Facts, myths, and controversies in vascular dementia

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Abstract

Significant progress in the field of VaD resulted from publication of the NINDS-AIREN Diagnostic Criteria for VaD (G.C. Román, T.K. Tattemichi, T. Erkinjuntti, et al., Vascular dementia (VaD): diagnostic criteria for research studies. Report of the NINDS-AIREN International Workshop. Neurology 43 (1993) 250–260). Epidemiological studies confirmed the importance of VaD as the second most common cause of dementia in the elderly, representing 15–20% of all cases of dementia. In Europe and North America, Alzheimer's disease (AD) predominates over VaD in a 2:1 ratio; in contrast, in Japan and China VaD accounts for almost 50% of all dementias. Case-control studies have identified risk factors for VaD including ageing, hypertension, diabetes mellitus, hyperlipidemia, recurrent stroke, cardiac disease, smoking, sleep apnea, and more recently, hyperhomocysteinemia, among others. Hypertension treatment may prevent VaD and AD. This finding has enormous importance from the Public Health viewpoint to decrease the future number of patients with dementia in the elderly.

Along with advances in the field of VaD came a number of controversies and damaging misconceptions and myths. Myth no. 1—Vascular dementia is a non-entity: The false idea that VaD does not exist is particularly destructive because it creates the perspective that VaD is unworthy of study or research. A condition that either does not exist or represents only a minute proportion of all cases of dementia in the elderly, lacks public health relevance and becomes a low priority for research by funding agencies and industry. In fact, vascular brain lesions are the commonest and most important component of dementia in the elderly. Myth no. 2—Vascular dementia is so difficult to diagnose that only experts can recognize and identify it accurately: VaD does exist and the diagnosis of post-stroke VaD, in particular is straightforward. Most cases fulfill NINDS-AIREN criteria for probable VaD; i.e., (1) there is acute onset of dementia demonstrated by impairment of memory and two or other cognitive domains, such as orientation, praxis or executive dysfunction; (2) relevant cerebrovascular lesions are demonstrated by neuroimaging; and (3) a temporal relation between stroke and cognitive loss is evident. In the donepezil trials on VaD, post-stroke dementia represented about 75% of the >1,200 patients enrolled. Myth no. 3—Improvement in clinical trials of cholinergics in VaD due to underlying AD, not to the vascular lesions. Experimental, clinical and pathological evidence has demonstrated cholinesterase deficits in VaD (independently of any concomitant AD pathology), including low acetylcholine in cerebrospinal fluid, and reduced choline acetyltransferase (ChAT) in the brain.

Keywords: Vascular dementia; Cholinesterase deficit; NINDS-AIREN criteria

1. Introduction

Vascular dementia (VaD) constitutes the second most common cause of dementia in the elderly, representing 15–20% of all cases of dementia worldwide [1]. Projections indicate that with progressive ageing of the populations, this will become the commonest form of dementia. The inherent increases in cardiovascular disease and stroke that occur with growing age, and the recognition of the import contribution of cerebrovascular disease (CVD) to Alzheimer's disease (AD), will result in an elevated incidence of VaD, both as the primary cause of the dementia, and as an important contributor to other forms of degenerative dementia. I review here some of the advances and controversies that have arisen in the field of VaD since the publication in 1993 of the NINDS-AIREN criteria by Román et al. [2].
2. The NINDS-AIREN diagnostic criteria for VaD [2]

Publication of the California criteria for ischemic VaD [3], and of the NINDS-AIREN criteria for multiple forms of VaD [2], resulted in a wave of interest in this field, with a surge of research publications in multiple related areas.

From the epidemiological viewpoint, the importance of VaD has been confirmed, among numerous other studies, by the European collaboration for dementia in population-based cohorts [4,5]. According to Chen [this issue], “European and North American studies have shown a predominance of AD over VaD with an overall 2:1 ratio, whilst the reverse is true for Japanese and Chinese studies where there is a predominance of VaD with an overall 2:1 ratio.” However, Chen calls our attention to the fact that few epidemiological field studies in Asia have utilized neuroimaging and the rates, therefore, should be interpreted with caution. Nonetheless, a recently published population-based study in Japan [6], which utilized screening by neuropsychologists and CT scanning, showed that VaD accounted for nearly half of the cases of dementia.

In summary, epidemiological data provide a consistent view of the importance of VaD in most populations [1]; in particular, numerous studies have called attention to the frequent occurrence of post-stroke VaD [7,8]. Variations in incidence and prevalence are found in different racial and ethnic groups, probably related to the preponderance of large-vessel atherothrombotic disease and cardiac embolism in some groups, and small-vessel disease from diabetes and hypertension in others.

