Frontal Lobe Hypometabolism Predicts Cognitive Decline in Patients With Lacunar Infarcts

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**Background:** A proportion of patients with subcortical lacunes will suffer progressive cognitive dysfunction, but the basis for this decline is controversial and little is known about predicting cognitive decline in these patients. Studies of Alzheimer disease have shown that imaging measures of temporal and parietal metabolism and blood flow predict disease course.

**Objective:** To determine whether regional cerebral glucose metabolism predicts cognitive decline by testing 2 opposing hypotheses: (1) temporoparietal activity predicts decline (based on the idea that concomitant Alzheimer disease causes decline) vs (2) frontal hypometabolism predicts decline (based on evidence that subcortical frontal circuits are especially vulnerable to small vessel ischemia).

**Design:** Prospective cohort study.

**Setting:** University outpatient dementia center.

**Patients:** A convenience sample of 26 patients with radiologically defined lacunes and baseline cognitive function ranging from normal to moderately demented.

**Main Outcome Measures:** Regional cerebral metabolism was quantitated in the form of atrophy-corrected positron emission tomographic activity ratios in cortical regions that were defined a priori. Patients were followed up at a mean of 1.8 years, and the dependent variable was rate of change in the Mini-Mental State Examination score.

**Results:** Bilateral and right hemisphere dorsolateral frontal metabolism significantly predicted cognitive decline, with right dorsolateral frontal metabolism explaining 19% of the variance. No other positron emission tomographic region was a significant predictor, nor were demographic variables or baseline Mini-Mental State Examination scores significant predictors.

**Conclusion:** Cognitive decline in patients with lacunes may result in part from progressive vascular compromise in subcortical frontal circuits.

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Patients with lacunar infarcts may be cognitively normal or may have cognitive impairments ranging in severity from mild deficits to severe dementia. The trajectory of cognitive function following lacunar infarction is also variable: stable in some cases, improving in others, but deteriorating in a significant proportion of cases. Although cognitive status is an important determinant of patient quality of life and need for care, there is currently no effective means of establishing a prognosis for these patients.

Different models of the mechanisms of cognitive failure with lacunar infarction lead to different ideas about how the prognosis might be established. One view, supported by autopsy series that find cases with lacunes and dementia also overwhelmingly have amyloid plaques and neurofibrillary tangles, is that coexisting Alzheimer disease (AD) is the primary cause of progressive mental deterioration in these patients. From this perspective, predicting decline amounts to diagnosing AD. Although the diagnosis of AD is problematic in patients with strokes or patients without dementia, a diagnostic marker for AD that could be detected in patients with lacunes might serve as a prognostic sign. One such candidate is temporoparietal hypometabolism or hypoperfusion. Positron emission tomography (PET) and single photon emission computed tomography studies have consistently found that reduced activity in these neocortical association areas is strongly associated with AD and worsens as the illness progresses. Also, there is evidence that metabolic...
Subjects and Methods

Subjects

Twenty-six patients were recruited through university dementia and neurology clinics, with subcortical (but not cortical) stroke identified on a magnetic resonance imaging (MRI) scan performed as part of the study protocol. All subjects had supratentorial lacunes, and most had multiple lacunes (mean number of lacunes, 4.3). The lacunes were widely distributed throughout the white matter, basal ganglia, and thalamus, without any hemispheric predominance to the distribution for the group as a whole. In all but 3 cases, caudate, thalamus, or both had lacunes; of the 3 cases that had single lacunes, 2 had thalamic involvement. Evaluation consisted of a general medical history and physical examination, neurological examination, laboratory evaluation of serum chemistry, blood cell count, vitamin B12 level, thyroid functions, and neuropsychological testing. Informed consent was obtained from each subject in compliance with local institutional review board policies. Data from most of these patients have been previously reported in a comparison of metabolic activity between stroke and control patients.

Subjects were excluded if they were younger than 55 years, did not speak English, had severe dementia (Clinical Dementia Rating Scale score of ≥2), had a history of alcohol or other substance abuse within 5 years of the onset of cognitive change (last 5 years for cognitively normal subjects), had a history of head trauma with loss of consciousness lasting longer than 15 minutes, had other significant neurological or psychiatric disorders, were taking medications that affected cognitive function, or had a serious unstable medical illness. In addition, subjects were excluded if the study MRI showed evidence of cortical infarction or structural brain disease other than cerebral atrophy, lacunar infarction, or white matter changes.

