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Toward a Pathological Definition of Vascular Dementia

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Abstract

To date, there are no widely accepted neuropathological criteria for vascular dementia, although creating such a standard is ranked high on the wish list of all the researchers in this field. Such criteria would make it possible to perform large multicentre clinicopathological studies and, consequently, to better understand which, how, and where vascular brain lesions lead to cognitive decline, as it is possible to do in Alzheimer's disease or Parkinson's disease. However, a major obstacle in the standardization of diagnosis is the fact that vascular brain lesions are a large group comprising heterogeneous changes that have different pathogenesis. Although it is accepted that some kinds of vascular changes cause cognitive impairment, it is not uncommon to find reports of the assumed same histological changes in control subjects. An indispensable first step is the unequivocal establishment of neuropathological criteria to uniform the definitions used for each one of the lesions, preferably based on its pathogenesis. In the present, non-standardized state of ambiguity, a given lesion is designated by different names between and within the clinical, radiological, and pathological settings, and several definitions simply overlap. Before attempting to create new criteria, a multidisciplinary group-task is urged to identify and minimize the uncontrolled proliferation of definitions. Only then, it will be possible to advance the understanding of how vascular brain changes affect cognition.

INTRODUCTION

The prevalence of dementia is expected to increase three fold in the next 40 years¹. Dementia can be caused by a wide range of pathological entities. Every dementia subtype has a specific pathogenesis and risk factors that must be understood in order to develop prevention and treatment strategies. Alzheimer's disease is considered the most frequent cause of dementia worldwide. However, there is a growing body of evidence that vascular brain lesions (VBLs) and cerebral vessel disorders (VDs), both isolated or in combination with other neurodegenerative disease, cause cognitive decline²⁻³. Indeed, vascular dementia (VaD) is already considered the second most common cause of dementia in the elderly in several series, and it may even outnumber AD cases in some series⁴. Currently, the prevalence of VaD ranges from 4.5 to 39% in clinical studies and from 0.3 to 85.2% in neuropathological studies.

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Certainly, part of this variability can be explained by the characteristics of the different populations or series, but the use of different diagnostic criteria is a major factor that must be taken into account. In order to establish the prevalence of cognitive decline caused by vascular changes and their consequences, it is crucial to have a sensitive and specific diagnostic tool, preferably one that can be used during life. To date, postmortem examination is considered to be the only accurate tool for the diagnosis of VaD, and clinicopathological studies report only poor to moderate sensitivity of the currently used clinical criteria⁶⁻⁷. Given that the neuropathological examination is considered the gold standard of diagnostic instrumentation, it seems logical to employ clinicopathological studies of large series to improve the accuracy of the clinical diagnosis, as has been done for other dementias⁸⁻¹⁴.

However, this strategy is hindered by the lack of a widely accepted neuropathological set of criteria for VaD. The diagnosis is usually made by the presence of vascular lesions, defined at the discretion of each pathologist, often of variable size or volume, in the absence of other degenerative lesions¹⁵⁻¹⁶. Several attempts to create a valid set of neuropathological criteria for VaD have been published for at least 80 years¹⁷, however all of them faced many limitations that prevented their broad acceptance. The aim of this paper is to detail which factors are preventing the creation of widely accepted criteria for VaD and to discuss solutions to overcome these limitations. Once accurate neuropathological criteria are reached, it will be possible not only to estimate the real prevalence of VaD, but also to improve the understanding on its etiology, pathogenesis, risk factors, and preventive and treatment options.

FACTORS PREVENTING THE CREATION OF WIDELY ACCEPTED CRITERIA FOR VASCULAR DEMENTIA

1) Vascular dementia is not a single entity

In many instances, VaD is treated as a single pathological entity that can be manifested in different ways, such as AD or Parkinson's disease. However, this is not the case. VaD is rather an umbrella term comprising a large group of heterogeneous lesions which have multifactorial pathogenesis and morphological substrate¹⁸. Actually, circulatory disturbances are one of main chapters of general pathology and include a wide range of pathological entities. For instance, cognitive decline can be caused by a series of strokes due to large vessel problems (multi-infarct dementia) or due to changes in the small vessels of the white matter as consequence of chronic hypoperfusion¹⁹. Therefore, the term VaD should be rather employed as a group name, like the tauopathies, and each of the entities belonging to this group should have its own definitions.

2) Definitions of vascular brain lesions (VBLs) and cerebral vessel disorders (VDs) are unclear, heterogeneous, and overlap

A good set of criteria requires the use of definitions with high inter-rater agreement. One of the biggest limitations facing the standardization of the criteria to diagnose VaD is the overlap of the definitions for VBLs and VDs¹⁸. Such lesions were described concomitantly in several countries for over 150 years. Usually, the definitions are mere descriptive-driven, rather than pathogenetically driven. As consequence:

a) A given pathological entity is labeled by different names among clinicians, radiologists, and pathologists -- or even worse, a single radiological or clinical definition corresponds to multiple neuropathological lesions. For example, three distinct changes such as arteriolosclerosis, white matter edema, and local myelin rarefaction may be called leukoaraiosis by radiologists. Van Straaten et al measured the inter-rater agreement on the

diagnosis for VaD, among six experienced radiologists. Although the raters had to make use of precise operational definitions for imaging findings, the agreement was only moderate²⁰.