Epidemiological studies have also revealed a number of risk factors linked with the development of VaD. See, DeCarli [this issue]. The most important ones include age, hypertension, diabetes mellitus, hyperlipidemia, recurrent stroke, cardiac disease, smoking, sleep apnea, and more recently, hyperhomocysteinemia. Most of these factors are eminently treatable and preventable, in particular hypertension (Hanson and Forcette, this issue) and hyperhomocysteinemia. See, Sachdev [this issue]. These findings have enormous importance from the Public Health viewpoint, to attempt to decrease the incoming epidemic of dementia in the elderly.

From the clinical viewpoint, the NINDS-AIREN criteria expanded the horizon from the narrow limits imposed by the multi-infarct dementia concept of Hachinski et al. [9]. Conditions such as “strategic stroke dementia” and subcortical VaD have been the theme of numerous studies, using research methods such as PET scan. Recognition of the behavioral and affective consequences of stroke led to the novel topic of “vascular depression.” See reviews by Dieguez et al., and Steffens [this issue]. Last but not least, beginning with the classic notion ofBinswanger disease [10], the discovery of frequent white matter lesions (WMLs) in the elderly brain, led to a large number of research studies using brain imaging, CT or more recently MRI, in correlation with neuropathology, neuropsychology, risk factor analyses, as well as psychiatric and neurological manifestations, both in clinic-based and population based-studies. See, Abstracts section [this issue]. Major advances have clarified the understanding of WMLs, lesions that once were called UBOs, unidentified bright objects, by analogy with UFOs, unidentified flying objects [11].

3. Myths and controversies in VaD

The last decade saw significant advances in the understanding of the mechanisms causing dementia as a result of cerebrovascular injury, in the identification of relevant risk factors, and in the development of potential means of prevention and treatment arising from controlled clinical trials. Along with these advances in the field of VaD came a number of controversies and damaging misperceptions. I review here the myths most frequently argued against the existence of VaD.

3.1. Myth no. 1: Vascular dementia is a non-entity

The rumors regarding the non-existence of VaD are persistent and harmful. The introduction of the term "Vascular Cognitive Impairment" (VCI) has contributed to this confusion. See, Román, VCI [this issue]. The false idea that VaD does not exist is particularly destructive because it creates the perspective that VaD warrants no study or research. A condition that either does not exist or represents only a minute proportion of all cases of dementia in the elderly, lacks public health relevance and becomes a low priority for research by funding agencies and industry.

Of course, VaD exists and there are no conceptual difficulties with the notion that dementia can result from stroke and cerebrovascular disease (CVD). In fact, post-stroke dementia has been known for more than 300 years, since 1672, when Thomas Willis first recognized “dullness of mind... forgetfulness... and foolishness” as sequelae of apoplexy [12]. Post-stroke dementia is the commonest form of presentation of VaD. It is characterized by a dramatic acute change in cognition occurring concurrently with a stroke. The all-too-typical history is that of a previously independent, intelligent and productive elderly person who suffers a stroke. The vascular brain injury causes limited motor and language deficits but abruptly the patient becomes unable to perform the basic and instrumental activities of daily living (ADLs and IADLs) forcing the family to provide a constant caregiver or an institution. Post-stroke VaD is readily recognized by relatives and is easily diagnosed by general practitioners. International studies have demonstrated that 20–25% of all ischemic strokes in patients older than 65 years of age result in VaD making post-stroke dementia a major cause of disability.

From the public health viewpoint, VaD contributes to burden of institutionalization from stroke. The loss of
executive function typically seen in VaD is the most important factor in the functional deficit. Royall [13,14] showed that declining executive control predicts change in functional status in normal elderly; the effect of executive control represented 40% of the variance and was stronger than age, baseline IADLs, comorbid disease or level of care. Pohjasvaara et al. [15], in a recent study of post-stroke patients in Finland, confirmed that executive dysfunction was the main determinant of abnormalities in both basic ADLs and IADLs. These authors suggested that executive function including IADLs may be more sensitive for the diagnosis of VaD and could accurately measure the effects of potential therapies.

In summary, VaD exists, is commonly seen on a daily basis in most clinic settings, in particular after stroke, and is an easily diagnosed form of dementia in the elderly representing an important cause of functional loss and institutionalization.

