ORIGINAL ARTICLE

Therapeutic Issues in Vascular Dementia: Studies, Designs and Approaches

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ABSTRACT: Vascular dementia (VaD) is a heterogeneous disorder resulting from various cerebrovascular diseases (CVD) causing cognitive impairment that reflects severity and location of damage. Epidemiological studies suggest VaD is the second commonest cause of dementia, but autopsy series report that pure VaD is infrequent, while combined CVD and Alzheimer's Disease(AD) is likely the commonest pathological-dementia correlate. Both diseases share vascular risk factors and benefit from their treatment. The most widely used diagnostic criteria for VaD are highly specific but not sensitive. Vascular Cognitive Impairment (VCI) is a dynamic, evolving concept that embraces VaD, Vascular Cognitive Impairment No Dementia (VCIND) and mixed AD and CVD. Clinical trials to date have focused on probable and possible VaD with beneficial effects evident for different drug classes, including cholinergic agents and NMDA agonists. Limitations have included use of cognitive tools suitable for AD that are insensitive to executive dysfunction. Disease heterogeneity has not been adequately controlled and subtypes require further study. Diagnostic VaD criteria now 13 years old need updating. More homogeneous subgroups need to be defined and therapeutically targeted to improve cognitive-behavioural outcomes including optimal control of vascular risk factors. More sensitive testing of executive function outlined in recent VCI Harmonization criteria and longer trial duration are needed to discern meaningful effects. Imaging criteria must be well-defined, with centralized review and standardized protocols. Serial scanning with quantification of tissue atrophy and lesion burden is becoming feasible, and cognitive interventions, including rehabilitation pharmacotherapy, with drugs strategically coupled to cognitive –behavioural treatments, hold promise and need further development.

RÉSUMÉ: Préoccupations thérapeutiques dans la démence vasculaire : études, plans, approches. La démence vasculaire (DVa) est une entité hétérogène résultant de différentes maladies cérébrovasculaires (MCV) qui causent une atteinte cognitive reflétant la sévérité et la localisation des dommages. Les études épidémiologiques suggèrent que la DVa est la deuxième cause de démence, mais des études anatomopathologiques de matériel prélevé à l'autopsie démontrent que la MCV pure est rare et que l'association MCV et maladie d'Alzheimer (MA) est vraisemblablement le plus fréquent corrélat pathologie-démence. Les facteurs de risque vasculaires sont communs aux deux maladies et leur contrôle est bénéfique aux deux maladies. Les critères diagnostiques les plus utilisés pour la DVa sont très spécifiques mais ne sont pas sensibles. L'atteinte cognitive vasculaire (ACV) est un concept dynamique en évolution qui comprend la DVa, l'atteinte cognitive vasculaire sans démence (ACVSD) et la MA avec MCV. Jusqu'à maintenant, les essais cliniques ont ciblé la DVa probable et la DVa possible. Les bénéfices ont été évidents dans les essais portant sur différentes classes de médicaments, dont les agents cholinergiques et les agonistes de la NMDA. Une des limites de ces études est l'utilisation d'outils cognitifs appropriés à la MA qui sont insensibles à la dysfonction exécutive. On n'a pas suffisamment tenu compte de l'hétérogénéité de la maladie et on devra faire des études sur les sous-types de démence. Les critères diagnostiques de la DVa ont été établis il y a 13 ans et devraient être révisés. On doit définir des sous-groupes plus homogènes et cibler l'amélioration des résultats cognitifs et comportementaux ainsi que le contrôle optimal des facteurs de risque vasculaires. Les critères d'harmonisation de l'ACV établissent les grandes lignes de tests plus sensibles pour évaluer la fonction exécutive et des essais plus longs devront être faits pour faire ressortir les effets significatifs. Les critères d'imagerie devront être mieux définis, avec révision centrale et protocoles standardisés. L'imagerie en série avec quantification de l'atrophie tissulaire et du fardeau des lésions est maintenant possible et les interventions cognitives, dont la pharmacothérapie de réadaptation avec des médicaments ciblant stratégiquement la cognition et le comportement, sont prometteuses. On doit poursuivre leur développement.

