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Dynamic Susceptibility Contrast MR Imaging of Regional Cerebral Blood Volume in Alzheimer Disease: A Promising Alternative to Nuclear Medicine

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BACKGROUND AND PURPOSE: **The goal of our study was to evaluate the sensitivity and specificity for Alzheimer disease of semiquantitative dynamic susceptibility contrast (DSC) MR imaging as compared with results of qualitative single-photon emission computed tomography (SPECT) in the same patients and with previously published semiquantitative SPECT results.**

METHODS: **Fifty subjects were studied: 19 patients with probable Alzheimer disease with moderate cognitive impairment, eight mildly impaired patients with possible or probable Alzheimer disease, 18 group-matched elderly healthy comparison subjects, and five elderly comparison patients with psychiatric diagnoses. Relative values of temporoparietal regional cerebral blood volume (rCBV) were measured as a percentage of cerebellar rCBV, and group classification was assessed with logistic regression. The DSC MR imaging results were compared with SPECT scans in these same subjects and with previously published semiquantitative SPECT data.**

RESULTS: **Temporoparietal rCBV ratios were reduced 20% bilaterally in the patients with Alzheimer disease. Using left and right temporoparietal rCBV as index measures, sensitivity was 95% in moderately affected patients with Alzheimer disease and 88% in patients with mild cases. Specificity was 96% in healthy comparison subjects and in psychiatric comparison subjects. Sensitivity with DSC MR imaging was considerably better than with visual clinical readings of SPECT scans (74% in moderate and 50% in mild Alzheimer disease cases), and was similar to previous published SPECT temporoparietal measurements (90%). Specificity with SPECT was 100% visually and 87% based on previous temporoparietal measurements.**

CONCLUSIONS: **DSC MR imaging of rCBV is promising as a safe, potentially lower-cost alternative to nuclear medicine imaging for the evaluation of patients with dementia.**

Alzheimer disease is a debilitating neurodegenerative disorder that results in progressive memory loss and cognitive decline. Neuropathologic sequelae involve generalized atrophy and microscopic alterations that consist of "senile" plaques and neurofibrillary tangles. The neuropathologic damage is often most severe in posterior temporal and inferior parietal lobes and limbic structures, with relative sparing of primary motor and sensory cortices (1–4).

Since Alzheimer disease often presents a characteristic pattern of neuropathologic damage focal to the temporoparietal regions, functional neuroimaging can be useful and effective in aiding clinical assessment in cases of possible or probable Alzheimer disease. Reduced temporoparietal cortex metabolism or blood flow was reported in studies that used positron or single-photon emission computed tomography; that is, PET (5–7) and SPECT (8–13). Temporoparietal deficits were not present in subjects without Alzheimer disease but with age-related memory loss (14).

The recent development of the dynamic suscepti-

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bility contrast (DSC) MR imaging technique enables the acquisition of regional cerebral blood volume (rCBV) images with MR imaging (15). DSC MR images display information similar to that provided by PET and SPECT (16), but with several advantages; that is, no ionizing radiation, high spatial resolution (1–2 mm), and low relative cost.

In the current study, we used DSC MR imaging to evaluate temporoparietal hemodynamic deficits in patients with probable Alzheimer disease, in patients with possible or probable early Alzheimer disease, and in nondemented elderly patients with psychiatric diagnoses, and compared these groups with elderly healthy comparison subjects. The sensitivity and specificity of DSC MR imaging to discriminate patients from control subjects was determined and compared with the sensitivity and specificity of clinical readings of SPECT scans acquired in the same subjects and with previously published SPECT data that used similar semiquantitative measures of temporoparietal hemodynamic function.

