Editorial

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Vascular cognitive impairment: Biomarkers in diagnosis and molecular targets in therapy

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The Editors of JCBFM have decided to focus a special issue on aspects of vascular cognitive impairment (VCI) and the role of vascular disease on other dementias to advance this important field. Interest in the role of vascular disease in cognition has been steadily increasing for the past several years, mainly due to the realization that worldwide aging of the population will result in a dramatic increase in the number of people with vascular disease. Also recognized is the role of vascular disease in accelerating other forms of dementia, including Alzheimer's disease. This growing awareness has resulted in a major effort to refine diagnostic criteria in order to more clearly delineate the multiple forms of cognitive impairment related to vascular diseases, and to separate vascular causes from those due to neurodegeration.[1–3] There is general agreement in the literature that terminology needs to be improved, since the commonly used terms "vascular dementia" and "multi-infarct dementia" define an end stage in the disease progression, in which dementia is dominant but fail to include the patients with milder forms of cognitive loss and the role of imaging in the diagnosis. The currently accepted term, vascular cognitive impairment (VCI), is an all-inclusive term and includes both large vessel and small vessel vascular disease. The former results primarily in cortical strokes often related to extracranial vessels and the heart, while the latter emphasizes the role of hypertension, diabetes, hyperlipidemia, and other less prevalent types of vascular disease. With the emergence of more studies based on imaging and autopsy data, it is becoming clearer that small vessel disease (SVD) is the major form of VCI. More importantly for clinical trials, the majority of the patients have SVD.[4–6] Treatment trials will need to focus on the SVD, which is progressive and has a more readily defined natural history than the sporadic course of the large vessel disease.[7] The challenge now is to identify the patients with SVD at risk for progressive disease in order to test agents that can prevent the progression or even reverse it. This is a difficult goal to reach because it requires a parallel effort to refine the diagnostic criteria while aggressively searching for novel agents in appropriate animal models.

One of the major prerequisites for effective design of treatment trials is the ability to separate the various forms of VCI and single out the progressive small vessel forms that would be more amenable to treatment. The consensus article in this issue describes potential biomarkers that can be used to select those VCI patients with SVD. The spectrum of SVD ranges from a pure form involving the deep white matter to a combination of vascular disease and neurodegeneration of the Alzheimer's disease type. Ideally, patient identification should be made at an early stage when treatments have the optimal chance of succeeding. Unfortunately, autopsy studies, while informative, only validate the brain disease at the time of death, and by that time most patients show a combination of all of the dementia types, obscuring how the pathology presented at the time of disease onset.[8] Therefore, biomarkers based on a combination of factors are going to be needed to identify patients with different forms of dementia at an early stage.

The reports in this issue reflect the thinking of the leading experts in VCI research. The papers describe the clinical and pathological features of the disease from a pathophysiology point of view. There are a number of studies based on MRI that indicate that white matter lesions that grow over time can be detected before changes in cognition are apparent. Other studies identify factors in the blood that suggest inflammatory changes in the vessels associated with small strokes and white matter hyperintensities (WMHs). Large series of patients with VCI and the features in the CSF associated with those patients are described. Sample sizes for clinical trials are estimated. The impact of pathological findings on cortical volume

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is described. A paper shows the mechanism of oligodendrocyte death based on cell cultures. Several reports are focused on the hereditary form of vascular disease called Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL).

Collaborative studies have been done by researchers in Europe as part of the LADIS (Leukoaraiosis And DISability) Study group to define the role of WMHs on MRI.[9] Independent studies of the CSF have been performed showing that biomarkers can be used to define the small vessel form of VCI. Few studies, however, have attempted to combine multiple biomarkers. To define a spectrum disorder, a single factor is rarely sufficient; a combination of multiple factors will be needed. When several factors are involved, a classification system is needed, which can involve either a list of know features or an automated classification system that uses the newer clustering methods available. These are included in high-level computer statistical programs such as R. For this a consortium of centers will be needed.

VCI is a dynamic multi-stage process with different etiological factors impacting each stage. It is entirely feasible that Alzheimer's disease could begin in a patient at an early age, manifesting only an abnormal accumulation of a protein, but that the pathology could be augmented with the passage of time by other disease processes through the addition of hypertensive vascular disease and other protein deposits. Similarly, a hypertensive patient with white matter changes over time could accumulate proteins related to Alzheimer's disease, resulting in a mixed dementia. Staging of the disease process is now possible with high-level MRI (spectroscopy, diffusion imaging, permeability studies, etc); CSF measurements augment the classification by adding insights into the integrity of the blood-brain barrier and the presence of neuroinflammatory factors. While the MRI methods indicate the physiology of the pathological changes, the CSF mirrors the pathological changes taking place in the brain as reflected in the drainage of interstitial fluid into the CSF. In some cases, blood is another potential biomarker.

The combined diagnostic modalities play a dual role in that they indicate the direction for future therapy trials. Blocking the progressive damage to the brain by vascular disease in combination with other forms of degeneration will be a great challenge in such a complex disease process. In this issue, experts have described the types of pathological processes involved which strongly implicate certain disease pathways. There is a parallel process of seeking the underlying pathology and developing biomarkers to identify the process during life, ideally in an early stage. Once major pathophysiological processes are identified, the next step will be treatment trials with appropriate agents. The consensus report is an attempt to begin that important process with the goal of developing by common agreement diagnostic criteria for SVD and optimal outcome measures to use to indicate efficacy of the agent tested. While this may seem an ambitious objective, it is important to begin.

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