Vascular dementia (VaD) is a heterogeneous disorder arising from different types of cerebrovascular disease (CVD) and resulting in cognitive impairments that reflect the severity, location and extent of underlying damage. It can be subclassified into multiple cortical infarct, single strategic infarct, hemorrhagic and subcortical ischemic VaD, recognizing that all lesion subtypes can co-occur. In most population studies, VaD is the second commonest cause of dementia after Alzheimer's disease (AD), in the order of 20%.[1] Population autopsy studies, however, suggest that pure VaD is less frequent (< 10% of cases), while combined CVD and AD is the commonest neuropathological finding.[2,3]

Investigation of VaD has been plagued by lack of accepted diagnostic criteria in part due to the heterogeneous etiologies. Hachinski introduced the term Multi-infarct Dementia in 1974,[4]

but later broadened the concept to Vascular Cognitive Impairment (VCI) to denote an at-risk state of cognitive disability not meeting criteria for dementia, but greatly in need of cardiovascular prevention strategies.[5,6] VCI, however, is a dynamically, evolving concept; some have used the term to encompass VaD, Vascular Cognitive Impairment No Dementia (VCIND) and mixed AD and CVD (AD/CVD),[7] and others have proposed the term Vascular Cognitive Disorder (VCD) as a new diagnostic category to cover this spectrum.[8]

Current consensus criteria for diagnosis of VaD, including DSM-IV[9] the ICD-10, the NINDS-AIREN[10] and the ADDTC[11] show only fair agreement.[12-14] The NINDS-AIREN criteria, widely used in clinical trials, show poor sensitivity (20%) but good specificity (94%) for probable VaD.[15] These criteria have been successful in selecting a distinct VaD population in recent drug trials, in which placebo groups showed little decline over six months unlike typical AD cohorts.[16,17]

The frequent co-existence of Cerebrovascular and Alzheimer pathologies in the elderly may help to explain the relative failure of consensus clinical criteria, which try to distinguish between these diseases. Population-based autopsy studies suggest that AD and CVD together explain 80% of dementia etiologies with mixed AD/ CVD accounting for 40-50% of cases.[2,3,18] In the landmark Nun study, only 57% of elderly women meeting pathological criteria for AD were demented during life, whereas 93% of those with small-vessel deep infarcts in combination with AD pathology, were demented (i.e. 20x the likelihood).[19] Less AD pathology was necessary for clinical expression of dementia when infarcts were present, though in another study this synergistic effect was only evident in the early stage of AD.[20] One recent radical overview of AD pathogenesis proposed that AD is a vasculopathy,[21] citing the high prevalence of microvascular changes in AD.[22]

Post-stroke dementia is estimated to occur in 26% of stroke patients by three months (cf 3% in age-matched controls)[23,24] and adversely affects recovery.[25,26] Cognitive impairment increases long-term dependence[27] and is associated with higher mortality (61% vs. 25%).[28,29] Silent strokes, usually lacunes, are also common (23% of community elderly) and are associated with cognitive decline, dementia and stroke.[30;31] [7593]

Neuropsychologically, VCD may reflect a variety of focal syndromes caused by cortical infarction, but a frontal-subcortical pattern (dysexecutive syndrome) is most commonly seen with multiple lacunar infarcts or with extensive white matter disease,[32] a syndrome called Subcortical Ischemic VaD.[33,34] A meta-analysis of the cognitive correlates of white matter disease, which appears as periventricular and deep subcortical hyperintensities on MRI or as hypodensity on CT scans, concluded that this subcortical and perventricular disease is associated in normal elderly with reduced performance on tasks of processing speed, immediate and delayed memory, executive function and global cognition.[35] Some studies have suggested there is a cumulative volumetric threshold around 10cc for adverse cognitive effects from periventricular white matter disease.[36,37] It is hypothesized that small lacunes (eg in the anteromedial thalamus)[38] can disrupt frontal-subcortical circuits and association tracts,[39,40] but this has not been well specified and warrants further study.[41-43] Recently, white matter hyperintensities that involve the cholinergic projections were selectively associated with executive dysfunctions in Alzheimer's Disease patients more significantly than measures of total lesion burden.[44]

The clinical significance of subcortical ischemic disease in dementia remains unclear, however.[41,45,46] A number of short batteries are now available for brief assessment of executive function.[47-50] Some simple cognitive tests can help distinguish Subcortical VaD from AD (e.g. SIVD worse on phonemic fluency and AD worse on recognition memory).[51] In the recent NINDS-CSN VCI Harmonization criteria, the neuropsychology working group put forward recommendations for a one hour, thirty minute and a five minute battery to assess the cognitive and behavioral profile of patients with cerebrovascular disease.[52] The five minute items are contained within a slightly longer battery that has been validated for detection of Mild Cognitive Impairment in clinical practice, called the Montreal Cognitive Assessment which is freely downloadable from the web (www.mocatest.org) and was also endorsed by the Harmonization group.[53]

