Cognition and Cerebral Blood Flow Fluctuate Together in Multi-infarct Dementia

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Longitudinal measurements of cognitive ability measured by serial testing using the Cognitive Capacity Screening Examination (CCSE) were correlated with cerebral blood flow (CBF) throughout (mean ± SD) 19.9 ± 12.6 months among 57 patients with multi-infarct dementia, 17 with dementia of the Alzheimer's type, 10 with both, and among 32 age-matched elderly normal controls. Longitudinal CCSE and CBF measurements among controls yielded stable normative values. Reduced mean CCSE scores correlated directly with CBF reductions in patients with multi-infarct dementia (p<0.0005) and dementia of the Alzheimer's type (p<0.028). Patients with multi-infarct dementia had CCSE scores with retest variability exceeding those of controls (p<0.001) and of patients with dementia of the Alzheimer's type (p<0.003). CCSE scores and CBF changed together 78.6% (p<0.001) of the time in patients with multi-infarct dementia compared with 66.2% of the time (p<0.01) in those with both, 62.9% of the time (p<0.05) in those with dementia of the Alzheimer's type, and 47.7% of the time (NS) in controls. Further analyses indicated that changes in CCSE scores and CBF were predominantly progressive declines in patients with dementia of the Alzheimer's type, whereas the changes were more bidirectional (both increases and decreases) in patients with multi-infarct dementia; these differences were also significant. Results support the diagnostic usefulness of the Hachinski ischemic scale and confirm that both cognition and CBF fluctuate together among patients with multi-infarct dementia, whereas patients with dementia of the Alzheimer's type exhibit a more stable course, with progressive declines in cognition and CBF. (Stroke 1988;19:163-169)

Although carefully controlled prospective studies of large numbers of well-identified cases are lacking, clinical experience with patients suffering from dementia suggest that dementia of the Alzheimer's type (DAT) is characterized by an insidious onset that is followed by slow, progressive declines in cognitive performance. Impairments of recent memory are the hallmarks of DAT, although there are usually accompanying declines in communication skills, interpersonal relationships, and behavior. Multi-infarct dementia (MID) characteristically begins with more abrupt onset, followed by a stepwise and fluctuating course. Sometimes there may be sustained improvements, particularly if risk factors for stroke such as hypertension and smoking are controlled. These risk factors are frequently present in patients with MID, and hypertension is the most prevalent. Based on such clinical criteria, Hachinski et al developed an ischemic scale that appears to be useful for screening and identifying patients with MID or with both types of dementia (MIX), separating them from patients with DAT alone. The modification of this ischemic scale used here and in previous publications assigns points weighted according to whether there was an abrupt onset of cognitive impairments (2 points), a fluctuating or stepwise course (1 point), the presence of somatic complaints (1 point), emotional incontinence (1 point), hypertension (1 point), a history of strokes (2 points), focal neurologic signs (2 points), and focal neurologic complaints (2 points). This ischemic scale has proven useful for distinguishing DAT from MID after confirming the diagnosis for each case at autopsy. The anatomic diagnosis predicted by the ischemic scale alone has been correct in about 89% of patients dying with DAT and in 71% dying with MID.

Cerebral gray matter blood flow (CBF) has been reported to be patchily reduced in MID patients, and regional vasomotor responses tested by inhaling carbon dioxide or oxygen mixtures have likewise shown the same type of bihemispheric patchy impairments. These CBF changes have been directly related to the severity of the dementia, estimated by cognitive testing, in patients with either MID or MIX but not in patients with DAT. CBF is reduced bilaterally in both forms of dementia. In DAT patients, gray matter blood flow is more diffusely reduced; in MID patients patchy regional CBF reductions are found particularly...
in the distribution of both middle cerebral arteries, and each regional CBF reduction has been shown to correspond to a zone of cerebral ischemia or infarction.\textsuperscript{10-13} These ischemic zones in MID frequently involve the thalamus bilaterally as well as the frontal and temporal cortex surrounding or adjacent to both sylvian fissures.\textsuperscript{13,14} Reductions of CBF in these regions correlate directly with cognitive impairments.\textsuperscript{13}

Our investigation was designed to examine whether serial measurements of cognition and CBF recorded concomitantly in groups of elderly patients with MID or MIX fluctuated, and if so, whether they exceeded fluctuations measured in a group of age-matched patients with DAT and in a group of age-matched elderly but neurologically intact volunteers who functioned as controls. We tested the hypothesis that patients with MID and MIX show greater test-retest variability for cognition and CBF than DAT patients and controls and that more direct relations between cognition and CBF are evident among MID patients than among DAT patients or the age-matched controls.

