Postmortem Examination of Vascular Lesions in Cognitive Impairment

A Survey Among Neuropathological Services

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Background and Purpose—A full appreciation of the presence of cerebral vascular lesions in cognitively impaired patients can be ultimately reached at the neuropathological level. However, there are no detailed guidelines regarding what neuropathologists should look for at autopsy in cases of suspected vascular dementia or vascular cognitive impairment. We aimed at surveying the postmortem neuropathological procedures used in different centers in examining brain lesions of presumable or possible vascular origin in cognitively impaired patients.

Methods—Thirteen laboratories participated in the survey by filling in a semistructured questionnaire. We reviewed sampling and histology procedures in use and the neuropathological definitions of some of these lesions. Neuropathological criteria for the definition of a vascular origin of the dementing process were also surveyed.

Results—A large variability across centers was observed in the procedures used for the neuropathological examination and the histology techniques. Heterogeneity existed also in the definition of commonly found lesions (eg, white matter alterations, small vessel disease), interpretation of whether or not the lesions were reputed to be of vascular origin, and consequently in the interpretation of the cause of cognitive decline.

Conclusions—The appreciation of the presence of neuropathologically verified vascular lesions in cognitively impaired cases may be heavily influenced by the laboratory tools used and also by the heterogeneity of the criteria applied in different centers. Harmonization of neuropathological procedures is badly needed in the field of vascular dementia and vascular cognitive impairment to better understand the association between various vascular lesions and clinical symptoms such as cognitive impairment. **(*Stroke*. 2006;37:1005-1009.)**

Key Words: dementia ■ dementia, vascular ■ diagnosis ■ pathology

Dementia is a major health problem in developed countries. It is generally thought that therapeutic and preventive approaches may vary according to different dementia subtypes, and typically, the cases of dementia are divided according to the underlying cause. However, establishing the main etiology in some cases of dementia is difficult. The general belief that the characterization of the causes of dementia can be definitively reached on pathological grounds is also echoed in current diagnostic criteria.[1,2] Concerning vascular dementia (VaD), 1 of the 2 main types of dementia, the diagnosis is reached when the most relevant brain lesions are considered to be of vascular origin. Despite this, the definition of vascular lesions does not always appear straightforward,[3] and the characterization of pathological lesions associated with vascular cognitive decline is a major current problem with important reflections for clinical practice and interpretation of epidemiological data.[4,5] A similar problem also affects the field of neurodegenerative dementias in which vascular lesions are frequently associated.[6,7] These difficulties are reflected in the difference found in pathological series of demented patients in terms of frequency of VaD cases;[8] these discrepancies might partly be explained by the heterogeneity in the pathological examination procedures used in different centers.

Although there is a general agreement that some types of vascular lesions may cause cognitive deterioration,[8–10] it seems crucial to reach a consensus on what is meant under the definition of "vascular." Moreover, it appears of interest to examine what is currently performed in neuropathology laboratories because harmonization is of the utmost importance for future work in the field. Standardization approaches have been previously undertaken in the field of Alzheimer disease[11] and should also be proposed for VaD.

With these considerations in mind, we aimed at surveying the procedures used in different centers in examining from

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the neuropathological point of view cases of possible VaD or vascular cognitive impairment. In particular, we surveyed brain sampling and histology techniques, pathological definitions of some lesions of possible vascular origin, and criteria applied for the final interpretation of autopsy finding in terms of the cause of cognitive impairment.

Methods

To collect all the supposedly needed information about the procedures used in different centers, a semistructured questionnaire was developed by consensus among 4 neuropathologists and 1 neurologist who had undergone neuropathological training. The form contained questions about the following areas: (1) general pathological procedures such as brain cutting, sampling, and staining; (2) parenchyma alterations assessment (type and definition criteria of each lesion); (3) vessel diseases (definition, sampling region, quantitative assessment); and (4) general issues such as interpretation of findings and definition of the appreciation of the role of vascular lesions in relation to the cognitive status and to other possible coexistent pathological diseases. Most of the questions allowed multiple answers. The form in its final version was then circulated among 13 centers selected on the basis of their recognized expertise in the pathological examination of cases of dementia or more specifically of VaD and their willingness to participate. Some of the centers were selected on the basis of ongoing collaborative studies and networks in the field of cognitive impairment.[12] No other specific criteria were followed to select the centers participating in the study. Six centers declined to participate because of a lack of interest in the topic or they never responded to the invitation.

