Left Frontotemporal Hypoperfusion Is Associated With Aggression in Patients With Dementia

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Background: Aggressive behavior is common in patients with dementia. Temporolimbic and prefrontal cortical lesions can produce pathological aggression; however, involvement of these structures has not been established in aggressive patients with dementia.

Objective: To study the relation between regional brain perfusion and aggressive behavior in patients with dementia.

Methods: We compared the pattern of regional cerebral perfusion determined with technetium Tc 99m–labeled hexamethylpropelene amineoxime single photon emission computed tomography in 2 groups of 10 patients with dementia with and without aggression, that were comparable for demographic factors, severity of cognitive impairments, and other behavioral symptoms as measured by the Neuropsychiatric Inventory.

Results: Patients with aggression revealed significant (P < .001) hypoperfusion in the left anterior temporal cortex; additional bilateral dorsofrontal and right parietal cortex were also found to be significantly hypoperfused.

Conclusion: These results indicated an association between aggression and decreased perfusion in the left anterior temporal cortex.

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Behavioral symptoms manifest in patients with dementia and have a major influence on quality of life and social affiliations for patients and caregivers. Among these behavioral problems, aggressive outbursts are frequent and may pose the greatest caregiver distress. Agitation or aggression are reported in 12% to 65% of patients with Alzheimer disease (AD) or other dementias. Aggressive behavior causes serious burden and depression in caregivers and increases the likelihood of hospitalization, early institutionalization, and abuse of patients. In the nursing home, aggressive behavior is associated with a need for increased staff supervision and the use of physical restraints. Moreover, aggressive behaviors may have severe adverse consequences, including injury, which may lead to the death of patients or others. Therefore, evaluation and management of aggressive behaviors are of considerable importance in the care of patients with dementia.

Although functional factors, such as pathological rearing, psychological trauma, and social stress, are important in the occurrence of aggression, regional brain lesions can produce pathological aggression in animals and humans. Among these regions, the temporolimbic and prefrontal cortices have been most frequently implicated. Aggressive verbalization and rage occur with stimulation of the amygdala and hippocampus in animals. Although destruction of the amygdala in monkeys and humans usually results in placidity, Rosvold et al reported that amygdalectomy in submissive monkeys increased aggression, suggesting that amygdalar dysfunction modifies aggressive behavior in a variety of ways. Recently, Zagrodzka et al reported that unilateral damage to the central nucleus of the amygdala alone increased the expression of aggressive behavior in the cat. Patients with temporal lobe epilepsy may have increased aggression during interictal periods in addition to ictal and postictal aggressive outbursts. Furthermore, violent patients with focal lesions are most likely to have focal temporal abnormalities on electroencephalography and structural abnormalities in temporal lobes. Functional neuroimaging studies using positron emission tomography
PATIENTS AND METHODS

PATIENTS

From a pool of 198 patients with dementia initially seen at the University of California Los Angeles (UCLA) Alzheimer’s Disease Center, 20 outpatients who met all clinical criteria described below, comparable across demographic and behavioral domains and divided equally into those with and without agitation/aggression, were studied. All patients had acquired persistent decline involving at least 3 of the following domains: language, memory, visuospatial skills, cognition (ie, calculation, abstraction, judgment, and others), and emotion or personality. All patients with AD met National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer’s Disease and Related Disorders Association criteria for probable or possible AD. All patients with vascular dementia met National Institute of Neurological Disorders and Stroke–Alzheimer’s Disease and Related Disorders Association International Workshop criteria for probable or possible vascular dementia; patients with large cortical strokes were excluded from the study. All patients with dementia who had Lewy bodies met the Consortium for Dementia with Lewy Bodies criteria for probable dementia with Lewy bodies. Diagnostic evaluation for all patients included complete medical history, physical and neurological examination, magnetic resonance imaging or computed tomographic imaging, technetium Tc 99m–labeled hexamethylpropylene amine oxime–SPECT imaging of the brain, and electroencephalography, and routine blood tests (including thyrotropin level, vitamin B12 level, and serological test for syphilis), and had caregivers who were willing to be interviewed. Exclusion criteria for all patients were delirium, history of alcohol or other substance abuse, history of head trauma with loss of consciousness, and history of psychiatric disorder preceding the onset of symptoms of dementia. Patients were physically well without pain or other identifiable precipitants of behavioral disturbances. Cognitive assessment included the Mini-Mental State Examination, the Consortium to Establish a Registry for Alzheimer’s Disease’s 10-word memory test, the modified 15-item Boston Naming Test, the Consortium to Establish a Registry for Alzheimer’s Disease visuospatial task (copying a circle, diamond, overlapping rectangles, and cube), and a verbal fluency task (animal name generation in 1 minute). The 20 patients chosen were representative of the 198 patient pool having a similar sex, age, Mini-Mental State Examination score, and educational level of the larger group; the pool was assembled from all patients seen in the UCLA Alzheimer’s Disease Center who had cognitive, behavioral, laboratory, structural, and functional (SPECT) imaging.