\textbf{Subjects and Methods}

\textbf{Patients and Controls}

Patients with MID, DAT, and MIX as well as neurologically normal elderly volunteers with and without risk factors for stroke have been recruited in the same manner during the past 8 years to participate in prospective studies of normal and abnormal aging. To encourage participation, periodic health examinations are offered at intervals of 3-6 months to all participants without charge. All participants are right-handed and have completed high school, the majority having university or college-level equivalents by virtue of vocational training. To exclude any secondary contributions to dementia because of excessive alcohol ingestion, patients who regularly drink \textgreater 4 ounces of alcohol per day are excluded. Patients who have suffered a major stroke and/or exhibited persistent dysphasia are also excluded, as are neurologically unstable patients such as those recovering from recent minor strokes and/or those who have suffered transient ischemic attacks within 3 months before admission to the study. Approximately 35\% are veterans, and the remainder were recruited from nonveterans to obtain representative groups of both men and women. Informed consent was obtained before participation and was signed by the patients and controls and/or the spouse or legal guardian if the degree of dementia was moderate to severe. Informed consent forms, as well as the protocols for CBF measurements and participation in the serial clinical evaluations, have been approved annually for the past 9 years by the Institutional Review Board of the Veterans Administration Medical Center, Houston, Texas.

Patients and controls were divided into four groups to compare longitudinal measurements of cognition and CBF (Table 1). The subjects have been followed for a mean of approximately 2 years, with return visits at intervals of every 3-5 months. Fifty-seven patients with well-established MID have been participating throughout the past 8 years in prospective studies of the natural history of dementia. Diagnosis was established by clinical history, medical and neurologic examinations, tests of cognition, and computed tomography (CT scanning) and/or nuclear magnetic resonance imaging (NMRI) of the brain. All patients with MID or MIX scored 4 or more on our modified version of the ischemic scale of Hachinski et al;\textsuperscript{15,16} for MID patients the mean ischemic scale score was 7.7. Cognition was measured using the Cognitive Capacity Screening Examination (CCSE), a modification of the Mini-Mental Status Examination (MMSE); the CCSE has been shown to be more sensitive than the MMSE in identifying demented patients, whereas both tests are comparable in specificity and correlate well with testing by the Wechsler Adult Intelligence Scale.\textsuperscript{15,16} All patients with dementia are required to score \textless=23 on the CCSE for admission to the study. MID patients were 44-88 (mean 67.6) years old and included 39 men and 18 women. In the MID group, the following risk factors for stroke were present: 43 had hypertension, 12 had hyperlipidemia, 30 had heart disease, 16 were heavy smokers (excess of one pack of cigarettes per day), and 11 had diabetes mellitus. All MID patients showed multiple small lesions of the brain by CT and/or NMRI.

Seventeen patients with DAT are being followed. Diagnosis of DAT was established by medical and neurologic examinations that included a history of gradual onset of memory loss, followed by slow progressive declines in cognitive performance and behavior. Diagnosis was based on criteria established by the report of the NINCDS-ADRDA work group\textsuperscript{17} as well as the Diagnostic and Statistical Manual of Mental Disorders III (DSM III).\textsuperscript{18} The ischemic scale score for all DAT patients was \textless=3, with a mean of 2.2. Seven patients had risk factors for stroke, including two with well-controlled hypertension; one patient gave a his-

\begin{table}[h]
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\begin{tabular}{|l|c|c|c|c|c|c|}
\hline
\textbf{Group} & \textbf{\(n\)} & \textbf{Age (yrs)*} & \textbf{Follow-up (mo)} & \textbf{No. of serial visits per patient*} & \textbf{Time between visits* (mo)} & \textbf{Ischemic scale score} & \textbf{CCSE} & \textbf{CBF (ml/100 g brain/min)} \\
\hline
Multi-infarct dementia & 57 & 67.6±10.3 & 23.1±13.4 & 5.1±2.3 & 4.5±2.2 & 7.7±1.6 & 20.8±5.5 & 61.23±6.26 \\
Dementia of Alzheimer's type & 17 & 70.1±12.7 & 16.4±14.8 & 4.6±2.1 & 4.9±1.9 & 2.2±0.8 & 13.3±9.0 & 59.51±6.08 \\
Mixture of dementias & 10 & 70.0±9.8 & 24.5±13.2 & 5.7±2.5 & 4.3±2.1 & 6.5±2.2 & 17.7±6.0 & 61.19±4.46 \\
Age-matched normal controls & 32 & 63.8±9.9 & 14.7±6.4 & 4.7±2.8 & 5.2±2.8 & - & 28.9±1.4 & 66.48±6.39 \\
\hline
\end{tabular}
\caption{Demography of Patients and Normal Controls}
\end{table}

Values are mean±SD. CCSE, Cognitive Capacity Screening Examination score; CBF, hemispheric gray matter blood flow.