b) A given pathological entity is known by different names among the pathologists. It happens both because a lesion has been described at the same time in two different centers, and the followers stick to the traditional nomenclature learnt first. For instance, Marie's "état lacunaire" is similar to Alzheimer and Binswanger's "arteriosclerotic brain atrophy" ²¹. In addition, some raters tend to detail the findings, while others tend to group them. Atherosclerotic lesions in small arteries can be defined either as atherosclerosis or as small vessel disease (SVD). Moreover, SVD can be further subclassified as small vessel atherosclerosis, arteriolosclerosis, lipohyalinosis, and fibrinoid necrosis ²². The descriptive term lacuna is used for small lesions of 5-15 mm³ in volume or 5-20 mm in diameter, regardless of their etiology ²³. Thus, lacunar infarcts, lacunar hemorrhages, and enlarged perivascular spaces of lacunar appearance are all termed as lacunes by some authors ²⁴⁻²⁵. In a survey with 13 neuropathology labs, Pantoni et al detected a high heterogeneity on the nomenclature and on morphological definitions used for a single lesion ¹⁶. In summary, there is no consensus on the definitions of vascular changes and therefore, a set of criteria tested in a certain site is rarely reproducible in other sites. Probably this overlapping also explains why no detailed morphologic substrates have been included in the currently used diagnostic criteria for VaD, e.g., DSM-IV, SCADDTC²⁶, NINDS-AIREN²⁷, and NINDS-Canadian Stroke Network harmonization standards ²⁸

Therefore, it is easy to conclude that definitions and nomenclature must be normalized by a multidisciplinary team to assure that any kind of criteria will be reproducible and accepted.

3) Lack of direct clinicopathological correlation

Dementia is a clinical syndrome. Therefore, a set of criteria for a given dementia subtype is defined based on the best knowledge about the neuropathological hallmarks underlying the clinical symptoms and intended to ensure a high clinic-pathological correlation. Rarely, a set of criteria reaches enough clinicopathological correlation on the first attempt, and modifications should be made with the passage of time, after testing and validation attempts using clinicopathological studies. For instance, the neuropathological criteria for frontotemporal lobar degeneration were subjected to at least three major modifications in the last 15 years ^{12, 14, 29-30}.

In the case of VaD, it has proven a very difficult task to define neuropathological thresholds for considering a lesion as causative of cognitive decline. In a classical paper published in 1970, Tomlinson and Blessed set a threshold of 60 ml of tissue loss for considering as vascular the causative factor of the cognitive decline ³¹. Since that time, the threshold has decreased. Kovari et al. in a study with 45 cases without significant AD pathology or macrovascular lesions showed that in a univariate model, cortical microinfarcts explained 36% of the variability of the last available Clinical Dementia Rating scores –CDR ³². In addition to the lower threshold, it is clear that the strategic of a lesion may matter more than the amount of tissue loss²⁷.

However, cognitive decline do not depend only on a certain amount of lesion in a strategic area. It is rather a complex equation involving the amount of tissue loss, location, and brain capacity of compensating the changes. It is not rare to find descriptions of non-demented patients presenting the same kind and severity of lesions found in demented patients. Many studies show a great proportion of VBLs and VDs in non-demented subjects ³³⁻³⁵.

For that reason, we can anticipate that no criteria will fit the whole population. Extra neuropathological factors, both genetic and environmental, will have to be taken into account.

Most of the dementias are mixed dementias

The literature reports a 3.4 to 73% overlapping between AD and VaD 6³⁶⁻³⁷. This overlapping makes difficult to estimate to which extent each disease contributes to the cognitive decline. In fact, the majority of the subjects older than 65 years do have some degree of AD-type changes and cerebrovascular lesions³⁸. Several studies demonstrated that cerebrovascular lesions lower the threshold of AD-type changes necessary to cause cognitive decline 3³⁹⁻⁴⁰. The burden of vascular and AD-type lesions are considered to be independent of each other, and are consistent with an additive or synergistic effect, but this effect could not be measurable so far 41⁴²

Methods used in routine neuropathological assessment are unsuitable for properly assessing vascular changes

In a routine pathological assessment, the brain is usually examined macroscopically at 1cm intervals and microscopically in selected areas and unilaterally, totalizing less than 5% of the brain volume. Therefore the odds of skipping a lesion are high. A whole brain assessment can be reached by applying whole brain embedding and cutting methods, or sampling guided by imaging. In both cases, the procedures are expensive and require a specialized facility with skilled technicians. In addition, staining methods for detecting discrete neuropathological changes, such as luxol fast blue for myelin or immunohistochemistry against GFAP for detecting cortical microinfarcts, are rarely used. Cortical microinfarcts is already considered causative of cognitive decline, but cannot be detected by imaging methods or routine hematoxylineosin staining.

FURTHER STEPS TOWARD A PATHOLOGICAL DEFINITION OF VASCULAR DEMENTIA

Considering all the facts discussed in this paper, it is easy to realize that before trying to establish a set of neuropathological criteria for the diagnosis of VaD, some prerequisites have to be fulfilled. It requires a multi-disciplinary team including groups worldwide. The task of this team would be to identify and minimize the overlapping to make uniform the definitions used for each VBLs and VDs, preferably based on its pathogenesis, and to set up an assessment protocol for the examination of each kind of lesion, including the areas and staining protocols. Such uniformity would make possible to perform large multicentre clinicopathological studies and, consequently, to better understand which, how, and where vascular brain lesions lead to cognitive decline. In summary, such harmonization is imperative to bolster further studies to develop pathogenesis-orientated therapeutic strategies for VaD.

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