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Original Study

Transcranial Doppler to Measure Cerebral Blood Flow in Delirium Superimposed on Dementia. A Cohort Study

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A B S T R A C T

Objective: Delirium superimposed on dementia (DSD) is frequently not diagnosed, at great cost. Both delirium and dementia are associated with cerebral hypoperfusion. A switch to anaerobic glycolysis in the central nervous system during delirium compared to Alzheimer's dementia (AD) suggests greater hypoperfusion in DSD. The main aims of this study were to investigate whether cerebral hypoperfusion could differentiate DSD from related entities, and the characteristics of that hypoperfusion.
Methods: Prospective cohort study of 44 Geriatric Medicine patients in 4 groups: (1) delirium, no history of dementia; (2) DSD; (3) acute illness without delirium or dementia; and (4) AD, no delirium. We measured CBF using transcranial Doppler to assess flow velocity (FV) and pulsatility index in the middle cerebral artery (MCA).
Results: DSD has lower FV than either AD or delirium alone, or acute illness (28.2 ± 4.7 vs AD: 41.3 ±15.7; $P = .040$; vs delirium 37.7 ± 8.2; $P = .009$; vs acute illness 43.0 ± 8.3; $P < .001$). A mean MCA FV cut-off of 32.25 cm/s diagnoses DSD with a sensitivity of 0.875 and specificity of 0.788, area under the curve 0.884; $P = .001$. Resolution of delirium improves FV ($P = .005$). FV correlates with delirium severity (delirium index $R = -0.39$; $P = .009$) and dementia (Mini-Mental State Examination, $R = 0.33$; $P = .029$, and Informant Questionnaire on Cognitive Decline in the Elderly, $R = -0.41$; $P = .005$).
Conclusions: Transcranial Doppler is a potential diagnostic and monitoring test for DSD. Correlation with clinical indicators of delirium suggests pathophysiological significance.

Delirium is a serious complication of illness, commonly affecting older patients, including more than 20% of hospitalized people over 65, and 70%–87% of those in intensive care, as well as being a major problem in long-term care.[1,2] It is a significant cause of preventable morbidity and mortality in older patients, substantially increasing healthcare utilization and costs.[1,3] Diagnosis is clinical, importantly informed by the corroborative history, however, 85% of delirious patients remain undiagnosed in hospital and 50% in nursing homes, or are misdiagnosed as having dementia, despite delirium being a medical emergency.[1,4] This is partly because of a lack of diagnostic tests, especially when superimposed on dementia.[5,6] Diagnostic indices are available, such as the Confusion Assessment Method (CAM), but it is unreliable in untrained hands.[7] Delirium is more common in people with dementia, is the most common acute driver of dementia, with which it shares many risk factors, and causes worsening of cognition and performance of activities of daily living, the clinical measures of dementia.[8,9] Delirium superimposed on dementia (DSD) is more frequently missed and results in higher mortality and readmission rates.[10–12]

We recently showed that cerebrospinal fluid lactate is elevated and neurone specific enolase decreased in delirium suggesting a switch to anaerobic glycolysis,[13] compared with Alzheimer's dementia (AD) where altered glucose metabolism is the most sensitive and specific marker of AD.[14] Abnormal glycolysis could lead to widespread neuronal dysfunction, triggering the clinical manifestations of delirium. Changes in glycolysis could be due to excessive demand for energy, toxins or reduced cerebral blood flow (CBF). The brain is dependent on glucose for energy production and inadequate

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CBF could disrupt glucose transport or its complete oxidation, thus lowering the efficiency of glucose metabolism.[13] Studies of CBF in delirium have been inconclusive, with variable findings ranging from no change to hypoperfusion and hyperperfusion.[15–17] Cerebral hypoperfusion predisposes to postoperative cognitive decline, which is linked to delirium.[18] Many patients with delirium also have dementia so the issue is complicated by evidence that decreased CBF is characteristic of AD, which also predisposes to delirium. However, CBF in delirium and AD has never been compared, therefore, it is unclear if the changes seen in delirium are due to underlying AD.[19] In addition, CBF declines by between 28% and 50% from age 30 to age 70.[20]

We investigated the hypothesis that DSD is associated with greater reductions in CBF by noninvasive, safe transcranial Doppler (TCD).