Magnetic Resonance Imaging

All subjects received a research MRI scan on a 1.5-T system. Double spin-echo sequences (repetition time, 5000 milliseconds; echo time, 20 milliseconds, 80 milliseconds; slice thickness, 3 mm) were used for radiological interpretation of lacunes, and T1-weighted volumetric data sets (repetition time, 7.9 milliseconds; echo time, 4 milliseconds; slice thickness, 1.3 mm) were acquired for use in region identification for PET data analysis. T1-, T2-, and proton density–weighted images were used by a single neuroradiologist to identify the presence of lacunes using criteria for dementia (CIND) (mean MMSE score, 27.6). Dementia was diagnosed according to the criteria used in the National Institutes of Neurological Disorders and Stroke–Alzheimer’s Disease and Related Disorders Association guidelines for the diagnosis of AD. CIND was diagnosed when neuropsychological testing revealed either circumscribed cognitive deficit or very mild deficits, which, according to informant report, did not affect daily function.

Clinical follow-up was obtained on average 1.8 years after the initial evaluation (range, 0.9-3.5 years). The MMSE, which was also obtained at baseline, was readministered at follow-up. When multiple follow-ups were available, the last score was used.

Abnormalities may precede symptoms in AD. Temporoparietal hypometabolism is especially interesting because of studies that have shown that it predicts both cognitive decline and survival in AD several years into the future. However, other autopsy studies suggest that in at least some proportion of cases cerebrovascular disease alone is responsible for cognitive impairment, even in the absence of large cortical strokes. Indeed, some studies of risk factors for dementia following stroke have identified small vessel strokes as conferring an especially high risk of dementia. Why this is so is uncertain, but a plausible account is that subcortical infarcts, because of characteristics of the cerebral vasculature, tend to occur within cortico-striato-thalamo-cortical anatomic loops that support the functioning of prefrontal cortex. Dementia may follow in part because of the generalized impact of the loss of cognitive regulatory functions of the frontal lobes. This model is supported by empirical descriptions of the cerebral vasculature by studies showing that lacunes predominantly occur in thalamus, basal ganglia, and the frontal white matter, all of which are important components of frontal-subcortical circuits, and by neuropsychological studies of vascular dementia that have shown a predominance of deficits associated with frontal lobe dysfunction. If dysfunction of the frontal lobes is indeed especially important in small vessel vascular dementia, then one might hypothesize that a marker of frontal dysfunction could prove to have prognostic value.

Functional imaging studies of ischemic vascular dementia (IVD) are considerably less uniform in their findings than are the studies on AD, but as more recent studies have used better defined diagnostic criteria to select more homogeneous groups, more consistent findings have emerged. These studies support the idea that subcortical infarcts impair cognition through their effects in cortex and prefrontal cortex and suggest that basal ganglia and prefrontal cortex are especially hypometabolic in small vessel IVD.

Thus, 2 opposing hypotheses regarding the prognostic value of metabolic imaging in IVD may be proposed. One is that temporoparietal hypometabolism will predict cognitive decline and the other is that frontal...
cerebrospinal fluid on the proton density–weighted images were classified as lacunes, as were discrete low-signal-intensity lesions on T1-weighted images in the basal ganglia, thalamus, or white matter. Because perivascular spaces are most common at the level of the anterior commissure, low-signal-intensity lesions of any size in the region of the anterior commissure were categorized as perivascular spaces. Outside that region, we used the arbitrary cutoff of less than 3 mm for perivascular spaces. Lesions representing exceptions to these criteria were classified according to the neuroradiologist’s judgment.