Methods

Subjects

Patients with possible or probable Alzheimer's disease determined by NINCDS-ADRDA criteria (17) were recruited as consecutive referrals from the McLean Hospital Memory Diagnostic Clinic. Two groups were formed on the basis of cognitive impairment: a mildly affected group of patients with possible or probable early Alzheimer disease (n = 8) and a moderately affected group of patients with probable Alzheimer disease (n = 19). Mini-Mental State Examination (MMSE) (18) scores of 24 or lower (out of a possible score of 30) defined the moderately demented group, and subjects with MMSE scores of 25 or higher were included in the mildly affected group. None of the patients in this study were severely demented (all had MMSE scores $\geq$ 14). Comparison subjects (n = 18) were volunteers recruited through the McLean Hospital from the local community and were screened by medical history, physical examination, and psychiatric evaluation. An additional group of nondemented elderly patients with primary psychiatric diagnoses of depression, schizophrenia, or schizoaffective disorder were included (n = 5) to further assess specificity of temporoparietal blood volume deficits to Alzheimer disease. Subject groups were matched on age (Scheffé post-hoc comparison with one-way analysis of variance found no two groups different at $P < .05$) and sex (χ^2 analysis, $P > .5$). Group demographics, including number, age, sex, and mean MMSE scores, are presented in Table 1. Some subjects enrolled in the current study were included in a methodological report (19).

Healthy comparison subjects were excluded for any history of major psychiatric or CNS illness. Subjects were excluded from all groups for a history of severe head injury, use of street drugs or oral steroids, current alcohol abuse or dependence, or loss of 25% or more of total body weight in the past year (12, 13). After providing a complete description of the study to the subjects, written informed consent was obtained; if a patient was not competent, consent was obtained from a spouse or guardian.

Image Acquisition and Analysis

Multisection T2*-weighted echo-planar images were acquired on a 1.5-T scanner retrofit with an Advanced NMR Systems (Wilmington, MA) whole-body echo-planar coil, with imaging parameters of 100/2000 (TR/TE), 50 sets of 10 image planes over 100 seconds, 128 × 256 matrix, 1.5 × 1.5-mm pixels (in-plane spatial resolution on the order of one pixel [1.5 mm]), and 7-mm-thick sections with a 3-mm gap. Twenty seconds after scanning began, during which time 10 sets of baseline images were acquired, subjects were administered IV 0.20 mmol/kg gadoteridol (Bracco Diagnostics Inc, Princeton, NJ) as a bolus over 6 seconds during image acquisition. Subjects were instructed to lie in the scanner with eyes closed during echo-planar scanning.

TABLE 1: Demographic information of subject groups

	Healthy Control Subjects	Probable AD (MMSE ≤ 24)	Po/Pr AD (MMSE ≥ 25)	Psychiatric Control Subjects
Patient No.	18	19	8	5
Age (yr)	72.1 ± 8.8	77.2 ± 7.4	80.6 ± 4.8	70.8 ± 9.2
Sex	9 F/9 M	12 F/7 M	3 F/5 M	2 F/3 M
MMSE	28.7 ± 1.0	18.7 ± 3.2*	26.6 ± 1.6	28.0 ± 1.2

Note.—MMSE indicates Mini-Mental State Examination score (maximum = 30); AD, Alzheimer disease; Po/Pr AD, possible or probable Alzheimer disease with mild cognitive decline (MMSE score ≥ 25).

No group differences on sex distribution by χ^2 analysis.

No two groups differed on age at $P < .05$ by Scheffé post-hoc comparisons with one-way analysis of variance.

* Reduced MMSE scores compared with other three groups ($P < .0001$).

CBV images were created by the DSC method (15, 19). As gadoteridol passes through the cerebral vasculature, it induces a susceptibility effect in proportion to the amount of contrast agent passing through each voxel. Since T2*-weighted echo-planar images are acquired every 2 seconds during the time of the gadoteridol bolus injection, whereas the first-pass curve lasts approximately 12 seconds, the images sequentially become proportionally darker then lighter in signal as the bolus passes through the brain. The time curve of image signal intensity at each pixel is then processed according to equations published by Belliveau et al (15). DSC MR images are created by integration of the area under this curve (a function of MR signal changes caused by gadoteridol transit) into a functional image of CBV at each pixel.