In the clinical context, subcortical ischemic vascular brain injury seen as hypodense areas on CT or subcortical hyperintensities on T2-weighted or FLAIR MRI increases with age and with the burden of vascular risk factors. The pathological substrates range from gliosis,[54] demyelination, and dilated perivascular spaces to arteriolar hyalinosis, amyloid angiopathy and lacunar infarcts.[55] Location, number, severity of damage and total volume may all contribute to the cognitive status.[56] Quantification of visible lesion burden is necessary but not sufficient to understand the impact of vascular injury in vivo. Although microinfarcts cannot be detected in vivio, new techniques such as Diffusion Tensor Imaging (DTI)[57,58] and proton Magnetic Resonance Spectroscopy,[59,60] can probe the health of otherwise-normal appearing white matter and detect differences in similar-appearing hyperintensities.

TREATMENT

The pathological interplay of AD and VaD is further underlined by emerging evidence of shared cardiovascular risk factors, such as hypertension, hypercholesterolemia and diabetes, and of cognitive benefits from treatment interventions, such as for hypertension.[61-63] There is accumulating evidence for cholinergic system compromise in VaD, both from animal[64] and human studies.[65] In a clinical dementia cohort, 60% of patients with VaD and 30% with AD had hyperintensities involving the cholinergic projections, and more severe involvment correlated with worse executive function.[38] In a double-blind, placebo-controlled, randomized clinical trial investigating the efficacy and safety of galantamine over 24 weeks in 592 patients with possible or probable VaD, the majority of whom had mixed Alzheimer's and Vascular Dementia, the treated group declined less in cognition and global function compared to placebo.[66] In two double-blind, placebo-controlled, 24-week trials of donepezil in 1219 probable/possible VaD, in which AD was excluded as far as clinically possible, cognition improved in the treated group and global function declined less compared with placebo.[16,17] In a recent 24 week placebo-controlled trial in 788 patients with probable VaD, the galantamine-treated group showed improvement in cognition but no difference in ADL's.[67] Memantine, a selective glutamate blocker also showed cognitive

benefit in two VaD trials, but there was no benefit in global function and the lower baseline MMSE scores was suggestive of concomitant AD.[68,69]

DESIGN ISSUES AND APPROACHES

There are several important considerations in designing and planning therapeutic trials for VaD.

1) *All stages and disease subgroups should be targeted for treatment trials:* In addition to pharmacotherapy approaches, these syndromes may be amenable to cognitive rehabilitation techniques, based on analysis of cognitive profile, to assist in compensation and the use of assistive devices. Cardiovascular risk profiling and vigorous treatment of major risk factors such as hypertension, hypercholesterolemia, homocysteinemia, and diabetes, along with healthy diet, exercise, smoking cessation and appropriate antithrombotic therapy must also be instituted.

2) *Improve homogeneity of subgroups:* We need to target etiologically meaningful subgroups for selection and stratification in trials and for analysis of results. For example, subcortical VaD appears to be the commonest VaD subtype, but has yet to be targeted in a large scale trial. Furthermore, we should be attacking the problem before cognitive decline leads to dementia, i.e. to functional dependency. Many individuals with subcortical ischemic disease have concomitant AD and should be specifically identified and analyzed within AD trials, where they will be common, given the usual average age.

3) *Types of treatment (disease modifying and symptomatic strategies) and duration of treatment:* Prevention therapies may have neuroprotective effects and this needs to be specifically investigated, e.g. use of angiotensin inhibitors/blockers, statins, and different anti-thrombotic agents, with cognitive-behavioural measures as primary outcomes. Given the relative cognitive stability of placebo groups in studies of probable VaD over six months, longer duration trials at least one year in duration are needed, with allowance for attrition from the annual cardiovascular event and mortality rates likely in this population. In addition, scientifically-based, cognitive enhancing therapies must continue to be developed. Emerging evidence for brain reorganization after stroke and the likelihood of adaptation to more slowly developing pathology such as Subcortical VaD, suggests that rehabilitation pharmacotherapy may be a promising approach, whereby drugs are coupled to augment cognitive interventions targeted at deficits such as attention, working and episodic memory.

