Interrelationship Between Delirium and Dementia

Cerebral Perfusion Changes in Older Delirious Patients Using 99mTc HMPAO SPECT

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Background. Prior studies describe variable cerebral blood flow changes in delirium. This study aims to investigate cerebral blood flow changes in older hospitalized patients with delirium, the population in which most cases of delirium occur.

Methods. Participants included hospitalized general medical patients aged 65 years and older with documented delirium and no relevant medical conditions or preexisting abnormalities on neuroimaging prospectively studied using 99mTc HMPAO single photon emission computed tomography (SPECT) scans obtained during and after resolution of delirium. Twenty-two patients enrolled in the study, of whom six completed both scans. All participants underwent neuropsychological assessment immediately prior to SPECT scanning. SPECT images were compared across all participants during delirium; for patients completing paired scans, within-patient comparisons were made.

Results. Visual assessment of SPECT scans revealed perfusion abnormalities in frontal (5 participants) or parietal regions (6 participants); scans were normal in 11 participants (50%). Region-of-interest analysis identified reduced blood flow (p < .01) in the left inferior frontal, right temporal, right occipital, and pontine regions. Analysis of paired scans revealed reversible abnormalities in three participants (p < .001), with decreased right parietal perfusion in two participants and increased left parietal perfusion in one participant.

Conclusions. The results of this study of a small group of general medical patients are suggestive that frontal or parietal cerebral perfusion abnormalities occur in delirium, and these findings need to be confirmed by future, larger studies. These results may help to improve basic understanding of delirium pathophysiology, to identify long-term changes, and to evaluate response to treatment over time.

Although epidemiological studies have identified clinical risk factors for delirium (1–3), and controlled clinical trials have demonstrated that delirium can be prevented (4,5), delirium remains a challenging condition to identify and treat, and the basic pathophysiology of delirium has yet to be fully described. Neuroimaging techniques that measure cerebral blood flow are increasingly used to provide anatomic localization of disease pathophysiology (6). Previous studies using single photon emission computed tomography (SPECT) or positron-emission tomography (PET) in delirium describe variable changes in blood flow. For example, delirium tremens is associated with globally increased cerebral perfusion (7), hepatic encephalopathy may result in reductions in temporoparietal and occipital perfusion and either increases or decreases in subcortical perfusion (8–12), and postcardiotomy delirium is associated with decreased parietooccipital and temporal perfusion (13). Many of these studies are case studies of patients with specific causes of delirium, rather than general medical patients who typically constitute the majority of patients with delirium in the hospital.

The aim of the present study is to use SPECT to determine patterns of regional cerebral perfusion among hospitalized general medical patients both during and after resolution of delirium. Determining distinct anatomic patterns in delirium might help to identify pathways underlying the clinical phenomena of delirium and clarify whether there are common neuroanatomic patterns among the diverse etiologies for delirium, findings which may in turn lead to more effective preventive and treatment strategies.

Methods

Setting and Participants
Potential participants were patients admitted to the general medicine floors at Yale–New Haven Hospital (YNHH; New Haven, CT) between November 5, 2001 and December 16, 2002. YNHH is a 944-bed urban teaching hospital with 200 general medical beds serving a large local community and referral population. Eligibility criteria included age ≥
65 years, presence of delirium as documented by the Confusion Assessment Method (CAM) (14), and absence of relevant medical conditions (epilepsy, drug and/or alcohol abuse, moderate to severe dementia, coma, severe illness, or respiratory isolation). Patients were excluded if computed tomography and/or magnetic resonance imaging (MRI) demonstrated any preexisting abnormalities, including tumors, large strokes, or focal atrophy. Of 103 consecutive patients meeting study eligibility criteria, 81 patients were excluded because of refusal to participate (n = 58), early hospital discharge (n = 10), illness, agitation or dementia (n = 7), poor quality scans (n = 3), inability to consent (n = 2), or incomplete neuropsychological testing (n = 1). Twenty-two patients met eligibility criteria and completed SPECT scanning and neuropsychological testing during delirium. Six of these patients were retested after resolution of delirium. The remaining 16 patients did not have complete clinical improvement of delirium prior to hospital discharge. A single patient who had paired SPECT scans but incomplete clinical improvement of delirium prior to hospital discharge (n = 10), illness, agitation or dementia (n = 7), poor quality scans (n = 3), inability to consent (n = 2), or incomplete neuropsychological testing (n = 1).