BEHAVIORAL ASSESSMENT

Caregivers were interviewed with the NPI following procedures previously described in which screening questions for each behavior were posed first. The caregiver was asked if the behavior represented a change from that exhibited by the patient prior to the onset of the dementia and was present during the past month. If a positive response was obtained from the screening questions, then the behavioral domain was explored with scripted questions focusing on specific features of the behavioral disturbance. The caregiver then rated the behaviors; scores from 1 to 4 (with 4 being the most severe) were obtained for the frequency and 1 to 3 (with 3 being the most severe) for the severity of each behavior (a composite score for each domain was the product of the frequency and severity sub-scores; maximum attainable score = 12). The NPI has been shown to be valid and reliable; raters receive specific training in NPI administration and are retrained periodically to prevent drift. The 10 domains assessed by the NPI are delusions, hallucinations, agitation/aggression, depression, anxiety, euphoria, apathy, disinhibition, irritability, and abnormal motor output. The cognitive assessment was done concurrently with the NPI.

SINGLE PHOTON EMISSION COMPUTED TOMOGRAPHY

For all patients, an intravenous line was placed and a 15-minute period was allowed to pass for patients to regain a quiet comfortable state before the intravenous administration of 1110 MBq of technetium Tc 99m–labeled hexamethylpropylene amine oxime (CereteC; Amersham, Arlington Heights, Ill). Room lights were dimmed and quiet was observed to minimize patient visual and auditory stimuli during the brain uptake phase for another 15 minutes following

or single photon emission computed tomography (SPECT) in aggressive individuals show hypometabolism or hypoperfusion in temporal lobes, particularly on the left side. Dysfunction of the prefrontal cortex also has been implicated in aggressive behavior. Increased aggressive feelings are reported by patients with focal orbitofrontal lesions. Neuropsychological and electroencephalographic studies support a relationship between frontal lobe dysfunction and aggression, and functional neuroimaging studies indicate an association between aggression and hypometabolism in the prefrontal cortices, especially the orbitofrontal cortex.

The underlying mechanism for aggression in patients with dementia is unclear and involvement of the orbitofrontal and temporolimbic cortex has not been established. Studies evaluating focal brain lesions related to aggression in dementia are lacking. Sultzer et al reported, in a study of 21 patients with AD, that the agitation/disinhibition factor score of the Neurobehavioral Rating Scale correlated with glucose metabolism in the frontal and temporal lobes, but they did not evaluate aggression separately.

In this study, we compared the pattern of regional cerebral perfusion between 2 groups of 10 patients with dementia with and without agitation/aggression as measured by the Neuropsychiatry Inventory (NPI). The NPI emphasizes noncompliance, refusal to cooperate with the caregiver, obstinace, resistance, cursing, kicking, and being “hard to handle” within the agitation/aggression section. Groups were comparable on all demographic factors, severity of cognitive impairments, and all other be-
injection of the radiolabeled substance. Approximately 1 hour after injection, during which time washout of the tracer from the brain had occurred, SPECT images of the brain were obtained using the a SPECT scanner (Picker Prism 3000XP SPECT scanner; Picker International Inc, Cleveland, Ohio) with low-energy, ultrahigh-resolution fan beam collimators. Images were reconstructed by filtered back-projection using lowpass filter, order 8, with a spatial frequency cutoff of 0.23 to 0.25 cycles per pixel. Transverse, sagittal, and coronal planes as 128 × 128-pixel slices were generated. Pixel sizes were nominally 3.56 × 3.56 mm. Resolution of the system was approximately 6-mm full-width half maximum.