Results

General Neuropathological Procedures (Table 1)

The vessels of the circle of Willis are examined in all the centers, and the majority of centers also examine the carotid arteries, the heart, and the kidneys (if no restrictions are imposed in the autopsy consent); however, only a minority examines the vertebral arteries. Most of the centers perform cutting of the entire brain (left and right hemisphere), whereas a few examine only 1 hemisphere, usually because the remaining is frozen. The brain is cut in the coronal plane in all centers; no one uses sagittal sectioning. Interestingly, transverse cutting (ie, the slice plane used in computed tomography and magnetic resonance scans) is performed in only 1 center. In most of the centers, sampling for microscopic evaluation is done in many cerebral areas. Staining of the entire coronal sections is used in 5 centers; specific stains for myelin are used quite consistently across centers.

Parenchyma Changes Assessment

Lesions are examined in the formalin-fixed brain in 8 centers and in stained coronal sections in the remaining 5 centers. Considering the question about which lesions among those listed in the questionnaire are considered vascular (Table 2), some lesions such as large and small infarcts are clearly and consistently across centers classified as vascular. For the etiological classification of other lesion types, discrepancies exist. For example, only about one third of centers attribute to white matter rarefaction of any degree a vascular significance. Also, when considering severe white matter rarefaction, only 6 of 13 centers consider it vascular. Other lesion types that were inconsistently considered vascular were cortical granular atrophy, laminar necrosis, and incomplete infarcts. Hippocampal sclerosis was defined as vascular in only 4 centers and enlarged perivascular spaces in 8. None of the centers considered the enlargement of lateral ventricles to represent a vascular lesion. However, even considering lesions that are consistently reported to be recognized as vascular, discrepancies exist. For example, a consensus does not exist in terms of definition of lacunar infarct (Table 3), and only 9 centers make a distinction between lacunes and

TABLE 1. General Pathological Procedures, Sampling, and Histology Techniques (survey questions are also reported#)

	n* (%)
Examination of large vessels and other organs (On a routine basis, do you examine?)	
Carotid arteries in the neck	9 (69.2)
Vertebral arteries	2 (15.4)
Willis circle vessels	13 (100)
Heart	9 (69.2)
Kidney	10 (76.9)
Sampling and brain cutting (Where do you sample, and how do you cut the brain?)	
Sampling from only half of the brain	5 (38.4)
Coronal cutting	13 (100)
Transverse cutting (in addition to coronal)	1 (7.7)
Sagittal cutting	0 (0)
Site of sampling for microscopic examination (Where do you sample for microscopic examination?)	
Middle frontal gyrus	12 (92.3)
Superior and middle temporal gyri	11 (84.6)
Inferior parietal lobule	10 (76.9)
Occipital cortex	12 (92.3)
Hippocampus with entorhinal cortex	12 (92.3)
White matter	12 (92.3)
Basal ganglia	11 (84.6)
Thalami	11 (84.6)
Cerebellum	11 (84.6)
Midbrain	11 (84.6)
Pons	11 (84.6)
Medulla oblongata	10 (76.9)
Basal structures	11 (84.6)
Any lesion seen macroscopically	12 (92.3)
Histology assessment: staining (Which of the following brain parts do you stain?)	
Coronal brain sections	13 (23.1)
Whole hemibrain	1 (7.7)
Entire lobes	2 (15.4)
Small blocks only	10 (76.9)
Histology assessment: staining (Which of the following stains do you apply?)	
Staining for myelin	11 (84.6)
Staining for nerve fibers	7 (53.8)
Silver staining	9 (69.2)
Staining for astroglial cells	7 (53.8)

*No. of centers performing that specific examination; #multiple answers allowed.

