Advances in Stroke 2003

Vascular Cognitive Impairment

J.V. Bowler, MD, FRCP

Developments in the field of vascular cognitive impairment over the past year have been evolutionary rather than revolutionary and spread across many aspects. However, even evolutionary changes may be radical, and it is in 3 particular aspects—those of treatment, prevention, and the evaluation of white matter disease—that evolution has been at its most rapid.

Treatment

Since 2002, 5 large, randomized studies of the symptomatic treatment of probable and possible vascular dementia have been published. This is a radical development, and these few studies exceed everything that has been published before. These comprise 2 studies of the anticholinesterase donepezil in vascular dementia,1,2 2 studies of the NMDA receptor antagonist memantine in mild to moderate vascular dementia,3,4 and a study of the anticholinesterase galantamine in “probable vascular dementia and Alzheimer’s disease combined with cerebrovascular disease.”5

While these findings are exciting and represent new developments, there are a number of cautions. The first is the relatively modest benefits seen in all these trials. For the anticholinesterases, the benefit on the ADAS-Cog amounts to about 3 points and to <1 point on the Mini-Mental State Examination (MMSE).7 While statistically significant, these effects are so slight that they may not be useful routine treatments but perhaps treatments that should be tried in all but maintained only in individual responders.

These drugs were originally developed for Alzheimer’s disease on the basis of the cholinergic hypothesis; much is made of the presence of a cholinergic deficit in vascular dementia, which probably occurs because of ischemic damage to the cholinergic projections, but this is proportionately considerably less than is seen in Alzheimer’s disease. Indeed, the presence of a cholinergic deficit is not required for the anticholinesterases to produce cognitive improvement8 and so the cholinergic hypothesis is neither necessary nor sufficient to explain the modest benefits. Memantine has slightly less effect than the anticholinesterases on the ADAS-Cog, perhaps a better effect (2 points) on the MMSE but no detectable effect on the Clinical Global Impression of Change (CGI-C) while its side effects are very close to placebo level. That the effects of these different classes of drug are of very similar magnitude raises the possibility that the effects are relatively nonspecific.

There is a further question as to what is actually being treated in these patients. The NINDS-AIREN9 criteria were used in these trials. They have been extensively criticized in several respects, but the relevant fault here is their Alzheimer-based origin.10 While the criteria produce a population different from that obtained by pure Alzheimer criteria, such as NINCDS-ADRDA,11 as witnessed by the almost universal lack of progression in the control groups in vascular dementia studies, it is noteworthy that in the galantamine study,5 where mixed vascular dementia and Alzheimer’s disease were recognized, the benefit of treatment was confined to those with mixed disease, supporting the notion that the bulk of the effect is on the Alzheimer component.

Prevention

The appearance of data on preventative treatment is also a recent phenomenon, the end product of a decade of exhortation of clinical trialists to include measures of cognition, however simple, in their trials of vascular treatments. A number of large, long-term studies have now reported that modifying vascular risk factors reduces incident cognitive impairment and dementia. In updated results from the Syst-Eur study,12 an reduction of 7 mm Hg in systolic and 3.2 mm Hg in diastolic blood pressure over 3.9 years halved incident dementia. The absolute figures are a little less impressive at 3 cases per 100 patient years. The PROGRESS study13 demonstrated a reduction, over 3.9 years of follow-up, in risk of dementia from 7.1% to 6.3% (nonsignificant) and in cognitive decline from 11% to 9.1%, this benefit being attributable to the prevention of recurrent stroke. Despite this association with the prevention of further stroke, there was a surprising lack of association of benefit with the drug regimen used. The main PROGRESS study results14 had shown that combination perindopril and indapamide were more effective than monotherapy in preventing stroke, probably because of a greater reduction in blood pressure. If stroke were the sole determinant of cognitive decline in PROGRESS, the same pattern of change would have been expected for cognition and this was not the case. The study used the MMSE to rate cognition and the DSM-IV to diagnose dementia. Both of these are optimized for Alzheimer’s disease, and it may well be that some of the effects seen in this study were confounded by mixed disease. There may, however, be levels of blood pressure change for which no treatment effect is demonstrable. In the SCOPE study15 of Candesartan therapy in 5000 individuals aged 70 to 89, the blood pressure difference between cases and controls was 3.2/1.6 mm Hg, and no effect on cognition was demonstrable over a mean of 3.7 years. Importantly, both groups enjoyed a
fall in blood pressure of approximately 20/10 due to permitted add-on therapy and both maintained a stable MMSE. It is likely that both groups were, in effect, treatment groups.