*Not significant by analysis of variance.
tory of treated heart disease, and four smoked cigarettes. Cognition was quantified at each return visit by CCSE testing as for the MID patients. The DAT group was 47–100 (mean 70.1) years old; there were 11 men and six women. All were right-handed and showed diffuse cerebral atrophy by CT and/or NMRI without focal lesions.

Ten patients had features of both MID and DAT and comprise the MIX patients. They were 49–81 (mean 70.0) years old; there were four men and six women. Risk factors in this group included hypertension in seven, heart disease in six, and cigarette smoking in one. Mean ischemic scale score for this group was 6.5. All showed both diffuse cerebral atrophy combined with multiple small lesions by CT and/or NMRI of the brain. These MIX patients had an ischemic scale score of at least 4 but also had DAT according to the criteria established by the DSM III.19

The controls consisted of 32 neurologically normal volunteers aged 40–87 (mean 63.8) years. This group consisted of a random sample of 32 consecutive volunteers who were admitted to the study during the same time interval as the patients and included 19 men and 13 women. Risk factors for this neurologically intact group included hypertension in 13, atherosclerotic heart disease in two, diabetes mellitus in one, and cigarette smoking in 12.

Measurement of Cerebral Blood Flow

The 133Xe inhalation method was used for measuring regional CBF as described by Obrist et al, with modifications developed in this laboratory for clinical application.20 After obtaining informed consent, 6–8 mCi/1 of 133Xe gas mixed with room air were inhaled for 1 minute. Clearance of the isotope was measured from 16 representative regions of both cerebral hemispheres during the ensuing 10 minutes by collimated sodium iodide crystal scintillation detectors mounted and distributed symmetrically over the frontal, parietal, temporal, and occipital regions. After correction for arterial recirculation, the fast component of clearance was used to estimate gray matter CBF using the two-compartmental model of Obrist et al.19 Mean ± SD bihemispheric gray matter CBF was calculated for each subject as indexes of brain perfusion and to determine individual test–retest variability of the measurement.

Statistical Analysis

To evaluate relations between cognition and cerebral perfusion, Pearson product-moment correlation coefficients were calculated between mean CCSE scores and mean CBF for each diagnostic group. Significance was determined using the t distribution.

Individual variability for tests of cognition as well as measurements of cerebral perfusion were quantitatively compared by calculating SDs among serial CCSE scores and CBF separately for each subject in each diagnostic group. Group differences of within-subject SDs were then tested using one-way analysis of covariance (ANCOVA), in which the diagnostic groups (controls, MID, MIX, and DAT) were compared using each subject's SD for serial CCSE scores or CBF as the dependent measure; length of follow-up and age were the covariates. Levene's test was employed to determine homogeneity of variance. For significant main effects, multiple post-hoc pairwise comparisons were tested using Tukey's "honestly significant difference" model with a 95% confidence interval adjusted for multiple comparisons.21

Another set of analyses was directed at determining any direct relations between CCSE scores and CBF fluctuations among individual subjects during prospective follow-up visits. The direction of change was analyzed using nonparametric statistics to determine whether CCSE scores and CBF fluctuated in the same or opposite directions at a frequency greater than would be expected during random fluctuations. If CCSE scores and CBF fluctuated randomly, the direction of change would be expected to agree no more than 50% of the time. The frequency with which CCSE scores and CBF for each diagnostic group fluctuated together was tested using the nonparametric sign test. This analysis was based on successive visits for a patient; a score was considered positive if CCSE score and CBF both increased or both decreased, and a negative score was obtained if CCSE score increased while CBF decreased or vice versa. When there was no change in either CCSE score or CBF on subsequent trials, it was treated as a tie on the sign test.

