglial leukocyte common antigen and class II MHC antigen expression (plus protracted expression of class I) is found in areas of degeneration of nerve cell bodies and dendrites (64). Evidence of clearcut infarcts must be viewed as the “tip of the iceberg” with respect to subinfarctive brain injury, and the latter may well contribute to IVD syndromes (68).

Table 2 summarizes various types of cerebrovascular disease observed in significant numbers of individuals with dementia. It bears re-emphasizing that “dementia” is a clinical syndrome, while neuropathologic abnormalities seen in the brain of an affected patient may only be associated with the dementia rather than its cause. However, in general, the spectrum of vascular disease implicated in IVD can be conceptualized as resulting from...
multifocal or diffuse brain disease, or focal ischemia causing infarcts of strategically important neuroanatomical regions (69). Focal disease is almost always the result of the types of vascular lesions—affecting large arteries, smaller arterioles or both—that have been the focus of this article, though they may also result from emboli to the brain (2, 57). Binswanger subcortical leukoencephalopathy (BSLE) remains a somewhat enigmatic entity (70–73). It is usually considered to result from the cumulative effect of multifocal white matter lacunar infarcts, though rarely one encounters a demented patient with severe white matter AS/LH and widespread leukoencephalopathy without obvious well-demarcated necrotic lesions—a recent individual in our series of dementia patients with the latter type of neuropathologic abnormality was considered (during life) to have spongiform encephalopathy.

Many familial microangiopathies are associated with stroke and dementia. One of the best characterized of these is the Dutch autosomal dominant form of cerebral amyloid angiopathy (hereditary cerebral hemorrhage with amyloidosis, Dutch type or HCHWA-D), caused by a point mutation at codon 693 of the beta amyloid precursor protein (74, 75). The severity of CAA-associated microvascular disease in HCHWA-D is clearly associated with the burden of brain parenchymal lesions (76, 77), though the mechanism of dementia in the absence of stroke in some HCHWA-D patients remains poorly understood. CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) results from mutations of the Notch 3 gene on chromosome 19p13.1 (78). Cerebral (and systemic) microvessels in affected patients show adventitial thickening by a PAS positive substance, and characteristic granular osmiophilic material (GOMs) adjacent to arteriolar smooth muscle cells, the latter seen only by electron microscopy (79, 80). Of interest, both familial CAA syndromes and CADASIL appear to reflect abnormalities of arteriolar smooth muscle cells leading to different types of microvascular degeneration, and thus might be characterized as “angiomyopathies.”

Proposal for Quantitation of Vascular Lesions of Possible Importance in IVD/SIVD

While the authors accept the limitations inherent in making judgments about pathophysiology of a dynamic process based upon autopsy brain specimens—ones often examined months or years after onset of a dementing illness—we suggest that a semiquantitative approach be taken to evaluating both cerebral vascular disease and brain parenchymal injury. Volumes of brain substance lost in the evolution of IVD/SIVD can be difficult to estimate in necropsy specimens (55) and may, in themselves, correlate poorly with cognitive impairment. We assess brain necrosis with respect to the size of regions of encephalomalacia, but also with reference to the location of injury, as follows: 1) Key gray matter locations, including hippocampi, frontal-subcortical loops, uni- and multi-modal association cortex and paralimbic cortex; 2) Cerebral white matter, including a judgment as to whether leukoencephalopathy appears “primary” or is the result of Wallerian degeneration related to cortical or white matter infarcts (see above); and 3) Non-key locations (i.e. regions in which ischemia might not directly contribute to cognitive or neurobehavioral impairment), including putamen, relay nuclei of the thalamus, posterior internal capsule, motor-sensory cortex, brainstem and cerebellum. In each of these anatomic regions, the volume of cystic infarcts is estimated and the number of lacunes and microinfarcts counted, yielding a crude score reflective of cerebrovascular disease in a given patient. Obviously there are problems inherent in this approach—e.g. presence of a large cystic infarct or even several substantial lacunes may, by definition, preclude the identification of microinfarcts. Nevertheless, this scoring system has been piloted on a subset of the 20 patients reported here, and—among 2 neuropathologists who evaluated cases independently (HVV, WGE)—led to an essentially identical rank order of cases by severity of disease. Details of this proposed scoring will be presented elsewhere when it has been fully refined and validated on a larger patient population.

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