For quantitative regional analysis, the cortex was delineated as a ring extending from the outer edge of the brain inward, with a fixed ratio of brain diameter (to account for differences in brain size) sufficient to include both sulcal and gyral cortex. The ring was automatically divided into five equiangular regions per hemisphere, symmetric about the interhemispheric fissure to account for head rotation (13, 19). Analyses were performed on the image that most closely passed through the center of the thalamus (approximately 10 mm superior to the anterior commissure-posterior commissure plane), and the next superior section (approximately 20 mm above the anterior commissure-posterior commissure). The lower plane was used to measure the temporoparietal cortex (second most posterior region of five, as displayed in Fig 1), while the sensorimotor cortex (third of five regions) was measured on the superior section. These regions coincide with those in previous SPECT reports (12, 13). Thus, regional analyses were hypothesis driven and limited to temporoparietal and sensorimotor cortices to avoid problems of multiple comparison. Ratios of index regional mean value to cerebellum mean value were analyzed as measures of relative rCBV. The cerebellum was chosen as the reference region because it is less affected than the cortex in Alzheimer disease and is, therefore, a better reference region than other cortical measures (20, 21). Blood vessels, which appear very bright on DSC MR images, were segmented (pixels more than 2 SD above the brain mean value were identified as

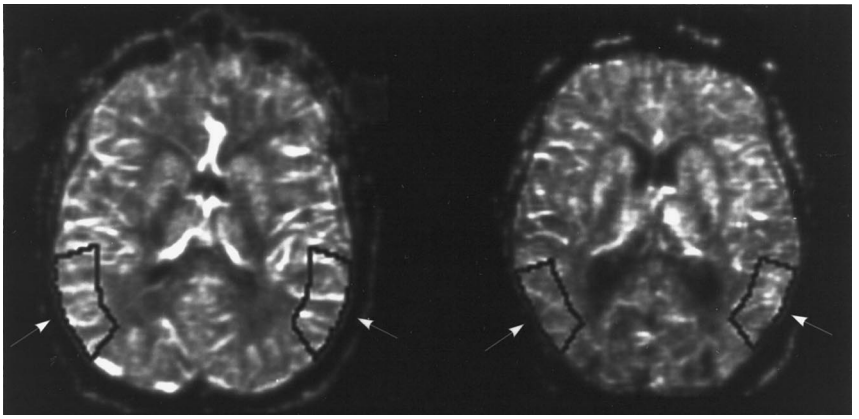

FIG 1. DSC MR image of rCBV in a 63-year-old patient with probable Alzheimer disease (MMSE score = 24; 1 year mild cognitive decline) (*right*) and a matched 64-year-old comparison subject (MMSE score = 29) (*left*). Temporoparietal regions are outlined with *black lines* and indicated with *arrows*. Bright objects in images represent blood vessels, with their thresholds determined and excluded by the analyses. The temporoparietal/cerebellum ratios for each subject were near their respective group mean: comparison subject, left temporoparietal ratio = 107% of cerebellum, right temporoparietal ratio = 109%; patient with Alzheimer disease, left temporoparietal ratio = 92%, right temporoparietal ratio = 85%.

TABLE 2: DSC MR imaging measures of regional cerebral blood volume as a percentage of cerebellar regional cerebral blood volume by subject group (group names as in Table 1)

Region	Healthy Control Subjects (n = 18)	Probable AD (MMSE ≤ 24) (n = 19)	Po/Pr AD (MMSE ≥ 25) (n = 8)	Psychiatric Control Subjects (n = 5)	F (*P*) (*df* = 3,45)
L temporoparietal	111.0 ± 7.2	91.2 ± 11.4*	98.5 ± 9.3†	108.0 ± 8.8	13.3 (<.0001)
R temporoparietal	112.8 ± 7.1	92.1 ± 13.9*	95.5 ± 7.2†	111.4 ± 7.9	12.6 (<.0001)
L sensorimotor	104.4 ± 8.7	91.6 ± 11.0†	100.2 ± 10.6	105.3 ± 9.0	5.1 (.004)
R sensorimotor	105.0 ± 11.4	94.1 ± 13.4	89.9 ± 9.2†	108.5 ± 9.8	3.7 (.02)

Note.—MMSE indicates Mini-Mental State Examination score (maximum = 30); AD, Alzheimer disease; Po/Pr AD, possible or probable Alzheimer disease with mild cognitive decline (MMSE score ≥ 25).