TABLE 2. Lesions Considered of Vascular Origin by Surveyed Neuropathologists (recorded answers to the question "Which of these lesions do you consider vascular?")

	n* (%)
Cerebral infarcts	13 (100)
Lacunar infarcts	13 (100)
Cortical microinfarcts+amyloid angiopathy	11 (84.6)
Multiple large infarcts+amyloid angiopathy	10 (76.9)
Enlarged perivascular space	8 (61.5)
White matter rarefaction (any degree)	4 (30.8)
Severe white matter rarefaction	6 (46.1)
Ventricular enlargement	0 (0)
Hippocampal sclerosis	4 (30.8)
Cortical granular atrophy	6 (46.1)
Laminar necrosis of the cortex	9 (69.2)
Incomplete infarcts	7 (53.8)

*No. of centers performing that specific examination.

microinfarcts. Concerning infarcts, their volume is assessed only by about half of the surveyed centers, and only 5 centers declare to assess incomplete gray matter infarction (Table 3). The definition of this latter type of lesion clearly represents an open issue; when we asked to report the definition, we obtained different answers. In some centers, incomplete infarction was defined as the presence of loss of neurons without obvious other tissue loss. In other centers, this term was used only for white matter changes characterized by myelin pallor; finally, some reserved the term incomplete infarction to describe laminar necrosis of the cortex. Other neuropathologists stated that they do not use the term or even that they do not exactly know what it means. Similarly, the definition of white matter rarefaction follows different criteria (Table 4), whereas a quantitative assessment of white matter changes is performed in only 4 of 13 centers. Finally, the presence of Wallerian degeneration is recorded in 7 of 13

TABLE 3. Definition of Lacunar Infarct According to Diameter, Volume, or Location and Assessment of Brain Infarcts (survey questions are also reported§)

	n* (%)
Definition of lacunar infarct (Which of the following define a lacunar infarct in your practice?)	
Any infarct with diameter <15 mm	3 (23.1)
Any infarct with diameter <15 mm and typical site#	10 (76.9)
Any infarct with diameter <15 mm associated with arteriolosclerosis	3 (23.1)
Any infarct with volume <1.0 mL	1 (7.7)
Assessment of brain infarcts (For brain infarcts, do you record or search?)	
Bilateral occurrence	13 (100)
Location	13 (100)
Total lesion volume	7 (53.8)
Multiplicity	12 (92.3)
Presence of incomplete grey matter infarcts	5 (38.5)

*No. of centers performing that specific examination; #basal ganglia, thalamus, pons, hemispheric white matter; §multiple answers allowed.

TABLE 4. Definitions Used for White Matter Rarefaction in Different Centers (recorded answer to the question "How do you define the rarefaction of white matter?"#)

	n* (%)
Appearance paler than normal	7 (53.8)
Loose appearance of myelinated fibers	8 (61.5)
Oligodendrocyte no. reduction	3 (23.1)
Axonal loss	6 (46.1)
Presence of gliosis	8 (61.5)
Combination of the above	3 (23.1)

*No. of centers performing that specific examination; #multiple answers allowed.

centers, that of gliosis of the white matter by 10 centers, and of the gray matter by 11 centers, although its quantification is performed in only 5 centers.