3.2. Myth no. 2: Vascular dementia is so difficult to diagnose that only experts can recognize and identify it accurately

As mentioned in the reply to the previous myth, the diagnosis of post-stroke VaD is straightforward. Most of these cases fulfill NINDS-AIREN criteria for probable VaD; i.e., (1) there is acute onset of dementia demonstrated by impairment of memory and two other cognitive domains, such as orientation, praxis or executive dysfunction; (2) relevant cerebrovascular lesions are demonstrated by neuroimaging; and (3) a temporal relation between stroke and cognitive loss is evident. In controlled clinical trials, post-stroke dementia represents about 75% of all patients enrolled.

Most of the diagnostic difficulties occur with the subacute, slowly progressive forms of VaD [16–18] that in the opinion of some clinicians could be confused with AD. A closer look at these subcortical forms of VaD reveals significant differences from AD. Some of the typical differences include the following: alterations of gait are unusual in AD while they are frequently observed in VaD; memory impairment is the hallmark of AD due to the early and selective loss of neurons and presence of neurofibrillary tangles in the entorhinal region of the hippocampus [19,20]. Patients with VaD typically have memory disturbances but these are less severe than in AD, mainly forgetfulness and problems with spontaneous recall that improve with clues and prompting [21]. Except for dysarthria, language and verbal fluency are usually unaffected in VaD. See, Desmond [this issue]. In fact, a severe dementia syndrome is relatively uncommon in SVD. In contrast, amnesia, in particular anterograde episodic memory loss (i.e., no new memories for distinct events or episodes, usually tested by story recall and word list learning) is usually the first and most severe cognitive manifestation of AD. This is probably the result of trans-entorhinal neuropathological AD lesions [19]. This pattern of progression and the possibility of early intervention led to the clinical characterization and recognition of the syndrome of 'mild cognitive impairment' as the earliest clinical form of AD [22]. Although also present in AD, involvement of frontal networks is relatively more common in VaD [23]. Patients with VaD often manifest changes in mood and personality, apathy and lack of activity; depressive features may be present, and crying spells are typical; patients appear perplexed and confused when doing simple chores due to disproportionate impairment in frontal executive functions and attention. Cognitive impairment in VaD usually has abrupt onset and cognitive abilities decline over time, generally in a stepwise or fluctuating manner that may relate to recurrent strokes. See, Desmond [this issue] for a review of neuropsychological differences between AD and VaD.

3.3. Myth no. 3: The improvement in clinical trials of AChEIs in VaD is due to underlying AD, not to the vascular lesions

There is experimental, clinical and pathological evidence of cholinesterase deficits in VaD [24]. Cholinergic dysfunction is well documented in VaD, independently of any concomitant AD pathology; these deficits consist of decreased levels of acetylcholine in the cerebrospinal fluid and reduced cholinergic markers such as choline acetyltransferase (ChAT) in the brain [25–28]. Hippocampal ChAT deficits of up to 60% have been reported in the brains of both AD and VaD patients. The cholinergic basal forebrain nuclei are irrigated by penetrating arterioles and are therefore susceptible to the effects of arterial hypertension. Moreover, ischemic lesions in the white matter and the basal ganglia can interrupt the cholinergic projections [29]. Selden et al. [30] described in the human brain two highly organized and discrete bundles of cholinergic fibres extending from the nucleus basalis of Meynert (nBM) to the cerebral cortex and amygdala. Mesulam et al. [31] demonstrated cholinergic innervation from ischemic pathway lesions in CEDASIL, a pure genetic form of VaD, entirely unmixed with AD lesions.

Cholinergic mechanisms play a role in the modulation of regional cerebral blood flow [32]. Stimulation of the nBM results in increased blood flow in the cerebral cortex [33]. This cholinergic vasodilatory system relies upon activation of both muscarinic and nicotinic cholinergic receptors and the response declines with age. Therefore, there is loss of cholinergic function in patients with VaD, and this is associated with reductions in cerebral blood flow [34].

The above observations provide reasonable arguments to justify the use of cholinesterase inhibitors in VaD, both unmixed with AD, as well as in patients with AD+CVD. Three of the acetylchoolinesterase inhibitors (AChEIs) approved for use in AD—donepezil, galantamine and rivastigmine—have been studied also in VaD. See review by Erkinjuntti [this issue]. The effectiveness of the NINDS-
AIREn criteria in clinically separating mixed dementia (AD+CVD) from AD and from relatively pure or unixed forms of VaD is reviewed by Román et al., later in this issue.

4. Conclusions

Significant progress in the field of VaD resulted from publication of the NINDS-AIREN Diagnostic Criteria for VaD (Román et al.[2]), including epidemiological data on prevalence and risk factors, and clinical studies that have confirmed the importance of VaD as a common cause of dementia in the elderly. Arguments are presented against a number of damaging myths surrounding this topic. After a dozen years of controversy, it is time to move away from nosological discussions into public health preventive actions.

References


