Strategic Subcortical Hyperintensities in Cholinergic Pathways and Executive Function Decline in Treated Alzheimer Patients

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Objective: To investigate changes in cognition, function, and behavior after 1 year in patients with Alzheimer disease being treated with cholinesterase inhibitors, in relation to the presence or absence of subcortical hyperintensities involving the cholinergic pathways.

Design: One-year prospective cohort study.

Setting: Memory Clinic, Sunnybrook Health Sciences Centre, University of Toronto.

Patients: Ninety patients with possible/probable Alzheimer disease who were being treated with cholinesterase inhibitors at baseline.

Interventions: Yearly standardized neuropsychological testing and brain magnetic resonance imaging (MRI). The Cholinergic Pathways Hyperintensities Scale (CHIPS) was applied to baseline MRIs to rate the severity of subcortical hyperintensities in cholinergic pathways. The consensus-derived Age-Related White Matter Changes (ARWMC) Rating Scale was used as a general measure of white matter disease burden.

Main Outcome Measures: Tests of global cognition, function, and behavior and specific cognitive and functional domains.

Results: Patients in the low CHIPS group were equivalent to those in the high CHIPS group with regard to baseline demographic characteristics, cognitive severity, and vascular risk factors. After covarying age and education, no differences were found after 1 year in overall cognition, function, and behavior or on memory, language, and visuospatial tasks. Patients in the high CHIPS group showed improvement on executive function and working memory tasks compared with those in the low CHIPS group. For the ARWMC scale, groups with and without white matter abnormalities were equivalent on baseline demographics and in cognitive, functional, and behavioral outcomes.

Conclusion: Cerebrovascular compromise of the cholinergic pathways may be a factor that contributes more selectively than does total white matter lesion burden to response to cholinergic therapy in Alzheimer disease, particularly on frontal/executive tasks.

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AD pathology and that the partial injury caused by vascular disease in the cholinergic pathways might be more amenable to treatment with CHEIs. Thus, we predicted that treated patients with more severe cholinergic pathways involvement (high Cholinergic Pathways Hyperintensities Scale [CHIPS] score) would show less decline compared with patients with no or minimal cholinergic tract involvement (low CHIPS score), especially on frontal/executive tasks.

METHODS

Participants were recruited from the Sunnybrook Dementia Study, a longitudinal imaging observational study of AD and other dementias, if they had sufficient English fluency, visual and auditory acuity to complete neuropsychological testing, and baseline magnetic resonance imaging (MRI) and neuropsychological testing less than 12 weeks apart. The study sample was derived from 183 patients of the Memory Clinic at the Sunnybrook Health Sciences Centre, University of Toronto, who met criteria of the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association for probable (n = 180) or possible (n = 3) AD, if cerebrovascular disease was the only other contributing pathology. Those with lacunar infarcts were excluded (Figure 1).

To be included, patients underwent standardized assessments at baseline and at annual follow-up visits. The baseline assessments occurred within 1 month before or after the start of therapy with donepezil hydrochloride or 2 months after the start of therapy with rivastigmine tartrate or galantamine hydrobromide. All patients were receiving treatment throughout the study, titrated to the maximum tolerated dose. All achieved the therapeutic range. The burden of cerebrovascular risk factors and comorbid disease was documented for each patient.10

Although patients had SHs on their MRIs, none had severe enough white matter disease to meet the imaging criteria established by the National Institute of Neurological Disorders and Stroke–Association Internationale pour la Recherche et l’Enseignement en Neuroscience for possible or probable vascular dementia.11

COGNITIVE ASSESSMENT

The cognitive assessment included the Mattis Dementia Rating Scale (DRS)12 as a test of general cognition; California Verbal Learning Test (CVLT)13 to assess learning and memory; Boston Naming Test14 as a language index; backward digit span test15 to measure working memory; Controlled Word Association Test using the letters F, A, and S16 as a test of phonemic fluency; Wisconsin Card Sorting Test (WCST)17; and Trail-Making Test A18 to sample executive functions. The Trail-Making Test B18 could not be used because several patients were unable to complete the test. The Rey-Osterrieth Complex Figure Test19 was used to probe visuospatial attention and visuoconstructive skill. The Disability Assessment for Dementia Scale (DAD) total score and separate scores for instrumental and basic activities of daily living were used to assess functional capacity.20 Behavioral symptoms were assessed on the Behavioral Pathology in Alzheimer Disease Scale (BEHAVE-AD).21

STRUCTURAL MRI

All brain images were acquired using a 1.5-T MRI system (Signa; General Electric Medical Systems, Milwaukee, Wis). A 12-minute, standard interleaved spin-echo acquisition (T2 and proton density [PD]) was performed in the axial plane, covering the whole brain and using 3-mm-thick sections (echo time, 30.80 milliseconds; revolution time, 3000 milliseconds; number of excitations, 0.5; field of view, 20 × 20 cm; and matrix, 256 × 192 pixels), as well as 3-dimensional T1-weighted imaging with 1-mm-thick sections (echo time, 5.35 milliseconds; flip angle, 35°; number of excitations, 1; field of view, 20 × 20 cm; and matrix, 256 × 192 pixels).