F test of analysis of covariance with age as covariate and Scheffé post-hoc analysis.

* $P < .0001$ vs healthy group; † $P < .05$ vs healthy group.

blood vessels) and were excluded from all regional analyses. The assumption was made that true brain parenchymal tissue pixels would be unlikely to have rCBV more than 2 SD greater than the mean brain pixel.

All subjects in each group also underwent regional cerebral blood flow (rCBF) imaging with hexamethylpropyleneamine oxime (HMPAO) SPECT. The digital SPECT scans were not available for quantitative analysis. However, the SPECT scans were interpreted visually by a neuroradiologist at the time of scanning and rated as having or not having the temporoparietal rCBF deficit characteristic of a patient with Alzheimer disease. Furthermore, comparisons were made between the DSC MR imaging results and those of previously published SPECT studies of patients with Alzheimer disease of similar severity and using similar methods of regional analysis as performed for the DSC MR images in the current study (12, 13). In these SPECT studies, similar section planes were used, and similar cortical rings were also defined semiautomatically and subdivided into five equiangular regions per hemisphere. The temporoparietal and sensorimotor regions were defined as described above.

For the DSC MR images, regional measures were compared between groups by analysis of covariance, with age as a covariate to account for any age-related effects. Regression analyses were used to assess relations between imaging and MMSE measures in the patients with Alzheimer disease (comparison groups had mean MMSE scores ≥ 28/30). Logistic regression was used between healthy comparison subjects and each of the three patient groups to determine the sensitivity of the hypothesized measures for correctly classifying patients with possible or probable Alzheimer disease and to determine the specificity of distinguishing both the healthy comparison subjects and the psychiatric comparison subjects from patients with Alzheimer disease. In making all measurements, the interpreter was blinded to the diagnosis. Sensitivity and specificity of DSC MR imaging regional analyses were calculated and compared with SPECT qualitative clinical readings, and also compared with SPECT regional semiquantitative analysis measures reported previously (12, 13).

Results

By applying the quantitative regional analysis method to the DSC MR images, we observed large bilateral rCBV deficits in temporoparietal regions (20% mean deficit) in moderately affected (MMSE scores ≤ 24) patients with probable Alzheimer's disease, but sensorimotor areas were substantially less affected (12% mean deficit), as shown in Table 2. In patients with possible or probable Alzheimer disease with mild cognitive impairment (MMSE scores ≥ 25), large bilateral temporoparietal deficits (15% mean deficit) were also observed, with smaller sensorimotor deficits (10% mean deficit). Nondemented psychiatric patients had temporoparietal ratios similar to healthy subjects. Age was included as a covariate in the above analyses of covariance because, although no two groups differed significantly in age, a difference of several years existed between some groups, and age can influence rCBV. MMSE scores did not correlate significantly with rCBV measures in the patients with Alzheimer disease.

Logistic regression was applied between healthy comparison subjects and each of the three patient groups to determine the ability of this technique to differentiate subject groups. Left and right temporoparietal ratios were used in the analyses as index measures. Sensitivity as measured by correct group

classification among moderately affected patients with probable Alzheimer disease was 95% (18 of 19 patients); among mildly affected patients with possibly early Alzheimer disease or patients with probable Alzheimer disease, sensitivity was 88% (seven of eight patients). Specificity as measured by correct classification of healthy comparison subjects was 94% (17 of 18 subjects). Specificity was also high for the nondemented psychiatric comparison group, in which five (100%) of five subjects were classified as similar to the healthy comparison group.

Logistic regression analysis of rCBV ratios in sensorimotor regions provided poor group classification. Sensitivity in moderately affected patients with Alzheimer disease was 68% (13 of 19 patients); in mildly affected patients with Alzheimer disease, sensitivity was 50% (four of eight patients). Specificity in healthy comparison subjects was 78% (14 of 18 subjects).