To further explore the nature of the relations between CCSE score and CBF, χ^2 analysis was also used to test for differences between diagnostic groups in the frequency of agreement between changes. Instances in which CCSE scores and CBF changes agreed were subdivided into the frequencies with which they both increased or both decreased and were analyzed. Analyses of variance (ANOVs) were used to determine whether there were any differences between diagnostic groups in the average length of time between visits, the mean number of visits per patient, and the total duration of follow-up. ANOVAs were not significant for two of the three time variables. Total duration of follow-up interval was significant at p<0.007 (see Table 1).

Results

As illustrated in Figure 1, Pearson product-moment correlation coefficients demonstrated significant correlations between mean CCSE scores and mean bihemispheric CBF among MID patients (r = 0.45, p<0.0005). Figure 2 shows the relation between CCSE scores and CBF for the controls as well as the DAT and MIX groups. DAT patients showed a significant positive correlation between CCSE scores and CBF (r = 0.53, p<0.03). Because of the stability of serial CCSE scores and CBF among controls, correlation between the variables was not significant (r = -0.14). Possibly related to the small number of MIX patients, positive trends for correlation between CCSE scores and CBF (r = 0.32) in this group were not significant.

Analyses of group differences in individual SDs for CCSE scores within subjects by ANCOVA were highly
Significant ($F_{(3,112)} = 13.14, p < 0.0005$). Length of follow-up was a significant covariate ($p < 0.01$), whereas age was not significant. Levene’s test for heterogeneity of variance was not significant. Group means of individual variability are displayed in Figure 3. Post-hoc analyses indicated that mean CCSE score variability was significantly greater among MID and MIX patients than among either DAT patients ($p < 0.003$) or controls ($p < 0.001$). The variability in CCSE scores among DAT patients was not significantly different than that among controls. Throughout this study, MIX patients performed similarly to the MID patients. Analyses of SDs for CBF within subjects by ANCOVA were significantly different ($F_{(3,112)} = 3.18, p < 0.04$). Length of follow-up was a significant covariate ($p < 0.02$), whereas age was not directly related to individual variability. Figure 3 shows that the within-subject variability for mean CBF was significantly greater among MID patients than among DAT patients ($p < 0.04$) or controls ($p < 0.001$). CBF variability was greater among MIX patients than among DAT patients or controls. The variability of CBF among DAT patients was not significantly different than that among the controls.

Comparison of frequency distributions indicated that CCSE scores and CBF changed in the same direction during successive trials 78.6% ($p < 0.001$) of the time in MID patients, 66.2% ($p < 0.01$) of the time in MIX patients, 62.3% ($p < 0.05$) of the time in DAT patients, and 47.7% (NS) of the time in controls. Comparisons between diagnostic groups demonstrated that CCSE scores and CBF changed in the same direction more frequently among MID patients than among DAT patients ($p < 0.01$) or controls ($p < 0.05$).

**Figure 1.** Mean Cognitive Capacity Screening Examination (CCSE) scores vs. mean bihemispheric gray matter blood flow (CBF) measured during serial visits among 57 patients with multi-infarct dementia (MID). Significant direct relations exist between CCSE scores and CBF ($p < 0.0005$).

**Figure 2.** Mean Cognitive Capacity Screening Examination (CCSE) scores vs. mean bihemispheric gray matter blood flow (CBF) measured during serial visits among 17 patients with dementia of Alzheimer’s type (DAT), 10 patients with both DAT and multi-infarct dementia (MIX), and 32 neurologically normal but elderly controls. Significant direct relations exist between CCSE scores and CBF in DAT patients, and similar nonsignificant trends are seen in the smaller number of MIX patients.
DAT patients also showed a significantly higher incidence of agreement among changes in CCSE scores and CBF than controls (p<0.05).

Comparing direction of change at times when CCSE scores and CBF changed in the same direction indicated that both cognition and cerebral perfusion decreased approximately one half of the time among MID patients (52.1%), MIX patients (57.5%), and controls (52.1%). However, among DAT patients, decreases occurred 65.4% of the time, which was significantly higher than for MID, MIX, and controls (p<0.005) by \( \chi^2 \) analysis of the frequency distributions.

Discussion

It is generally agreed that CBF is reduced in patients with organic dementias of both the Alzheimer's or vascular types when compared with age-matched normal controls. Regarding average CBF values, some investigators have reported significantly lower CBF in patients with MID compared with those with DAT; whereas other studies have reported equal reductions of CBF in both forms of dementia. More recently, it has been consistently demonstrated that overall CBF reductions in both MID and DAT correlate directly with the severity of dementia rather than with the diagnostic category. Regional CBF reductions in both forms of dementia are bilateral but differ because they are patchy in MID, more diffuse in DAT, and intermediate in MIX.