Cognitive Assessments and Variables

The Mini-Mental State Examination (MMSE) was used as an overall measure of cognitive function (15). Attention, which is invariably impaired in delirium, was measured with the Digit Span Test (16) and vigilance subtest from the Cognitive Test for Delirium (CTD) (17). The presence and severity of delirium were documented using the CAM (14), a validated and widely used instrument for the diagnosis of delirium, and additional measures of delirium severity included the Delirium Rating Scale-98 (DRS) (18) and the CTD (17). Preexisting dementia was assessed using the Modified Blessed Dementia Rating Scale (19), and functional status was determined using the Index of Activities of Daily Living (20). Admitting diagnoses, severity of illness, laboratory results, vital signs, and medications were obtained from a brief nurse interview and review of the medical records.

SPECT Imaging

Immediately following cognitive testing, participants were taken to the SPECT scanner, placed in a darkened, quiet environment, and after 5 minutes injected with 962 MBq (26 mCi) of 99 mTc HMPAO. Fifteen minutes after injection, participants were placed in a two- or three-headed SPECT camera (Axis 3000 or Prism 2000; Phillips Medical Systems, Best, The Netherlands) outfitted with high-resolution parallel hole collimators. To minimize anticipated head movement, a series of seven serial 5-minute images were obtained into a symmetric photopeak window centered at 140 keV. The serial SPECT scans were summed, transverse reconstructed, and filtered using a 3-D low-pass ramp filter with order 4.0 and cutoff 0.26. Homogeneous attenuation correction was performed by using the Chang method (21) with an attenuation of 0.11/cm.

SPECT Analysis

Analysis of SPECT blood flow images was performed in three ways: (i) visual analysis of scans; (ii) semiquantitative region of interest (ROI) analysis; and (iii) statistical parametric mapping (SPM99: Wellcome Department of Imaging Neuroscience, London, U.K.; http://www.fil.ion.ucl.ac.uk/spm/) of paired scan data sets.

Images were reviewed independently and by consensus by two board-certified nuclear medicine physicians (J.S., A.D.) and a neurologist (H.B.) with extensive clinical expertise in SPECT perfusion studies and qualitative interpretation of perfusion abnormalities. Reviewers were blinded to specific clinical information about individual participants. All scans were compared with the participant’s baseline computed tomography and/or MRI to ensure that the perfusion changes did not correlate with an existing anatomic lesion.

For the semiquantitative ROI analysis, initial normalization of the participant scans was performed using SPM99 with MedX 3.4 (Sensor Systems, Sterling, VA), implemented on a Linux platform (7.0; Red Hat Software, Inc., Raleigh, NC) by a protocol published previously (22,23). Briefly, the SPM realign function was used to create a mean image and reslice the reconstructed images. Images were then spatially normalized to the SPM SPECT template in the SPM standard anatomical space (MNI space). Smoothing was performed using a 10 × 10 × 12 mm Gaussian kernel. Proportional scaling to the global mean was performed using an analysis threshold of 0.8.

Following established methods (24), circular ROI measuring 6024 mm³ were defined for the cerebellum, inferior frontal, superior frontal, parietal, temporal, and occipital lobes. A circular ROI measuring 3528 mm³ was defined for the pons and midbrain. The regions were placed over representative areas on a normal MRI template in standard anatomical space (see http://www.mrc-cbu.cam.ac.uk/Imaging/mnispace.html) by two separate observers (J.S. and A.D.). The SPECT scans were coregistered to the MRI, and the same regions were pasted over the normalized SPECT images. The numbers of counts in each ROI were calculated and normalized to the mean counts in the two cerebellar regions for each participant to create a blood flow ratio. The cerebellum was used as the reference region because it has not been found to be significantly involved in delirium and because of low variation of counts in this region. Comparisons of blood flow ratios were made against age- and handedness-matched controls (n = 11) from a standard SPECT databank.

The data from six participants with paired scans were compared using a paired-sample t test for areas of relative hyper- and hypoperfusion on SPECT images obtained during active and then resolved delirium. The extent threshold (k) below which clusters were rejected was 125 voxels, which is equivalent to a volume of 1 cm³ and corresponds to the approximate resolution of brain SPECT imaging. The voxel level threshold was set at 0.01.

RESULTS

Participant Characteristics

Participant characteristics are presented in Table 1. On average, participants were ≥80 years old, with 12 years of
have complete cognitive data was included in the paired scan analysis (Table 4). Blood flow ratio analysis (Table 3). A single additional participant who did not participants were used for the visual analysis (Table 2) and the region of interest emission computed tomography (SPECT) scans and cognitive data. These 22

