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STROKE (H ADAMS, SECTION EDITOR)

Vascular Cognitive Impairment and Post-Stroke Cognitive Deficits

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Abstract Vascular cognitive impairment (VCI) and focal post-stroke cognitive deficits are an unfortunately common occurrence. Despite this, our understanding of risk factors for development of VCI and treatment thereof is embarrassingly limited. While no FDA approved treatments exist for VCI, recent and ongoing research sheds some light on the problem, showing some efficacy of cholinesterase inhibitors and antidepressants, treatment of vascular risk factors, and other investigational drugs. Treatments for focal cognitive impairments such as aphasia and neglect are also limited, primarily by the size of studies that have been done. With the more widespread acceptance of the AHA-ASA diagnostic criteria for VCI and its subtypes, perhaps we will start to see more in the way of compelling treatment trials.

Keywords Vascular dementia · Dementia · Mild cognitive impairment · Vascular cognitive impairment · Stroke · Aphasia · Neglect

Introduction

Stroke is the leading cause of death worldwide, ranking third in the United States [1]. Perhaps more importantly, those who survive strokes have various neurologic deficits, including cognitive impairment. A recent analysis of a London registry of stroke patients revealed an overall prevalence of 22 % of cognitive impairment after stroke and that this percentage persisted up to 14 years out [2]. Vascular dementia is second only to Alzheimer disease as a cause of dementia [3], and this does not include patients who have single domain cognitive deficits, such as aphasia or neglect, after a stroke.

Cognitive impairment after stroke is, therefore, an unfortunately common problem and will likely become more of one as people live longer. In this brief review, we discuss current terminology related to these cognitive impairments, risk factors, and recent clinical trials and reviews on prevention and treatment of cognitive impairment related to cerebrovascular disease.

Terminology and Diagnostic Criteria

Recent years has seen the rise of the term, vascular cognitive impairment (VCI), culminating in a statement by the American Heart Association/American Stroke Association in 2011 defining the term and explaining the rationale behind its use [4••]. VCI does not entirely supplant previously used terms, but provides a logical "umbrella" term to describe various degrees and patterns of cognitive impairment related to cerebrovascular disease.

Older terms, such as "multi-infarct dementia," first suggested by Hachinski [5], tend to be limiting in scope. For instance, this term suggests that it takes multiple infarctions to cause dementia, but single strategic infarctions can also clearly cause dementia as well. Probably the most commonly used term and today is vascular dementia (VaD), also coined by Hachinski and colleagues [6]. There are several sets of diagnostic criteria for vascular dementia the most commonly used being the National Institute of Neurological Disorders and Stroke — Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) criteria. The NINDS-AIREN criteria, presented in Table 1, require documented dementia, evidence of cerebrovascular disease on exam or by imaging, and that the 2 must be "reasonably related" [7]. Vascular dementia proved to be a more useful

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Table 1 NINDS-AIREN criteria for vascular dementia

1. Dementia: cognitive decline from a previously higher level of functioning and manifested by impairment of memory and of 2 or more cognitive domains. Excludes disturbances and consciousness, delirium, psychosis, severe aphasia, or major sensorimotor impairment precluding neuropsychological testing as well as systemic or brain disorders that could account for deficits in memory and cognition.
2. Cerebrovascular disease: presents of focal signs on neurologic exam or brain imaging evidence of relevant cerebrovascular disease.
3. A relationship between the above 2 disorders, manifested or inferred.

From Roman GC, Tatemichi TK, Erkinjuntti T, et al. Vascular dementia: diagnostic criteria for research studies. Report of the NINDS-AIREN International Workshop. Neurology. 1993;43:250–60

construct, but still excludes those with less severe cognitive impairments in those with single domains there are impaired after stroke. In addition, the criteria required memory impairment, a feature more associated with Alzheimer Disease that with cerebrovascular disease.

The 2011 American Heart Association-American Stroke Association (AHA-ASA) criteria (Table 2) did away with the requirement for memory impairment. They also defined vascular mild cognitive impairment (VaMCI) to describe clear and measurable changes to cognition that are not severe enough to impair activities of daily living [4••]. These criteria clearly broadened the net to include cognitive impairments that are clearly related to cerebrovascular disease, increasing to sensitivity from the NINDS-AIREN criteria. Still left out from these criteria are patients who have deficits in a single cognitive domain after stroke.