Qualitative visual clinical analysis was performed on SPECT scans from all subjects by a nuclear medicine clinician who assessed whether the scans showed evidence of temporoparietal perfusion deficits characteristic of Alzheimer disease. The sensitivity of clinical readings was lower for all groups with Alzheimer disease; 74% (14 of 19) of moderately impaired patients with probable Alzheimer disease and 50% (four of eight) of mildly affected patients with possible or probable Alzheimer disease were considered to have imaging findings consistent with a diagnosis of Alzheimer disease. The sensitivity for clinical interpretation of SPECT scans in all patients with possible or probable Alzheimer disease was 67% (18 of 27 patients) compared with 93% (25 of 27 patients) for temporoparietal rCBV ratios with DSC MR imaging. None of the 18 control subjects or five nondemented psychiatric comparison subjects were considered to have imaging findings consistent with Alzheimer disease. Thus, the overall specificity with qualitative SPECT was 100% (28 of 28 subjects) compared with 96% (27 of 28 subjects) for DSC MR imaging.

Discussion

Until recently, imaging of regional cerebral hemodynamic or metabolic function was limited primarily to nuclear medicine techniques, such as SPECT and PET. With the advent of echo-planar MR imaging, potentially lower-cost, higher-resolution, radioactivity-free methods for observing brain hemodynamic function, such as DSC MR imaging, became available. The current study suggests that, clinically, DSC MR imaging is a powerful tool, comparable with SPECT when similar methods of analysis are used. However, with the important other advantages that DSC MR imaging offers, it may be considered a cost-effective alternative to nuclear medicine for facilities in which echo-planar MR imaging is an option.

The findings of this study establish the capability of DSC MR imaging to detect rCBV deficits with high sensitivity and specificity in patients with Alzheimer disease, even in patients with mild cognitive decline. Using relative quantitative measures with this new technique, severe deficits in temporoparietal rCBV were observed in patients with Alzheimer disease compared with matched elderly comparison subjects, with excellent group discrimination, whereas sensorimotor regions were less affected. Temporoparietal rCBV deficits were present even in those patients with possible or probable Alzheimer disease who displayed only mild cognitive symptoms (MMSE scores ≥ 25; $n = 8$). This observation suggests that this method may be promising in the examination of subjects with early Alzheimer disease, although the small sample size of mildly affected patients requires replication in a larger study. Furthermore, the results of this report also establish the specificity of the temporoparietal rCBV ratio deficits (ie, healthy comparison subjects and comparison patients without Alzheimer disease who had primary psychiatric diagnoses did not have temporoparietal rCBV defects). The deficits were also regionally specific to the temporoparietal regions, whereas other regions, such as the primary sensorimotor cortex, were relatively spared, consistent with neuropathologic findings (1–4). Thus, this study confirms that DSC MR imaging has high sensitivity in the assessment of rCBV deficits associated with Alzheimer disease, even early in the illness, and high specificity with a low false-positive rate among both healthy comparison subjects and patients without Alzheimer disease.

Our findings establish that DSC MR imaging has a clinical usefulness similar to that of nuclear medicine techniques, such as SPECT or PET. The semiquantitative DSC MR imaging results of the current study were consistent with previous semiquantitative SPECT and PET functional imaging studies in Alzheimer disease (5–14, 21, 22). Previously published SPECT rCBF research with similar analytic methods (12) yielded nearly identical results to the rCBV differences found in the current study (18% SPECT temporoparietal Alzheimer disease deficit; 8.5% Alzheimer disease deficit in the sensorimotor cortex). These SPECT results and the current DSC MR imaging analyses both had discriminant ability of approximately 90%. Thus, when similar semiquantitative regional analytic methods were applied, DSC MR imaging and SPECT were comparable in clinical capability. Although semiquantitative analyses with DSC MR imaging and with SPECT had similar discriminant ability, sensitivity of semiquantitative analysis with either imaging technique was superior compared with qualitative visual clinical assessments (23). As with PET and SPECT, DSC MR imaging can be applied to a variety of neuropsychiatric disorders, including stroke, tumor, multiple sclerosis, closed head injury, and substance abuse (24, 25).