**Table 1. Participant Characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value (N = 22)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y, mean (SD)</td>
<td>82.1 (7.9)</td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>15 (68)</td>
</tr>
<tr>
<td>White, n (%)</td>
<td>19 (86)</td>
</tr>
<tr>
<td>Married, n (%)</td>
<td>8 (36)</td>
</tr>
<tr>
<td>Education, y, mean (SD)</td>
<td>12.3 (4.0)</td>
</tr>
<tr>
<td>Right-handed, n (%)</td>
<td>22 (100)</td>
</tr>
<tr>
<td>Functional impairment*, n (%)</td>
<td>12 (55)</td>
</tr>
<tr>
<td>Previous history of n (%)</td>
<td></td>
</tr>
<tr>
<td>Cerebrovascular accident</td>
<td>4 (18)</td>
</tr>
<tr>
<td>Dementia</td>
<td>2 (9)</td>
</tr>
<tr>
<td>Parkinson’s disease</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Admitting diagnoses, n (%)</td>
<td></td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>3 (14)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2 (10)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>2 (10)</td>
</tr>
<tr>
<td>MMSE*, mean (SD)</td>
<td>19.6 (4.4)</td>
</tr>
<tr>
<td>DRS*, mean (SD)</td>
<td>17.7 (5.3)</td>
</tr>
<tr>
<td>CTD*, mean (SD)</td>
<td>21.9 (5.6)</td>
</tr>
<tr>
<td>Digit Span, forward*, mean (SD)</td>
<td>5.0 (1.3)</td>
</tr>
<tr>
<td>Digit Span, backwards*, mean (SD)</td>
<td>6.3 (2.5)</td>
</tr>
<tr>
<td>Attention Span, mean (SD)</td>
<td>16.2 (3.7)</td>
</tr>
<tr>
<td>Vigilance**, mean (SD)</td>
<td>47.7 (13.9)</td>
</tr>
<tr>
<td>Overall delirium rating, n (%)</td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>10 (45)</td>
</tr>
<tr>
<td>Moderate</td>
<td>11 (50)</td>
</tr>
<tr>
<td>Severe</td>
<td>1 (5)</td>
</tr>
</tbody>
</table>

Notes: *Data are for the 22 participants who had usable single photon emission computed tomography (SPECT) scans and cognitive data. These 22 participants were used for the visual analysis (Table 2) and the region of interest blood flow ratio analysis (Table 3). A single additional participant who did not have complete cognitive data was included in the paired scan analysis (Table 4).

1Impairment in at least one activity of daily living (bathing, transferring, grooming, walking).

2Scored 0–30, measures a range of cognitive abilities; lower score reflects greater cognitive impairment.

3Scored 0–46, considered delirious above 17.75.

4Scored 0–30, considered delirious at or below 19.

5Scored 0–7, measure of attention, high score is normal.

6Scored 0–12, measure of attention, high score is normal.

#Scored 0–12, measure of attention, high score is normal.

**SD** = Standard Deviation; MMSE = Mini-Mental State Examination; DRS = Delirium Rating Scale; CTD = Cognitive Test for Delirium.

with the most common contributing factors being medications (77%), preexisting dementia or cognitive impairment (59%), infection (50%), dehydration (36%), metabolic (36%), hypoxia (14%), and immobility (14%).

**Qualitative Visual SPECT Analysis**

Qualitative visual analysis of the SPECT scans revealed perfusion abnormalities in 11 participants (50%) (Figure 1 and Table 2). Five participants had perfusion abnormalities in the frontal lobes, with two bifrontal perfusion decreases, one left frontal perfusion decrease, one left frontotemporal perfusion decrease, and one left frontal perfusion increase. Six participants had perfusion abnormalities in the parietal lobes, with four left parietal perfusion decreases, one right parietal perfusion decrease, and one bifrontal perfusion decrease. The participant with a left frontal perfusion increase also had a right occipital perfusion decrease, and one of the participants with a left parietal perfusion decrease also had a diffuse cortical perfusion decrease. The remaining 11 participants had no detectable perfusion abnormalities. Seven of the 11 participants with perfusion abnormalities and 8 of the 11 participants without perfusion abnormalities had baseline cognitive impairment on the Modified Blessed Dementia Rating Scale. Comparison of delirium severity among participants with perfusion changes and those without demonstrated a nonsignificant trend toward perfusion changes occurring in participants with more severe delirium (DRS for abnormal scan, 19.8 ± 5.4 vs 15.6 ± 4.5 for normal scan group, p = .06).

**Semiquantitative ROI Analysis**

Delirious participants had significant (p < .01) decreases in regional blood flow ratios in the pons, left inferior frontal, right temporal, and right occipital lobes compared to controls (Table 3). Correlation between regional blood flow in the left inferior frontal lobe and cognitive performance on attention tests approached statistical significance (p = .057, data not shown).