Interestingly, evidence for an effect of the statins is weaker. The PROSPER study\(^{16}\) followed 6000 individuals aged 70 to 82 for 3.2 years, half of them randomized to receive pravastatin, and was unable to demonstrate any benefit on stroke, cognition or activities of daily living but did show a benefit on myocardial infarction and TIA. Several cognitive rating scales were used here including the Stroop, which is sensitive to subcortical disease, and it is unlikely that the study was artifactually negative through use of inappropriate tests of cognition. In a 4-year observational study of 1000 postmenopausal women, statin users had a trivially (1\%) higher score on a modified Mini-Mental State Examination.\(^{17}\)

Given the established benefits of the statins in preventing adverse vascular events, the discrepancy between these and antihypertensive therapy requires some explanation. This may lie in the fact that subcortical vascular dementia is the single commonest form of vascular dementia and that hypertension is, by a very considerable margin, the most powerful treatable risk factor. Cholesterol has little association with small-vessel disease and the plaque-stabilizing, antioxidant, and other properties attributed to the statins may not be relevant to lipohyalinosis and so to small-vessel disease. Taking these observations together, it is readily possible to see why different treatments may have differing effects.

**White Matter Disease**

Recent sophisticated developments in imaging now offer new prospects for the quantification of white matter dysfunction, which is important as subcortical vascular dementia is the single commonest form of vascular dementia. Further understanding of white matter disease has been limited by the insensitivity of CT scanning to leukoaraiosis and, conversely, the high sensitivity of MRI. On MRI, a wide variety of pathologic changes from simple myelin edema through to incomplete infarction,\(^{18}\) but not frank infarction, appear the same on standard sequences. The functional consequences and recovery potential for these differing degrees of damage are not the same. Simple volume measurements are additionally confounded by the importance of location. This is exemplified in completed stroke, where attempts to correlate closely infarct volumes with cognitive change routinely fail because of the overriding importance of lesion location. This has generally been overlooked for leukoaraiosis but is important and will further confound the problems arising from highly sensitive imaging. However, while the cortical location of cognitive function is sufficiently well characterized that a neurologist can look at a brain scan and predict the pattern of cognitive deficits, the same does not apply to white matter lesions.

A solution to the combined problems of severity and pattern of cognitive loss requires both that the tract that the lesion lies in be identifiable and the degree of damage to that tract quantifiable. The past 2 years have seen an explosion of work using diffusion tensor imaging to map out white matter tracts, a process termed tractography.\(^{19}\) It is probable that in the near future we will have the imaging ability to identify the tracts affected by white matter lesions. While this will remain a research tool for the foreseeable future, it is quite possible that published maps of the major pathways set against landmarks visible on standard CT scans will become available such that cognitively important and unimportant white matter lesions might be readily distinguished. In addition, diffusional anisotropy can be used to quantify white matter tract disruption and is sensitive enough to detect age-related changes in the absence of visible leukoaraiosis in a way that correlates with neuropsychological testing.\(^{20}\) Furthermore, functional impairment can be seen beyond the visible boundaries of a lesion.\(^{21}\)

Functional MRI may also allow the direct quantification of loss of cortical function as a result of disconnection through damage to afferent pathways. The phenomenon, termed diaschisis, has been recognized for almost a century,\(^{22}\) but traditional functional imaging by PET and SPECT have not demonstrated an ability to detect, map, and quantify subtle changes of the kind that might be seen as a result of small, deep, and incomplete infarcts.\(^{23}\) Functional MRI may well be better. Both aphasia and neglect have been correlated with decreased cortical blood flow at appropriate locations following deep infarcts.\(^{24}\)

The ability to predict the cognitive domain affected by a lesion and to quantify the deficit will have several consequences including the development of surrogate markers for preventative treatments, the demonstration of cortical responses to symptomatic treatments, and improvements in diagnostic and prognostic accuracy. This last point will apply particularly where mixed vascular dementia and Alzheimer’s disease are suspected, as it may allow the determination not only of whether any vascular disease present is contributing to cognitive decline, but also by how much. This will become increasingly common as the high prevalence of mixed dementia is increasingly recognized.\(^{25,26}\)

These developments now have a new forum for their exposition, the International Society for Vascular Behavioral and Cognitive Disorders (http://www.congresx.se/VASCOG2003/), and this is itself an important development. It will meet for the second time in Florence in 2005, and those interested in the field should plan to attend.

While there have been significant developments in many aspect of vascular cognitive and behavioral disorders over the past year, the developments in treatment and prevention are the most radical, representing almost virgin territory, and the most important, as they offer the immediate prospect of both prevention and help with symptoms. The preventative data have arisen because cardiovascular investigators have increasingly recognized cognitive impairment as a legitimate outcome measure and have included it in their trials. However, many trials are still being designed without such assessments, and it is important that this changes. Developments in functional imaging offer the prospect of quantifying damage and loss of function; at present this is not readily possible short of very detailed neuropsychological testing and functional assessments, and even then the available rating scales are imperfect being subject to practice, floor, ceiling, and cultural problems, etc. While not yet of day-to-day
importance, functional imaging may finally offer the cerebral
equivalent of cardiac output or glomerular filtration rate.

References


**KEY WORDS:** Advances in Stroke I cognitive disorders
Vascular Cognitive Impairment
J. V. Bowler

Stroke. 2004;35:386-388
doi: 10.1161/01.STR.0000115301.12426.2B
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2004 American Heart Association, Inc. All rights reserved.

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/35/2/386

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/