PET studies were performed on a PET scanner (ECAT EXACT HR PET scanner, CTI/Siemens, Knoxville, Tenn) using the glucose metabolic tracer fludeoxyglucose F 18 within 3 months of clinical evaluation and MRI, using methods that have been detailed previously. All subjects performed a continuous verbal recognition memory task during the tracer uptake phase of the PET scan. The data were reconstructed using standard 2-dimensional filtered back-projection techniques. Metabolic activity was quantitated by defining regions of interest and normalizing atrophy-corrected regional activity to atrophy-corrected whole brain counts. The regions were outlined using procedures developed locally for the analysis of whole brain PET data sets that are described in detail elsewhere. The approach uses a coregistered T1-weighted 3-dimensional MRI data set for anatomic region specification and analysis of the PET data. Two-dimensional regions of interest are operator-drawn, and their surfaces are tiled together into a closed triangular mesh polyhedral surface model, defining a 3-dimensional region or volume of interest (VOI). The VOI metabolic rates or activity values are adjusted for the effects of partial volume caused by cerebral atrophy by using the segmented MRI data set as prior information, in a manner described by Meltzer et al. The MRIs were smoothed to the resolution of the PET scanner by first reorienting the magnetic resonance volume into the registered voxel space of the PET data, then smoothing via a nonuniform gaussian convolutional kernel. The nonuniform smoothing was implemented by computing at each voxel location an appropriate 3-dimensional gaussian kernel based on the known axial, radial, and tangential blurring characteristics with respect to the tomograph center. Then the proportion of each VOI containing brain and cerebrospinal fluid is determined using the convolved MRI data set, and this proportion is applied to the calculated metabolic rate to correct the VOI for atrophy.

All VOIs were drawn on the 3-dimensional T1-weighted MRI by either of 2 operators blind to patient classification, using a set of rules for guiding the boundaries of the VOIs. The VOIs were drawn using detailed rules to guide the region boundaries. Interoperator reliability of region drawing in our laboratory is high, with differences in regional cerebral metabolic rate for glucose (rCMRglc) in regions drawn by different operators averaging less than 3%. Volumes of interest were selected a priori based on our hypotheses with the goal of sampling neocortical association areas of high importance to memory and a variety of other cognitive functions. The regions drawn were dorsolateral frontal cortex (DLF), orbitofrontal cortex, temporal lobe (middle and posterior neocortex), inferior parietal lobe, calcare cortex, and hippocampus. Hippocampus was selected because of its obvious importance to memory, and calcare cortex, which is sensory cortex, was chosen as a control region against which to test the specificity of findings in regions of association cortex. Hippocampus included the subiculum, horn of Ammon, and associated white matter tracts. Whole brain counts were determined by drawing a VOI that encompassed the whole brain, including both cerebral hemispheres, the posterior fossa, and subcortical structures, and then applying calculations outlined above, including atrophy correction. Thus, the PET data were analyzed in the form of count ratios, with atrophy-corrected VOI counts normalized to atrophy-corrected whole brain counts.

RESULTS

As a primary test of both hypotheses, a multivariate model regressed rate of change in the MMSE score on the bihemispheric ratios for DLF, orbitofrontal cortex, temporal lobe, inferior parietal lobe, calcare cortex, and hippocampus. The only significant term was that for DLF (F1,25 = 12.42, P < .01). All other terms had P values greater than .14. The Figure shows the effect plot for DLF derived from this model and illustrates that subsequent rate of decline is greater when baseline DLF metabolism is lower. As follow-up analyses to this finding, we performed simple regressions of the rate of change in MMSE score on right and left DLF. Right DLF was significant (R2 = 0.19, F1,25 = 4.8, P = .04) but left DLF was not (P > .15). Inspection of the scatterplots revealed one possible high-influence outlier with a rate of change approximately 9 points per year. Excluding that case yielded very similar results: right DLF was significant (P = .03), and left was not significant (P > .10). To ensure that the negative findings for temporal and parietal VOIs were not a consequence of dividing variance shared between VOIs, we performed simple regressions using the bihemispheric and unilateral ratios for temporal lobe, inferior parietal lobe, and hippocampus as single predictors of MMSE score change. No model was significant (P > .15 for all).

Because the scans were done using a behavioral task during tracer uptake, we examined the relation of task performance to the key variables of this study. An overall measure of accuracy on this task, corrected for false-positive responses, is Pr. Bilateral and right DLF are the PET regions that predicted MMSE score decline, and both were significantly related to Pr (R2 = 0.22, P < .02 for bilateral and R2 = 0.31, P < .01 for right). However, Pr did not predict MMSE score decline. Although an initial analysis suggested a trend (P = .06), the scatterplot showed one high-influence outlier and removal of that single case made the relation clearly nonsignificant (P = .55).