IMAGE PROCESSING

Spatial alignment of all 20 SPECT data sets was accomplished via 12-parameter affine registration. All data sets were first aligned to one randomly selected target to obtain an “average SPECT” which in turn was registered to the International Consortium of Human Brain Mapping probabilistic atlas. To minimize resampling of data, the 2 above warping fields were concatenated and applied to each SPECT data set. The relative perfusion scans of each patient then underwent linear intensity normalization, on a voxel-by-voxel basis, to the global mean intensity value of all 10 patients within each group, thus equalizing the mean intensities across intragroup data sets. This normalization step did not alter the variance of data.

Once all normalized data sets were in the common International Consortium of Human Brain Mapping probabilistic atlas space, a voxel-by-voxel subtraction was conducted between the aggressive and nonaggressive groups. Subvolume thresholding (SVT) was used to create a statistical map of these subtraction results as previously described. Briefly, SVT uses the probabilistic anatomical partitioning of the International Consortium of Human Brain Mapping atlas (partitions include the frontal, parietal, temporal, insular, and occipital cortex, along with the putamen, caudate, thalamus, and cerebellum) to model the different regions as separate stationary random fields thereby accommodating nonuniform global brain activity. In addition, the probability clouds of the International Consortium of Human Brain Mapping atlas allow us to control for spatial errors, imposed by registration and anatomical variability, by weighting the contribution of voxel intensities based on their location within an anatomical cloud. Thus, voxels within the center of a region have the highest probability of belonging to that region while voxels at the edge of a region have a lower chance of being accurately identified owing to registration error and normal anatomical variability.

The SVT approach departs from other functional imaging techniques. In the first step of significance evaluation, an estimate of the pooled variance for the average voxel intensity, which is dependent on the topology of the anatomical subvolume of interest, is used to assess the globally significant variability of data within each region separately, permitting a functional-anatomical test of the subtraction paradigm. This novel approach is particularly suited for the assessment of functional imaging studies in dementia since parietal and temporal regions may have significantly different means and variances, across subjects, than frontal or subcortical regions given the local pathological distribution of dementing disease. Ignoring these potential differences by modeling the entire data set as a stationary random field, done by many other functional assessments, will obliterate disease-specific variability. After the first SVT step identifies globally significant regions, the second step maps the location of voxels, with a difference z score above 2.5, in those regions. This is a standard procedure in most functional statistical mapping techniques with 2 exceptions: (1) voxel location tests are run only over those regions identified by the global search in step 1 and (2) variance estimates are pooled over subjects and across voxels. Once the locations of voxels within a region of interest have been assigned a z-score value, a significance level must be determined for voxels above a z-score threshold. The SVT local search within globally significant regions derived from the between-group subtraction is corrected for multiple voxelwise testing to control for type I errors in assessing significance. For each of the selected voxels outside of our a priori hypothesized regions, a Bonferroni correction is conducted by dividing the significance level associated with the z score by the number of voxels constituting a single search (this voxel number is equal to the size of the full-width half maximum of the scanner—6 mm). For voxels within our a priori hypothesized regions, we employed a bootstrap analysis to determine the significance of the selected voxels.

bavioral symptoms captured by the NPI, including delusions, hallucinations, disinhibition, irritability, apathy, anxiety, and depression. We hypothesized that patients with dementia with significant agitation/aggression would have significantly lower anterior temporal and lateral orbitofrontal perfusion on SPECT analysis compared with patients without agitation/aggression.