Small Vessel Assessment (Table 5)

Of interest, heterogeneity exists across centers even in the definition of a small vessel. Some centers identify small vessel on the basis of diameter size, whereas others identify small vessel on the basis of location (eg, in subcortical areas). This notwithstanding, all except 1 center reported to perform

TABLE 5. Small Vessel Disease Assessment (survey questions are also reported#)

	n* (%)
Definition of small vessels (What do you mean for small vessels?)	
All vessels with diameter <500 μm	6 (46.1)
Only arterioles	1 (7.7)
All vessels deeper than cortex	6 (46.1)
All vessels with diameter <50 μm	1 (7.7)
All the vessels within the brain parenchyma+all vessels with a diameter <500 μm in the leptomeningeal space	1 (7.7)
Sites of small vessels examination (In what cerebral region do you examine small vessels?)	
Cortex	10 (76.9)
White matter	12 (92.3)
Basal ganglia	11 (84.6)
Thalamus	10 (76.9)
Brainstem	8 (61.5)
Staining of small vessels (What staining do you apply to examine small vessels?)	
Hematoxylin and eosin	11 (84.6)
Masson's trichrome	2 (15.4)
Van Gieson's elastica	4 (30.8)
Other	4 (30.8)
Alterations reputed as hallmarks of small vessel disease (What do you define as small vessel disease?)	
Hyaline degeneration of tunica media	11 (84.6)
Loss of smooth muscle cells in tunica media	3 (23.1)
Thickening of vessel wall+lumen narrowing	12 (92.3)
Lypohyalinosis	10 (76.9)
Necrotic aspects in the vessel wall	9 (69.2)

*No. of centers performing that specific examination; #multiple answers allowed.

routine evaluation of small vessels. Brain areas for small vessels examination are also different to some extent. Hematoxylin-eosin is the staining of choice for small vessels evaluation in most centers, whereas more specific stains are seldom used. None of the centers assess the density of small vessel per unit area. Considering histological aspects of small vessel disease, some findings such as hyaline degeneration of tunica media, vessel wall thickening and lumen narrowing, lypohyalinosis, and necrosis of the wall are rather consistently recognized as hallmarks of small vessels disease, whereas the isolated loss of smooth muscle cells is not considered as such by all the investigators.

Cerebral Amyloid Angiopathy (Table 6)

Assessment of cerebral amyloid angiopathy (CAA) is specifically performed in all autopsy cases in 8 of the 13 interviewed centers. In the remaining ones, CAA is assessed only for specific reasons such as the presence of cognitive decline or suggestion by routine histological assessment. However, the staining methods for assessing CAA were rather different across centers. Surprisingly, none of the centers use thioflavine S, a method strongly suggested by the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) group.[13] Quantification of CAA is performed in 10 of 13 centers.

Interpretation of Findings

The questions for this part were left open and were mainly aimed at exploring how pathologists summarize and interpret the presence of vascular lesions in relation to the occurrence of cognitive decline. In response to the question of when a patient is considered to have vascular alterations in the brain, 5 of the 13 centers indicated that this statement appears in their final report when a certain subjective threshold of the above-discussed lesions is surpassed. In the remaining centers, the presence of any amount of vascular changes is considered sufficient. In 1 center, a patient is defined as having vascular lesions when severe gross atherosclerosis of the circle of Willis or substantial infarct or CAA associated with microinfarcts are found; in another, when the vascular lesions are considered more severe than minimal; and in 1 center, when a territorial infarct or multiple lacunes or small vessel disease are found. In 2 centers, the requirement for defining a demented patient as having vascular lesions is that these latter are in the parenchyma (ie, lesions of the vessels are not considered).

TABLE 6. CAA Assessment (survey questions are also reported)

	n* (%)
Assessment (When do you search for amyloid angiopathy on a routine basis?)	
In all autopsy cases	8 (61.5)
Only in patients with cognitive decline	1 (7.7)
If suggested by hematoxylin and eosin	4 (30.8)
Histological methods (What histological methods do you use to assess amyloid angiopathy?)#	
Only hematoxylin and eosin	0 (0)
Only Congo red	3 (23.1)
Thioflavine S	0 (0)
Only β-amyloid antibodies	4 (30.8)
Congo red+β-amyloid antibodies	6 (46.1)
β-amyloid antibodies+silver impregnation	1 (7.7)

*No. of centers performing that specific examination; #multiple answers allowed.