The AHA-ASA criteria also attempted to tackle the issue of mixed dementia, that is, dementia related to both neurodegeneration (usually Alzheimer Disease) and cerebrovascular disease. These 2 conditions are common in older adults, and coexist frequently [8]. In fact, nearly half of those with the diagnosis of probable Alzheimer disease have mixed pathology on autopsy, most frequently cerebrovascular disease [9]. While not discounting the existence of dementia with truly mixed etiology, the criteria include the term *possible* to cases where the etiology is unclear, and *probable* for cases of "pure" vascular etiology [4••]. While from a research perspective, this distinction is quite important to help delineate the effects of cerebrovascular disease on cognition, in clinical practice, the line is not always so clear.

Clinical and Neuroradiological Features

While still at heart clinical, the diagnosis of VCI, regardless of the criteria used, requires evidence of cerebrovascular disease. Due to this requirement, acquisition of a brain computed tomography (CT) or magnetic resonance imaging (MRI) scan is usually an important part of making the diagnosis. Most typically, widespread small vessel ischemic disease would be expected, but 1 or more discrete strokes or hemorrhages may also be seen. In the case of cerebral amyloid angiopathy, diffuse microhemorrhages are seen.

Given the range of imaging findings, it should come as no surprise that the clinical presentation of vascular cognitive impairment would be heterogeneous as well. That being said, certain clinical features are more commonly seen, however. In addition to focal cognitive deficits such as aphasia from dominant hemisphere lesions and neglect from nondominant hemisphere lesions, a specific pattern of deficits seen with the widespread involvement of periventricular white matter has been described. These include slowed mentation, executive dysfunction, encoding-based memory deficits, and mood disturbances, including pseudobulbar palsy, abulia, and depression [10].

One important difference between the NINDS-AIREN and AHA-ASA criteria involves the requirement for memory impairment. Many researchers have argued that memory impairment should not be required for the diagnosis of dementia [11]. While memory loss is a key clinical feature in Dementia of the Alzheimer Type [12], there is no reason to believe that it must be seen in all dementias, and in fact, the diagnostic criteria for other dementias such as frontotemporal dementia and primary progressive aphasia specifically require that memory be relatively spared [13, 14]. In patients who do have memory problems, they tend to be more related to difficulty with encoding new information, thereby limiting acquisition, rather than the pattern of rapid forgetting seen in Alzheimer Disease, with is related primarily to poor retention [10].

Clinical features outside of cognition that support a diagnosis of vascular cognitive impairment include focal motor and sensory signs of stroke, but also gait disturbance (specifically magnetic and parkinsonian gaits), falls, urinary symptoms, and personality change. These features are included in

Table 2 AHA-ASA criteria for vascular cognitive impairment

Exclusions: drug or alcohol abuse/dependence within 3 months, delirium.

Cognitive impairment must be reasonably related to cerebrovascular disease.

Vascular Dementia (VaD): must meet criteria for dementia (multi-domain cognitive impairment affecting activities of daily living). Diagnosis of dementia must be based on cognitive testing. Impairments in activities of daily living cannot be from motor or sensory deficits. No gradual decline in cognition can be documented predating the first stroke.

Vascular Mild Cognitive Impairment (VaMCI): must fit criteria for vascular dementia above, except activities of daily living should be normal or only mildly impaired.

From Gorelick PB, Scuteri A, Black SE, et al. Vascular contributions to cognitive impairment and dementia: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2011;42:2672–713

the NINDS-AIREN criteria as supporting features for vascular etiology [7].

Risk Factors

Since vascular cognitive impairment by definition is caused by cerebrovascular disease, one might predict that vascular risk factors would all predispose to VCI. However, this relationship has not borne out as would be expected. In fact, the only vascular risk factor that clearly predisposes one to VCI is hypertension, and even then, clinical trials have been discordant [4••, 15, 16].

Possibly the clearest risk factor for development of vascular cognitive impairment is having multiple strokes. In a 2009 review [17], Pendlebury and Rothwell found that dementia predating one's first stroke has a 10 % prevalence. Another 10 % develop dementia soon after their first stroke. However, of those with recurrent strokes, more than a third had dementia.