Cholinergic Pathways Hyperintensities Scale

Axial sections from T2- and PD-weighted MRIs were used to rate SHs in cholinergic pathways using a recently developed visual rating scale (Figure 2 and Figure 3).

Age-Related White Matter Changes Rating Scale

Axial sections from either T2- or PD-weighted MRIs were used to evaluate the degree of white matter changes visible in the baseline images.22 The images were assessed in random order by 2 experienced raters (C.B. and F.G.) blind to clinical and demographic information.

STATISTICAL ANALYSES

Groups were separated into low CHIPS (score, < 4) and high CHIPS (score, ≥ 4) groups by using a median split (median score, 4). The median split supported the clinical impression that a total score of 0, 1, 2, or 3 represented few hyperintensities with minimal pathway involvement. Independent-samples t tests were performed for age, education, duration of illness, and baseline Mini-Mental State Examination (MMSE) score. We performed χ² analyses, including the Fisher Exact test, for sex, number of vascular risk factors, and cerebrovascular, cardiac, and peripheral vascular disease. The P values were corrected for multiple comparisons by using the Holm correction.23

Groups were separated into patients with and without lesions in the subcortical gray and cerebral white matter on the basis of ratings of the Age-Related White Matter Changes Rating Scale (ARWMC), also using a median split (median rat-

Figure 1. The process of arriving at the 90 study patients with Alzheimer disease (AD). MMSE indicates Mini-Mental State Examination.
We performed independent-samples t tests for the means of continuous variables and χ² analyses, including the Fisher Exact test, for categorical variables (as described in the preceding paragraph). Again, the P values were corrected for multiple comparisons by using the Holm correction.

Spearman rank correlation coefficients were used to compute associations between the 2 rating scales. Two raters (C.B. and F.G.) independently assessed a validation sample while blinded to clinical information to derive intraclass correlation coefficients as a measure of interrater and intrarater reliability. The CHIPS rating scale showed excellent agreement for both interrater (intraclass correlation coefficient, 0.97) and intrarater (intraclass correlation coefficient, 0.94) reliability.

Separate repeated measures multivariate analyses of covariance (MANCOVAs) were performed for CHIPS and ARWMC scores to compare the groups on cognitive, functional, and behavioral measures, after covarying age and education.

RESULTS

The 90 patients followed up in this study were comparable on baseline demographic characteristics of age, education, and MMSE score (mean score, 23.3) to those lost to follow-up (mean MMSE score, 18.1) and to those unwilling to continue the longitudinal study (mean MMSE score, 23.2). In addition, we found no significant difference between the 3 groups with regard to MMSE score (Figure 1).

Because most of this sample was recruited when donepezil was the only CHEI available, most (approximately 80%) were receiving donepezil and the rest were receiving rivastigmine or galantamine in equal proportions. No patients discontinued the study because of adverse events. When adverse effects did occur, patients were successfully switched to another CHEI right away.

CHIPS MEASUREMENTS

Forty-two patients had no or minimal cholinergic pathway involvement and constituted the low CHIPS group. CHIPS involvement was identified in 48 patients, who constituted the high CHIPS group (range, 0-48 white matter changes). The low CHIPS group was not significantly different from the high CHIPS group on baseline demographic characteristics, cognitive severity, vascular risk factors, or the presence of cerebrovascular, cardiac, and
peripheral vascular disease after correcting for multiple comparisons (Table 1). The groups did not differ significantly on baseline neuropsychological performance after correcting for multiple comparisons (Table 2).

There was a significant group × time interaction on the overall MANCOVA (F1,73=4.4; P=.04) after covarying age and education. The repeated measures MANCOVA results indicated no significant differences over time in scores on the MMSE, overall DRS, Boston Naming Test, CVLT (acquisition after 5 trials, long delay free recall), Trail-Making Test A, and Rey-Osterrieth Complex Figure Test. Furthermore, no difference was seen in functional ability or behavior between the 2 groups after 1 year.

Compared with the low CHIPS group, the high CHIPS group showed a significant increase on the number correct on the WCST (F1,73=9.5; P=.002) and fewer perseverations to previous response after 1 year (F1,73=8.5; P=.005). The high CHIPS group also showed less decline on the backward digit span test (F1,73=6.9; P=.01) (Table 3).
Forty-eight patients had no or minimal white matter changes, whereas 42 patients had more severe changes (range, 0-19 white matter changes). The group with no or minimal changes did not differ significantly from the more severe group on baseline demographic characteristics, cognitive severity, and vascular risk factors after correcting for multiple comparisons (Table 4). There were also no differences in the baseline neuropsychological performance.