4) *Diagnostic and inclusion criteria, including neuroimaging:* Current criteria for VaD are more than 13 years old and urgently need updating. We may need to revise and broaden the current criteria for dementia so that memory is not a necessary condition, but rather one of the domains potentially affected. We must upgrade awareness and skills in assessment of executive functions, which the new VCI harmonization criteria will help to standardize. The severity criterion for interference with activities of daily living can be retained to apply to the individual patient and satisfy a clinically meaningful threshold for dementia. The requirement for focal signs should be downgraded from core to a supportive feature. Neuroimaging criteria should be selected to support diagnosis of different entities across the spectrum of VCIND, mixed AD/CVD and VaD. These should be flexible and incorporate new developments in neuroimaging that have been validated clinically and pathologically. (See Chertkow and Black in this supplement).

5) *More attention to executive functioning for inclusion and outcome measurement:* We need to incorporate assessment of executive functions, which can be meaningfully fractionated, based on cognitive neuroscience and evolving knowledge of subregional, frontal-mediated cognitive processes,[70] frontal-subcortical circuits,[39] and compensatory interactive brain networks activated in performing various tasks. Functional Magnetic Resonance Imaging and PET studies are helping to reveal critical nodes in these networks, and how they change with aging and injury.[71] Until recently, the choice of tests was ad hoc but through the recent Harmonization criteria process, the key cognitive domains can be probed in a standardized way, with items that are relatively culturally and linguistically neutral.[52] These core standardized tests can be longer or shorter depending on the context or question to be answered, and can be enhanced by additional conventional or more theoretically-driven tasks as needed.

6) *Neuroimaging both for selection and monitoring change:* Given our understanding that AD and CVD pathologies interact in the aging brain, computer-assisted, tissue -classification volumetric studies of dementia should account for vascular parenchymal injury as well as atrophy[41,72,73] T1-weighted images, which are suitable for grey-white matter tissue classification, are less sensitive to white matter pathology, so T2 weighted or FLAIR images must be obtained to allow quantification of lesion burden. Since standardized visual rating scales for white matter hypeintensities have limited reliability,[74,75] especially for detecting subtle longitudinal change, quantitative, intensity-based, volumetry is likely needed. Though such measures are not yet validated as surrogate outcomes, they should be incorporated into clinical designs to evaluate the effect of treatment on the lesion burden as well as atrophy. This can be done by imaging with standardized protocols that provide for both clinical evaluation on site, preferably with use of rating scales, as well as for centralized interpretation and quantitative analysis. The NINDS-CSN VCI Harmonization criteria include recommendations for imaging protocols as well as core clinical assessment that could allow comparison between sites and different studies in the future.[52] Multisite studies have become much more feasible now with digital images and web –based technologies. Advanced MRI techniques particularly DTI, quantitative T2, Magnetization Transfer and MRS hold promise, but need more development.

CONCLUSION

Designs and approaches for future clinical trials will depend on new evolving criteria for Vascular Cognitive Disorders. More homogeneous subgroups need to be defined and targeted for appropriate therapies, including optimizing control of cardiovascular risk factors, to improve cognitive-behavioural outcomes. Longer trial periods will likely be required to discern meaningful benefits. Clearly, more sensitive measures of executive functioning must be included as well as behavioural

status. Imaging outcomes will require standardized protocols, quantitative analysis and possibly advanced measures such as changes in fractional anisotropy derived from DTI. Serial scanning to quantify changes in tissue atrophy and lesion burden is becoming feasible with computer-assisted techniques, though not yet validated as surrogate outcomes. Akin to blood storage, scans can be archived for future analysis. Cognitive rehabilitation interventions, including rehabilitation pharmaco-therapy in which drugs are strategically coupled to cognitive–behavioural treatments, have great promise and are in urgent need of further development.

COMPETING INTERESTS

The author has received honoraria for CME and ad hoc consultation from manufacturers of anti- dementia drugs, including Pfizer Inc, Novartis Pharmaceuticals, Janssen-Ortho, and Lundbeck. She has also had research grants from Eisai and Pfizer Inc, Novartis Pharmaceuticals, Janssen-Ortho, Myriad Pharmaceuticals and Sanofi-Aventis.

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