Treatment of Vascular Cognitive Impairment

There are still no FDA-approved treatments for VCI or any of its constituent diagnoses. There are a fairly large number of clinical trials showing some positive effect. Improvements in cognitive function tend to be modest, but many reach clinical significance. Determining clinical relevance is more difficult. By and large, drug trials have failed to show improvement in global functioning, activities of daily living, and quality of life. For this reason, treatment of vascular cognitive impairment is primarily symptomatic. However, many recent studies and reviews are worthy of note.

Cholinesterase Inhibitors

Three cholinesterase inhibitors, donepezil, galantamine, and rivastigmine, are FDA-approved in the treatment of all stages of dementia of the Alzheimer type. These medications work by inhibiting the breakdown of acetylcholine, presumably ameliorating a cholinergic deficit.

The AHA-ASA statement on VCI found class IIa, level A evidence for the use of donepezil or galantamine in VCI [4••]. This statement was based on numerous trials showing some improvement in cognitive measures, but not in global functional measures. In a recently published 6-month study of donepezil in vascular and mixed dementia, a significant but modest improvement was seen in a variety of cognitive test scores, but also in a subjective measure of global function, the CGI [18]. With regards to rivastigmine, a recent Cochrane review found only 1 study that was adequately powered for their analysis [19]. This study showed improvements in cognition, but no statistically significant effects on global functioning, behavior, or activities of daily living [20].

Given their proven efficacy in dementia of the Alzheimer type, some research has probed the relationship between indicators of Alzheimer pathology vs risk factors for vascular disease. In a trial of donepezil in vascular dementia (by the NINDS-AIREN criteria), a variable effect was seen between patients with or without hippocampal atrophy [21]. The group with hippocampal atrophy that were given a placebo had a decline in cognitive scores (Vascular-Alzheimer Disease Assessment Scale – Cognitive Subscale, VADAS-cog) in the 24-week trial, whereas the group without atrophy on placebo showed improvement. Both groups who received donepezil showed improvement on the VADAS-cog, significantly higher than the placebo control for their respective groups. Conversely, in a trial of rivastigmine in Alzheimer disease, the subgroup of patients that had documented vascular risk factors had significantly more benefit in terms of ADL scores than the subgroup without vascular risk factors. However, the global functioning scores were only better for those with vascular risk factors who received the rivastigmine capsule, and the opposite was found with the patch, making interpretation of these findings difficult [22].

Antidepressants

A trial of escitalopram started within 3 months of a stroke showed improvement on memory and global cognition measures (Repeatable Battery for the Assessment of Neuropsychological Status, RBANS delayed memory and total scores) at 12 months compared with groups not receiving escitalopram, even when controlled for depression [23•]. This finding complements recent studies showing improved motor recovery and overall improvement on the National Institutes of Health Stroke Scale (NIHSS) with administration of antidepressants (serotonin-specific reuptake inhibitors or tricyclic antidepressants) [24–26]. The mechanism of this effect is not well-established, but theories include serotonergic modulation of cholinergic transmission [27], effects on neuroplasticity in the hippocampus [28], and enhancement of neurovascular regeneration [29].

Secondary Prevention of Vascular Disease

Randomized control trials regarding the effect of secondary prevention of vascular disease on cognition are limited by the fact that we cannot ethically withhold treatment proven to prevent ischemic stroke, myocardial infarction, or peripheral arterial disease from a control group. A recently published paper evaluating outcomes of patients in a large stroke registry found that "appropriate vascular risk management," defined as clinically indicated use of antihypertensives, antithrombotic

agents, and lipid lowering drugs, was associated with reduced long-term risk of cognitive impairment. In patients with ischemic strokes without history of atrial fibrillation, independent effects were seen with antihypertensives, the combination of aspirin and dipyridamole, and statins. No similar effect was seen with the use of antihypertensives after hemorrhagic stroke [30••].

Citicoline

The IDEALE study looked at the effectiveness and safety of citicoline, an endogenous choline source involved in the biogenesis of acetylcholine and phospholipid membrane, in VaMCI [31]. The study found stabilization of cognitive scores compared with mild decline in the control group at 9 months. Scores measuring activities of daily living were not significantly different among groups. The medication was well-tolerated and safe. A longer-term study would be needed to see if citicoline would prevent conversion from VaMCI to VaD.