We then asked when a patient is considered to have exclusively vascular lesions. Also in this case, the answers were rather sparse, and sometimes the pathologists reported to be uncomfortable with this statement. In some centers, the criterion is mostly based on the absence of evidence of other types of lesions, but the following answers were also reported: presence of vascular lesions in associative areas; presence of infarcts in the absence of Alzheimer disease pathology; exclusion of substantial degenerative pathology by silver or immunostaining (1 center each); and 1 pathologist declared that a patient is never defined as having solely vascular pathology in his center.

The last question aimed at assessing criteria for defining under neuropathological examination a cognitively impaired patient to have primarily vascular lesions. The following findings were reported by the various services to reflect this condition: (1) accompanying changes not sufficient to cause dementia; (2) accompanying lesions of the Alzheimer or Lewy body type of mild degree; (3) large multiple left hemispheric infarcts or angular gyrus infarcts or multiple lacunes in the putamen, caudate, or thalamus or multiple microinfarcts in the cortex, basal ganglia, and thalamus; (4) multiple infarcts and only mild Alzheimer-type changes; (5) severe vascular lesions and minimal lesions of other types; (6) volume of vascular lesions >30 mL; (7) predominant vascular lesion in associative areas; (8) substantial vascular pathology and absence of Alzheimer disease changes; and (9) severity of senile changes not exceeding those reputed as age related. The pathologist of 1 center stated that this definition is impossible to be reached solely on neuropathological grounds and requires additional clinical and neuroimaging data.

Discussion

We performed an explorative survey aimed at gathering data about neuropathological procedures used in different centers in assessing cases of dementia with a focus on vascular pathology; to the best of our knowledge, for the first time, an overview of these procedures is provided. The most relevant result of the survey is the finding of a significant heterogeneity across centers in the pathological procedures for assessing lesions with possible or even definite vascular origin and, surprisingly, also in the consideration of what lesions are considered expression of a vascular process. The examination of the results of the survey also suggests that, at present, the assumption contained in some diagnostic criteria sets[1,2] that pathology may provide final demonstration of a vascular etiology of dementing syndromes is likely to be biased by a number of methodological limitations besides the fact that pathological diagnostic criteria do not exist. In this regard, it is to be noted that our study was not aimed at developing or proposing new criteria for the pathological diagnosis of VaD because this was felt premature considering the present status of knowledge of the topic and that even clear definitions for many lesion types are still lacking. In this sense, it seems

advisable that future guidelines be issued not only to better define the type of lesions to be searched for in cases of VaD or vascular cognitive impairment but also to define the technical procedures for that purpose. In the meantime, abandonment of terms such as "lacune," which are the source of confusion in the field and a careful description of brain lesions in terms of morphology, size, number, and site, could allow at least the comparison between different studies. Overall, the present survey shows that neuropathological procedures are heterogeneous and that different neuropathological services apply different definition and criteria even for lesions such as infarcts and small vessels disease that are considered to be among the hallmarks of vascular cognitive impairment. Moreover, the study of some lesions is not customarily performed by all the centers. Finally, the interpretation of findings is subjected to major interindividual variability. At present, it seems reasonable to conclude that the appreciation of the contribution of pathologically detected vascular lesions to cognitive impairment is likely to be heavily influenced by researchers' methods and beliefs.

A limitation of this study was in the choice of the participating centers that did not follow any specifically structured protocol and, therefore, might have been biased by several factors. This notwithstanding, we believe that the expertise of the involved centers provides sufficient support for the argument that such a variability in fact exists in the assessment and interpretation of brain vascular lesions. It might be supposed that the heterogeneity could be even higher should centers with less expertise be involved in the survey.

In conclusion, a large variability in the pathological assessment of lesions of possible vascular origin has been shown by this survey. A consensus agreement of the procedures to be followed and criteria for evaluation of lesions similar to those existing for Alzheimer disease[11,13,14] and dementia with Lewy bodies[15] is urgently needed.

Appendix

Survey Participants

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