Cognitive deficits, measured by lowered CCSE scores, may be expected to reflect degrees of functional impairment of neurons regardless of etiology or depression of metabolic status. It is reasonable to assume that MID and DAT are both capable of causing the same degree of cognitive declines, in which case both causes of dementia may be expected to show similar reductions in average CBF. These assumptions are supported by our study since significant relations exist between low CCSE scores and overall reduced CBF in both forms of dementia whether secondary to MID or to DAT. However, cognition and CBF fluctuated to a greater extent in MID patients than in DAT patients. These observations support the concept that fluctuations in cognitive performance are directly related to similar fluctuations in cerebral perfusion among patients with vascular dementia. The absence of any correlation between CBF and CCSE scores among controls could be due to the restricted range. Correlations between CBF and cognition measured by the Wechsler Adult Intelligence scale have been previously demonstrated among controls as well as among patients with cognitive impairments.

Results of our current study, concerned with the relations between CCSE scores and CBF, indicate that periodic changes in cognition occur concomitantly and are directly related to fluctuations in cerebral perfusion. These fluctuations are bidirectional in MID patients, but DAT patients show a significantly greater propensity for progressive declines in both cognition and cerebral perfusion. Although the lower mean CCSE scores among DAT patients could influence the amount of variability, such a "cellar effect" would restrict the lowering of CCSE scores among DAT patients. Since the results of our current study demonstrated that both CCSE scores and CBF showed a preponderance of decreases among DAT patients, lower mean scores do not account for significant differences between groups. It is concluded that these differences in the relations between CCSE scores and CBF reflect the basic pathophysiologic mechanisms underlying these two distinct clinical categories of dementia.

A recent prospective study of neurologically normal elderly volunteers who subsequently developed either MID or DAT demonstrated that CBF was reduced among MID subjects for at least 2 years before dementia developed. In contrast, DAT patients maintained normal CBF immediately prior to the onset of clinical symptoms of dementia, and CBF slowly and progressively declined thereafter. Reduced cerebral perfusion in DAT patients appears to reflect a lowered neuronal metabolic demand that progresses slowly but correlates directly with decreases in cognitive performance. Studies using positron emission transaxial tomography have shown a direct reduction in glucose utilization that apparently precedes reductions in CBF in DAT patients.

Although focal ischemic lesions reduce CBF in patients with MID, this cannot explain the episodic increases in both CCSE scores and CBF. Vascular dementia appears to be related to cumulative episodes of ischemia that adversely affect neurons in and around the ischemic zones during periods of inadequate blood supply, but a potential for recovery in some neurons persists. For example, increases in regional
CBF in MID may be due to reestablishment of blood flow by development of a collateral circulation or by dissolution of cerebral thrombi or emboli so that spontaneous improvements in cognition may follow. However, prolonged and severe periods of regional ischemia are likely to result in focal infarctions that impair cognition. These focal infarcts may be visualized as areas of hypodensity and reduced local CBF by CT scanning and as zones of increased signal intensity on T2-weighted NMRI.

If relations described between cerebral blood supply and cognition obtain, they provide useful implications concerning prevention and treatment of MID. Maintaining adequate cerebral perfusion in patients with MID should provide positive clinical results by preventing additional focal lesions and by preserving remaining neuronal function at optimal capacity. In recent prospective studies of a large group of MID patients, optimal control of blood pressure, cessation of cigarette smoking, and surgical revascularization among a subgroup of patients with severe bilateral extracranial occlusive disease has been reported to result in improved cerebral perfusion and evidence of improved cognitive performance. Likewise, improved cognition has been reported in a group of patients with transient ischemic attacks following carotid endarterectomy.

Longitudinal studies of CCSE scores and CBF in patients with MID confirm earlier clinical assumptions that temporal fluctuations in neurologic performance correlate with fluctuations in CBF and are not seen among patients with DAT or among elderly normal subjects. Such clinical observations provided the basis for developing the Hachinski ischemic scale for predicting the diagnosis of MID versus DAT. The diagnostic value of documenting such fluctuations in neurologic and cognitive performance among demented patients is supported by the present findings.

Acknowledgment

Mrs. Barbara Williams Clark processed the manuscript.

References


**KEY WORDS** • dementia • cerebral blood flow • cognition
Cognition and cerebral blood flow fluctuate together in multi-infarct dementia.
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doi: 10.1161/01.STR.19.2.163

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1988 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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