Cerebrolysin

A recent Cochrane review evaluated a number of studies of cerebrolysin for vascular dementia. Cerebrolysin is a peptide from purified pig brain proteins, which is felt to have neurotrophic and neuroprotective activity. It is given intravenously 5 days a week for 4 weeks, with subsequent maintenance dosing. While several trials were identified, the reviewers only found a single large trial rated as good quality. Based on a review of this and several small trials, they found that cerebrolysin did improve general cognitive function, executive function, and global function without serious adverse effects [32]. Further study and clinical utility may be limited by the less than convenient administration, but still, the data show some signal for efficacy.

Ginkgo Biloba

A standardized extract of Ginkgo Biloba, EGb 761, is one of the most studied herbal remedies in dementia research. A 2010 meta-analysis showed that it was well-tolerated, and that change scores for cognitive testing were in favor of the extract vs placebo. However, much like studies of other dementia drugs, effect size was relatively modest, and there was no statistically significant improvement in ADL or global function scores. Furthermore, some of these changes appear to be driven by a subgroup with probable Alzheimer disease, which also showed statistical significance for ADL improvement as well [33]. A more recent study of EGb 761 for the GOTADAY study group, not included in that review, showed improvement in cognitive measures and ADL measures in both Alzheimer and vascular dementia groups, but only included 71 patients with VaD [34]. These results show promise for ginkgo as a research target for the treatment of dementia in general, including VaD.

Ongoing Trials

Several trials for prevention of vascular cognitive impairment are ongoing. Two trials of note both look at primary prevention, ASPREE and SPRINT-MIND. While its role in the secondary prevention of vascular disease is well-established, its role in primary prevention is not as well understood. The ASPREE trial is a clinical trial evaluating the prevention of cardiovascular disease and vascular dementia with low-dose aspirin in the elderly. The study is ongoing, with the goal to follow 15,000 subjects aged 70 years or more for an average of 5 years [35, 36]. The ongoing Systolic Blood Pressure Intervention Trial – Memory and Cognition in Decreased Hypertension (SPRINT-MIND) looks to see of tighter blood pressure control parameters further decrease risk of vascular disease, and will specifically look at cognitive impairment [37, 38].

The NeuroAiD II(MLC901) in Vascular Cognitive Impairment Study (NEURITES) aims to test a traditional Chinese medicine that is readily available in much of Asia, with the design of an allopathic medical study. MLC901 is a combination of 9 different herbal components, and has been shown to increase cerebral blood flow velocities in stroke patients. The study aims to look at cognition, mood, activities of daily living, brain, and retinal imaging in a 24 week double-blind randomized placebo-controlled trial in VCI [39]. If successful, this study would be the first Phase II clinical trial to look at a traditional Asian medicine with such rigor.

Treatment of Focal Cognitive Deficits after Stroke

Two reviews of drug therapy for post-stroke aphasia report numerous positive clinical trials for the medications piracetam and the cholinesterase inhibitors galantamine and donepezil. While each trial is small, evidence is amassing that these medications are helpful in at least a subset of post-stroke aphasia patients [40•, 41]. Responders to these medications tend to have milder aphasia, anomia, and subcortical location of stroke [41, 42].

Transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (TDCS) have also been studied extensively in post-stroke aphasia [43, 44]. While positive trials abound, these techniques, which induce electrical currents or cause changes to membrane potential, respectively, whether to use anodal or cathodal stimulation or whether to stimulate the affected or contralateral hemisphere has not been well worked out. In 1 study, a positive result was found when

cathodal stimulation was applied to the dominant (affected) hemisphere, while anodal stimulation was predicted to cause improvement instead [45]. Clearly, our understanding of how these techniques work is still in development.

Speech therapy is a well-established treatment for post-stroke aphasia, though the acceptance of its use is relatively recent [40•, 41]. A recent trial looking at whether more intensive speech therapy would have greater efficacy was negative, and was perhaps not powered sufficiently, but did show a trend toward greater improvement in language measures and functional communication measures with intensive therapy [46]. Cognitive rehabilitation for neglect is not as well established. A Cochrane review was positive for immediate improvement in neglect measures, but this did not translate to lessened functional disability [47].

Conclusions

Treatment options for vascular cognitive impairment remain limited and poorly supported. The acceptance of the term, vascular cognitive impairment, has led to some standardization in the criteria and the language used regarding cognitive changes related to cerebrovascular disease. Hopefully, this standardization will translate to more reproducible and applicable studies into the understanding of and treatment of these conditions.

Compliance with Ethics Guidelines

Conflict of Interest HyungSub Shim declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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