Although DSC MR imaging does provide similar functional information (and has similar discriminant ability for Alzheimer disease) to that of SPECT and PET, DSC MR imaging has several advantages over other functional brain imaging techniques. Acquiring a PET or SPECT scan set in addition to a structural image requires separate imaging sessions in two scanners, often in different divisions of the hospital (MR

imaging and nuclear medicine). This adds significantly more cost as compared with structural imaging alone, and requires added scheduling and inconvenience to the patient. Since both structural and functional imaging can occur in a single session with DSC MR imaging, it has significantly lower cost than PET or SPECT when combined with structural MR imaging; a recent cost-effectiveness study indicated that these savings can amount to several hundred dollars per case (26). The main cost of DSC in addition to structural MR imaging is the contrast agent, which is often used routinely in MR imaging already, and thus the incremental cost above that of structural MR imaging alone is minimal. Furthermore, the spatial resolution of DSC MR imaging (~1.5 mm in-plane at 1.5 T) is superior to that of PET and SPECT, and DSC MR imaging does not expose the patient to any ionizing radiation.

Limitations of the current study need to be considered. Group classification is prone to bias in small samples and requires cross-validation to be generalizable beyond the current sample. Additionally, a potentially confounding factor in all functional brain imaging studies is the contribution of atrophy effects to measurements of brain function in neurodegenerative disorders, such as Alzheimer disease. Changes observed in rCBV may reflect tissue loss as well as functional decline, and further studies are required to assess the effects of brain atrophy on measurements of functional change. However, in a recent study, researchers reported that temporoparietal hypometabolism persisted even after partial volume correction, suggesting that a true reduction in cerebral function occurs in Alzheimer disease (27). Because our study groups comprised an age spread of several years, and age is a factor in brain atrophy (28, 29), we performed analyses of covariance with age as a covariate to account for age-related effects. An additional limitation of the current study was that digital SPECT scans were not available for semiquantitative analysis in the same subjects in whom DSC MR images were available; therefore, we could only compare the semiquantitative results of DSC MR imaging with the qualitative SPECT readings in the same subjects and with the semiquantitative SPECT measures published previously in other reports. Although this is clearly a shortcoming of the current study, our goal was to assess whether DSC MR imaging might be an alternative to nuclear medicine imaging in patients with Alzheimer disease, and the data presented here at least preliminarily support that view. Future studies will be needed to verify DSC MR imaging as a valuable tool by comparing it directly with semiquantitative assessments of nuclear medicine scans in the same subjects, and one report making such direct comparisons supports DSC MR imaging as correlating closely with nuclear medicine imaging (16).

Several other areas need additional research. Evaluating a larger sample, including greater numbers of very early cases for which diagnosis is unclear, and studying more patients with non-Alzheimer disease memory deficits and dementias (such as vasculopathic, particularly small vessel occlusive, disease) will provide more information about the sensitivity and specificity of DSC MR imaging. This is a limitation of the current study, and future work will need to compare patients with Alzheimer disease against these other patient groups to determine specificity with greater confidence. Also important will be following up patients with Alzheimer disease over time to help better define the relationship between clinical progression, such as memory dysfunction, and regional hemodynamic function measured with DSC MR imaging. In turn, this information might provide a means to assess the efficacy of clinical interventions in slowing the pathophysiological changes associated with Alzheimer disease.

Conclusion

DSC MR imaging is a promising alternative to nuclear medicine perfusion imaging for patients suspected of having Alzheimer disease. The results of this study using semiquantitative analysis of DSC MR imaging were comparable in sensitivity and specificity to previous SPECT studies using similar semiquantitative analysis techniques in similar subject groups. Relative regional measurements of temporoparietal ratios with either DSC MR imaging or SPECT were more sensitive and had higher discriminant capability than did qualitative clinical assessment of SPECT scans. DSC MR imaging was effective in assessing possible or probable Alzheimer disease, even in early mild cases, with MMSE scores of 25 or higher (out of a possible score of 30). Several important advantages available with DSC MR imaging include no ionizing radiation, high spatial resolution, reduced time and inconvenience, and relatively low incremental cost.

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