We also examined the predictive power of demographic and baseline characteristics to see if they inde-
Hypometabolism of dorsolateral prefrontal cortex proved to be a relatively strong predictor of global cognitive decline in patients with lacunes, explaining about 19% of the variance in rate of MMSE score change. Dorsolateral prefrontal metabolism predicted change substantially better than baseline MMSE score, the presence of dementia, or basic demographic characteristics of subjects. In contrast, we found no evidence that temporal or parietal metabolism is predictive of cognitive trajectory in these patients. Thus, these findings form a double dissociation with previous findings regarding functional imaging as a predictor of global cognitive decline; temporalparietal activity predicts decline in AD but not in subcortical stroke, whereas frontal activity predicts decline in subcortical stroke but not in AD.

There are at least 2 prior reports that functional measures may prognosticate cognitive change in cerebrovascular disease. Rogers et al. reported in 1986 that cerebral blood flow, as measured by xenon computed tomography methods, was abnormally low 2 years before the onset of symptoms in patients who developed vascular dementia. In addition, Gur et al. reported that abnormal electroencephalograms in nondemented patients with ischemic stroke predicted the incidence of dementia in the subsequent 2 years. These studies suggest that measures of brain function can reveal early evidence of pathology that either directly cause cognitive decline or increase the risk of decline.

Other studies support the idea that defining the risk of cognitive decline subsequent to stroke is not a simple matter of predicting risk of cerebral ischemia. For example, in a study of stroke patients who were initially nondemented, Tatemichi et al. studied numerous variables, including risk factors for stroke, but found only age, prior stroke, and cortical atrophy predicted the emergence of dementia. Greater ischemic risk indeed seems to increase the likelihood that a patient having stroke will be demented, but age, education, and other comorbid medical conditions also increase this likelihood.

Our finding that right but not left DLF metabolism predicts decline may be an example of type II error and could reflect sampling vagaries or the effects of the verbal memory task used during the uptake period. However, it is worth considering that there may be a more substantive basis for the lateralized association. Interestingly, prior reports on prognostic imaging markers in AD have found a stronger relation between right hemisphere pathology and decline. Also, our previous analysis comparing patients with lacunes at different levels of cognitive function with controls showed between-group differences in right but not left DLF.

A number of cautions ought to be noted regarding these findings. First, we do not have histopathological data, and the likelihood is that some of these patients have AD. Two factors argue that most do not. Temporoparietal hypometabolism typical of AD was not found in a prior analysis that included most of these cases. Also, the rate of decline in the demented cases, −1.5 MMSE points per year, is less than what is generally reported for patients with AD. Second, we also do not have much evidence about what caused the progression of symptoms in those patients who declined, since neither PET nor MRI studies were done at follow-up. Third, IVD is a heterogeneous disorder. We deliberately focused on patients with lacunes and no cortical strokes, but the applicability of these findings to cases with different types of strokes is uncertain.

The significance of these findings lies not so much in the application of functional imaging to the clinical prediction of decline, but rather in the implications that they carry for the pathogenesis of cognitive impairment with lacunes. Other PET studies have shown that metabolic abnormalities can be measured before cognitive symptoms...
are apparent, which suggests that metabolic measurements can be more sensitive than cognitive measurements or that physiologic compensation can permit normal function in the face of disease. In either case, metabolic prediction implies that the underlying pathologic condition is progressive. Our hypothesis that frontal metabolism predicts cognitive course was derived from a conceptual model of subcortical IVD that emphasizes the important role of damage to subcortical fronto-striatal circuits in causing dementia. It may be that diminished frontal metabolism reflects progressive compromise of small arteries that supply the subcortical nuclei and white matter tracts of these fronto-striatal circuits. The present data, however, only show a relation between frontal metabolism and global decline, since the MMSE measures “frontal” cognitive function indirectly at best. Evidence of a direct link between frontal hypometabolism, progressive loss of executive function, and global decline would be more compelling evidence of this mechanism.

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