**Paired SPECT Analysis**

Analysis of the paired SPECT scans, performed during delirium and after delirium resolution, revealed no differences
in perfusion by qualitative visual analysis; however, significant \((p < .001)\) perfusion changes were detected with SPM in the parietal lobes in three of six participants (Table 4). Two participants demonstrated decreases in perfusion in the right parietal lobe, and one demonstrated increased perfusion in the left parietal lobe. The mean time interval between the first and second scans was 2.67 days (standard deviation 1.51), with a median of 2 days and range of 1–5 days. The mean change in score in the DRS (second score minus first score) was \(-7.17\) (standard deviation 8.21), with a median of \(-8.0\) and range of \(-19\) to 3. There were no significant baseline differences between participants who had paired scans compared to those having only a single scan, in terms of age, gender, race, handedness, MMSE, and DRS (data not shown).

**DISCUSSION**

Unlike prior studies that focused on specific causes of delirium, this study, although relatively small scale, is currently the largest of its type, and importantly, included patients with delirium from multiple etiologies to more accurately represent the typical clinical condition. Qualitative visual analysis of the SPECT scans identified changes in frontal and parietal lobe perfusion in half of the participants. Semiquantitative analysis revealed significant changes in the blood flow ratios in the left inferior frontal, right temporal, right occipital, and pontine areas. Correlation of the scans with attention scores, one of the hallmarks of delirium, suggested that inattention was associated with perfusion abnormalities in the left inferior frontal region. Analysis of paired SPECT scans in six participants who were studied in delirious and nondelirious states suggests that changes in perfusion occur in the parietal lobe.

The neuroanatomical localization of delirium pathology has implications for understanding both symptoms and underlying mechanisms. Some of the key features of delirium, including inattention, disorientation, and comprehension deficits, have been associated with regional pathology. For example, attention is associated with the nondominant posterior parietal and bifrontal areas, the thalamus, and the pons (25,26); orientation is associated with nondominant parietal, medial orbitofrontal and temporal cortex (27,28); and comprehension is associated with frontal and temporal regions (29,30). Thus, the predominance of findings in the frontal and parietal regions and pons (by ROI analyses) is an important result in this study, and is consistent with what is known of the neuroanatomical localization of important delirium symptoms.

There are a number of limitations to this study. Because participants must lie still for the SPECT scan, only those...
persons with hypoactive delirium could be included. Inclusion of participants with more prominent delirium symptoms, where changes may be more evident, or use of other functional imaging techniques, might allow for detection of subtle perfusion changes. In addition, changes in global blood flow could not be determined, and such changes in perfusion might play a critical role in delirium. In contrast to the visual assessment and SPM analysis of the paired scans, the ROI analysis identified trends, but not statistically significant differences in the parietal lobe. This discrepancy may be related to the small sample size (i.e., inadequate power) or to methodological errors (i.e., positioning of the ROI in the parietal lobe), or could reflect variability of perfusion changes in this region, as observed in the paired scan analysis with increased perfusion in one participant and decreased perfusion in others. A reduction in blood flow in the pons, an area critical for attention, was detected only in the ROI analysis, and further confirmation of this finding is needed.

Delirium is a heterogeneous, global process resulting in fluctuating mental status that likely involves widespread electrophysiological and neurochemical abnormalities. For these reasons, delirium is inherently challenging to study. Furthermore, patients most likely to suffer from delirium are older patients who commonly have preexisting brain abnormalities, such as atrophy, vascular insults, tumors, or dementia, which could contribute to changes in blood flow independent of delirium, and making comparisons across individuals is difficult. To minimize effects of multiple variables, within-individual comparisons of paired scans obtained in delirious and nondelirious states were intended to address this methodological challenge. Unfortunately, logistical difficulties (such as early discharge or persistence of delirium) made it possible to obtain paired scans in only 6 of the 22 participants, and limited the conclusions that can be drawn from this study. Furthermore, although on average the paired participants had a 41% reduction in severity of delirium score, they may not have fully recovered by the time of the second scan. Controls from a normal SPECT database were used, rather than controls chosen from the same hospitalized cohort who did not develop delirium, and it is possible that changes seen on the paired scans may have been the result of treatment, underlying medical illness, or other aspects of the hospitalization. Although there were no baseline differences between participants who were able to have paired scans compared to those who had only a single scan, the findings from these six individuals cannot be generalized across all participants. Future studies will benefit from strong efforts to obtain serial scans on individuals with delirium, to more fully characterize longitudinal changes, and to better understand the variability in severity and recovery from delirium.

Despite the considerable challenge of enrolling actively delirious and ill patients, this study was able to obtain SPECT scans in a sizable number of general medical patients and provides important preliminary data in the study of functional brain changes in delirium. The results suggest potential involvement of the frontal and parietal lobes in the neuropathology of delirium. Because delirium is such an important clinical syndrome, and because little is known about the fundamental pathophysiology of delirium, efforts to unravel the underpinnings of delirium represent a crucial step along the path toward providing necessary and appropriately targeted improvements in treatment and preventive strategies. Moreover, these results may provide a basis to identify long-term changes and to evaluate response to treatment over time.

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REFERENCES


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