Table 1 and Table 2 show the demographic features, psychotropic medications, Mini-Mental State Examination (all other cognitive indices assessed by our battery were comparable between groups), and behavioral profiles of the 2 groups. Of the 10 aggressive patients with dementia 8 were diagnosed as having AD, and 2 were diagnosed as having vascular dementia. Of the 10 nonaggressive patients with dementia 8 were diagnosed as having AD, 1 was diagnosed as having dementia with Lewy bodies, and 1 was diagnosed as having normal pressure hydrocephalus. Agitation/aggression was the only behavior assessed by the NPI that was statistically significant (P < .001) different between the 2 groups. The Figure and Table 3 show the Talairach and Tournoux atlas location of the peak significance for regions with significantly lower perfusion in the 10 patients with dementia who had high aggression scores compared with the 10 nonaggressive patients. Patients with aggression revealed statistically significant (P < .001) hypoperfusion in the left anterior temporal cortex (Brodman areas 20, 21, and 38); the difference in the orbitofrontal cortices was not significant. Besides the regions we hy-
Several studies have suggested that aggressive behavior is associated with demographic factors including male gender, increased age, education level, and psychotropic medications. Mini-Mental State Examination scores, and cognitive performance, all of which were similar between the patients groups with and without aggressive behavior. Moreover, because aggression has been associated with other neuropsychiatric manifestations including delusions, hallucinations, irritability, and depression, we also ensured that the neuropsychiatric symptoms in the 2 groups were comparable. This approach aids identification of the brain regions that, when dysfunctional, may be specific to aggressive behavior.

Generalizability of this study is limited by the small sample size. The study demonstrated a clear association between aggressive behavior and hypoperfusion in the left frontal region but failed to demonstrate the expected involvement of the orbitofrontal cortices in patients with dementia. This failure might be caused by the lack of statistical power due to the small sample size.

The anterior temporal cortex has reciprocal connections with the amygdaloid complex. The amygdala has abundant connections with association cortices of multiple cortical sensory systems; visceral brain areas including brainstem and hypothalamus; basal ganglia; and other limbic structures such as parahippocampal gyrus, insula, and cingulate cortices. Anterior temporal structures have been posited to play an important role in associating sensory experiences with emotion. Dysfunction of these areas has been implicated in causing abnormal emotional associations to external sensory stimuli, and in provoking inappropriate aggressive acts to trivial or misinterpreted stimuli.

In addition to involvement of the left anterior temporal cortex, we found significant regional hypoperfusion in the right and left dorsolateral frontal and right superior parietal regions. Within the prefrontal regions, the disturbances of orbitofrontal cortices have been linked most often to aggression; however, several studies have shown the involvement of the dorsolateral frontal region in aggression. Dorsolateral frontal regions are considered important to critical thinking and planning, and reduced metabolic activity in these regions may lead to misinterpretation of environmental and social situations, which might be related to aggressive behavior. Raine et al described significantly decreased glucose metabolism in both superior parietal regions in murderers as compared with normal controls. These findings also are compatible with the fact that aggressive behaviors are more frequent in patients with frontotemporal dementia, who usually have dysfunction of dorsolateral frontal regions as well as of anterior temporal structures, as compared with patients with AD. The superior parietal lobes are critical for sensorimotor integration providing subjective knowledge of both the world and one’s own body. Dysfunction of the superior parietal lobes may cause the sensory information processing deficits and abnormal assessments of both the world and one’s own body resulting in abnormal emotional responses.

This study bears importantly on the understanding of agitation in dementias. Agitation encompasses many behaviors including aggressive behavior assessed by the NPI. The pathogenesis of agitation in dementia is controversial with some investigators considering it a primary symptom of brain dysfunction and others viewing it as a symptom of psychopathology. In this study,
patients had comparable levels of nonaggressive behaviors, differing only on the aggression/agitation scores of the NPI. Regional brain dysfunction was identified as the correlate of these behavioral differences. These observations support the hypothesis that this type of agitation can occur as a primary behavioral disturbance with unique anatomical underpinnings.

**CONCLUSIONS**

We prospectively studied aggressive behaviors in patients with dementia and the relevant regional cerebral hypoperfusion by using SPECT and an established method of neuropsychiatric assessment in dementia. We demonstrated an association between aggression and decreased perfusion in the left anterior temporal cortex. Our results support previous reports of anterior temporal involvement in aggressive behaviors, irrespective of disease origin. This finding might predict the development of aggression and the effectiveness of therapeutic interventions used for the patients with dysfunction in this region.

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