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Featured Articles

Magnetic resonance imaging-measured atrophy and its relationship to cognitive functioning in vascular dementia and Alzheimer's disease patients

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Abstract

Background: Recent pathological studies report vascular pathology in clinically diagnosed Alzheimer's disease (AD) and AD pathology in clinically diagnosed vascular dementia (VaD). We compared magnetic resonance imaging (MRI) measures of vascular brain injury (white matter hyperintensities [WMH] and infarcts) with neurodegenerative measures (medial-temporal atrophy [MTA] and cerebral atrophy [CA]) in clinically diagnosed subjects with either AD or VaD. We then examined relationships among these measures within and between the two groups and their relationship to mental status.

Methods: Semi-quantitative MRI measures were derived from blind ratings of MRI scans obtained from participants in a research clinical trial of VaD (N = 694) and a genetic epidemiological study of AD (N = 655).

Results: CA was similar in the two groups, but differences in the mean of MTA and WMH were pronounced. Infarcts were significantly associated with CA in VaD but not in AD; MTA and WMH were associated with CA in both. WMH was associated with MTA in both groups; however, MRI infarcts were associated with MTA in VaD but not with MTA in AD patients. MTA was strongly associated with Mini-Mental State Examination scores in both groups, whereas evidence of a modest association between WMH and Mini-Mental State Examination scores was seen in VaD patients.

Conclusions: MRI data from two dementia cohorts with differing dementia etiologies find that the clinical consequences of dementia are most strongly associated with cerebral and medial-temporal atrophy, suggesting that tissue loss is the major substrate of the dementia syndrome.

Keywords: Alzheimer's disease; MRI; Dementia; Vascular; Hippocampus; Atrophy

1. Introduction

Research on dementia has focused on understanding and differentiating dementia subtypes to identify clinical and pathophysiological characteristics unique to each disorder. However, data strongly suggest that late-life dementia,

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commonly attributed to Alzheimer's disease (AD), is actually a complex process often because of the combined effects of multiple pathologies [1]. Magnetic resonance imaging (MRI) is one method by which the extent, impact, and possible etiology of regional brain pathology can be quantitatively assessed [2]. Early attempts to compare MRI measures among clinically diagnosed AD and vascular dementia (VaD) subjects, however, were relatively small and inconclusive [3]. More recent reports of the qualitative assessment of MRI differences between AD and VaD patients with larger samples have suggested that medial-temporal atrophy (MTA), particularly hippocampal atrophy, is uniquely associated with clinical AD as opposed to VaD [4]. In fact, hippocampal atrophy is considered the imaging hallmark of clinical AD and is strongly associated with AD pathology [5–8]. Bastos-Leite et al, however, reported a high rate of MTA in a well-characterized sample of VaD patients and an association of MTA with cognitive functioning in the same group [9]; similarly other MRI studies have found extensive hippocampal atrophy in patients with suspected VaD [10] and hippocampal sclerosis has been associated with severe hippocampal atrophy on MRI [2]. Global cerebral atrophy also has been associated with cognitive performance in both AD and VaD patients [11]. Although VaD has characteristically been associated with white matter hyperintensities (WMH) in addition to infarction, WMH have been negatively correlated with cognitive functioning in persons with normal cognition, VaD [12], mild cognitive impairment [2], and AD [13], suggesting that the effect of this pathology transcends clinical diagnosis.

Given the evidence for the complex nature of brain diseases underlying the dementia syndrome, we therefore sought to investigate the relative effect of cerebral atrophy, MTA, WMH, infarcts, and Mini-Mental State Examination (MMSE) scores among cognitively normal, AD, and VaD individuals. To accomplish this aim, we first characterized the different levels of atrophy and vascular pathology observed in each group. We then examined the functional relationships between atrophy, vascular pathology, and cognitive impairment within the AD and VaD groups. Given the presumption that VaD is solely because of vascular pathology, we hypothesized that MRI infarcts and WMH should be strongly associated with global cerebral atrophy (CA) in the VaD group. Conversely, given that the dementia attributable to AD is solely because of AD pathology, we hypothesized that MTA—as an excellent marker of AD pathology—would be strongly associated with CA in the AD group. To test the possibility, however, that hippocampal atrophy can result from either vascular or AD pathology [2], we also examined the relationship between MTA and vascular markers. We again hypothesized that MTA would be weakly associated with vascular markers (white matter hyperintensity and stroke) in the VaD group and unassociated with vascular markers among the AD subjects. Finally, we investigated the relationship between all the MRI and cognitive ability (MMSE) within the two dementia groups. We hypothesized that vascular markers would have a stronger association with MMSE in the VaD group, but that MTA would have the strongest association with MMSE in the AD group.

2. Methods

2.1. Subjects

We studied VaD patients diagnosed using Neuroepidemiology Branch of the National Institute of Neurological Disorders and Stroke - Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) criteria, AD patients diagnosed using National Institute of Neurological and Communicative Diseases and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria, and cognitively normal relatives (mostly siblings) of the AD patients. A total of 826 randomized subjects meeting NINDS-AIREN criteria for VaD were recruited for an industry-sponsored clinical trial evaluating the safety and efficacy of donepezil in VaD, of which approximately 31% met clinical criteria for probable VaD [14] (clinicaltrials.gov NCT00165737); 655 AD patients meeting NINCDS-ADRDA criteria for AD and 756 cognitively normal (CN) relatives of the AD patients were Caucasian participants of the Multi-Institutional Research in Alzheimer's Genetic Epidemiology (MIRAGE) Study, a multisite, multiethnic, family-based genetic study of AD [15–17]. The recruitment and evaluation of MIRAGE subjects was overseen and approved by Boston University Human Subjects Protection Committee. Ethics review panels appropriate for clinical trials also oversaw VaD subject collection and study design. Written consent was obtained from all subjects (or guardians of subjects).

2.2. Data

Both the MIRAGE and VaD studies were large multicenter studies. MRI scanner strength, model, and settings used varied by collection site, necessitating the use of semi-quantitative measures of atrophy and vascular disease. All MRI scans were scored by a single rater (C.D.) blinded to screen failure status in the VaD study and AD status in the MIRAGE study (proband vs control). Although the rater was aware of the study for which the person was recruited, he was blinded to clinical syndrome in both studies as MIRAGE included both AD and normal controls and the VaD study included both VaD and AD patients. Among the 826 VaD subjects, 132 did not receive an MRI and were excluded from comparisons other than basic descriptive statistics. Scans were scored for left and right MTA using Scheltens' scale (0-4 integer, where most severe atrophy = 4), cerebral infarction (presence/absence), and number of infarcts (NI). The average MTA (left and right) was used as our measure MTA in analyses described later. Global atrophy and WMH were rated on a visual analog scale (0-100), with 100 representing severe atrophy and extreme WMH,