The MANCOVA results were not significant for changes in cognitive performance on the ARWMC after 1 year, taking into account age and education (F1,73=1.02; P = .32). The correlation between the CHIPS and ARWMC scores was high (Spearman ρ = 0.78; P < .001).

Treated AD patients with a high CHIPS score decline less after 1 year on executive and working memory tasks believed to implicate left dorsolateral prefrontal function, whereas no differences emerged in overall white matter disease burden, even though ARWMC scores correlated with CHIPS scores.

Previous studies6,24 demonstrate that estimates of total white matter lesion volume do not correlate with global...
cognitive impairment or memory impairment; rather, white matter lesion burden is thought to contribute primarily to the dysexecutive syndrome. Some evidence suggests that SHs within the frontal white matter tracts are especially detrimental relative to other locations and may relate particularly to dorsolateral prefrontal function. Although cholinergic tracts were not specifically examined in those studies, the presence of SHs in cholinergic pathways correlated with poorer scores on executive function tasks in a preliminary study of patients with AD and vascular cognitive impairment.

In our methodology study using CHIPS, strategically located SHs in cholinergic pathways correlated with performance on the DRS, an executively loaded cognitive battery. The general white matter disease burden scale, however, did not correlate with cognitive performance, although it was highly correlated with the CHIPS score. This suggested that strategic compromise of the cholinergic pathways may more specifically relate to executive functions.

Eleven patients overlapped between the current study and our methodology study. In the present study, although there was a trend toward a significant correlation, the correlation may not have reached significance because of the smaller range of CHIPS scores (0-48). The CHIPS scores ranged from 0 to 70 in the previous study. The risk of clinical expression of dementia increases when the burden of neuropathologic changes exceeds a certain threshold, but this can be modified by various genetic and environmental factors. In particular, the risk can be amplified by the presence of vascular pathology. This finding has been corroborated in other studies, which also suggested that white matter lesions can influence the clinical expression of AD pathology in an additive or synergistic manner. In some studies, most of the variance for cognitive loss was explained by vascular lesions and not by neurofibrillary tangles or amyloid plaques, particularly when the AD changes were mild.

Given no differences in baseline neuropsychological performance between the low and high CHIPS groups in our sample, it is possible that patients with AD and SHs in cholinergic tracts may be reaching the same level of cognitive impairment as those with little white matter disease but by different mechanisms. Partial injury to cholinergic projections could exacerbate executive impairments, requiring less damage to the cholinergic neurons from AD pathology for the same degree of impairment. The resulting cholinergic synaptic deficiency may be more amenable to rescue by acetylcholinesterase inhibition, expressed as less decline in some executive function tasks. Recent trials of vascular dementia treated with CHEs report positive, though modest, cognitive benefits. A recent study suggested that damage and disintegration of the cholinergic pathways in vascular dementia of Binswanger type may be due in part to a preferential susceptibility of these pathways to ischemic lesions.

A few studies using computed tomography and MRI have examined the influence of SHs on cognitive decline in patients being treated for AD. In general, results suggest that the presence of SHs may be associated with increased response to therapy after 1 year, no response, or worse response after 6 months. Those studies have been limited in that they were based on a small sample size, used simple cognitive measures, and studied white matter lesions that were spread throughout the hemispheres and included lacunar infarcts.

Studies are lending credibility to the idea that white matter lesions due in part to vascular risk factors play a role in the evolution of AD dementia. Ischemic white matter lesions have consistently been associated with a history of hypertension. Such injury increases the likelihood that individuals with AD lesions will express the dementia syndrome, and some suggest that these subjects may be more likely to benefit from cholinergic therapies. Unrecognized cerebrovascular disease in AD becomes especially common in older age. The frequency of silent infarcts increases with age, and silent infarcts increase risk of clinical dementia.

However, involvement of cholinergic pathways may explain only part of the story; myelinated association fibers in the superior longitudinal fasciculus that join anterior and posterior cortical regions likely intermingle with the unmyelinated cholinergic pathways and are also important for working memory and executive control. Hence, it is possible that some of these differential effects could relate to association tract compromise as well. Application of new techniques such as diffusion tensor imaging may allow better appreciation of injury to the long association tracts such as the superior longitudinal fasciculus.

Further replication in larger community-based samples would be informative, and periods of follow-up longer than 1 year would be needed to determine more definitively whether strategically located SHs in cholinergic pathways affect cognitive decline in patients with AD and influence response to CHEs.

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