Methods

This cohort study was approved by the Human Research Ethic Committee. Written informed consent was obtained from all patients or their person responsible, where the patient lacked capacity. In 2011 we recruited consecutive consenting patients in four groups with (1) acute illness and delirium but no history of dementia; (2) acute illness with delirium and a history of dementia, the DSD group; (3) acute illness without delirium or dementia; and (4) no acute illness or delirium, known (Alzheimer's dementia) AD. Groups 1–3 were recruited from the Acute Geriatrics inpatient ward and were diagnosed by geriatricians based on clinical experience and the CAM.[21] Patients admitted to the Geriatrics ward are screened with the CAM in the Emergency Department. Patients with AD were recruited from both a general geriatric outpatient clinic and a cognitive disorders clinic, with AD diagnosis based on Diagnostic and Statistical Manual, 4th edition, and National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association criteria for probable Alzheimer's dementia. Cognitive and psychological assessments were conducted by a geriatrician and a neuropsychologist.

Patients were excluded if they had (1) possible impaired cerebral vasoreactivity because of (a) sonographic evidence of severe extracranial stenosis (>70%); (b) sonographic evidence of intracranial stenosis, and (c) presence of territorial infarcts larger than one third of the hemisphere; and (2) no insonation window or a poor signal. Patients with underlying dementia or history of delirium during current hospitalization were excluded from the acute illness group.

Patients were first screened for the presence of an insonation window. After a TCD measurement was taken, all subjects underwent baseline assessments through the completion of the clinical measures listed below. No intervention was performed on any of the patients for this observational study.

Assessments

Cognitive and psychological assessments were conducted using the Mini-Mental State Examination (MMSE);[22] the Confusion Assessment Method (CAM);[21] the delirium index (DI);[23] the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE);[24] and the Geriatric Depression Scale (GDS).[25] Physiological and functional status assessment were carried out using the Barthel index;[26] the modified Instrumental Activities of Daily Living (IADL) index;[27] the Acute Physiology, Age, Chronic Health Evaluation (APACHE) II;[28] and the Charlson comorbidity index (CCI).[29] The IQCODE was asked in regard to the patient's status relative to the pre-hospitalization status. For patients in groups 1–3 who were in hospital, the Doppler and CAM were repeated second daily until discharge. No testing was done prior to hospitalization. Group 4 were assessed only once. The order of testing was the same for all groups. The results in Table 2 refer to the initial testing.

TCD Imaging

We used the QL modular software and Doppler-Box from DWL Compumedics for analyzing transcranial spectral signals derived from systolic velocity, diastolic velocity, FV, and pulsatility indices generated by the MCA. The transtemporal approach of insonation was performed with the patient either lying supine on the examination bed or sitting upright in a chair and the head straight in both positions. The 2 MHz pulsed TCD probe was positioned according to the criteria of Aaslid,[30,31] which allowed identification of the MCA. All measurements were stored on hard disk for off-line analysis. The average of right and left FV and PI were used for analyses if both MCA could be insonated adequately. A single measurement was made on every second day of their hospitalization for patients in the delirium and acute illness groups. A one-off reading was taken from all patients with AD from the outpatient clinic. All TCD readings were taken by one person (Z.Z.L.) to reduce variability.

Statistical Analysis

SPSS 21 for Windows (SPSS Inc, Chicago, IL) was used in this study. A 2-tailed P value of less than .05 was considered significant. For parametric data, t tests were used for univariate analysis, while Mann-Whitney U was used for nonparametric data. Multivariate analysis was performed with logistic and binomial regression. Fisher exact test was used to compare proportions. Receiver operating characteristics curve was calculated using a nonparametric distribution assumption. Missing data were excluded listwise. A sample size calculation indicated that this sample size would be sufficient to detect a 20% difference in CBF. Groups were compared on their initial TCD and CAM only. However, initial and postdelirium TCD was compared in groups 1+2 with initial and final TCD in group 3.

Results

Between May and September 2011, a total of 86 patients were screened and 44 patients were eligible for inclusion and consented to participate in this study (Figure 1, online only). Patient characteristics (Table 1) were similar in the 3 groups except for age. Age was significantly lower in the AD group compared with the delirium [difference 9.5 years; 95% confidence interval (CI) 1.4–17.7; $P = .025$], and acute illness groups (10.0 years; 95% CI 2.1–18.0; $P = .026$). There were no significant differences in the reasons for hospitalization between the acute illness and delirium groups. There was a trend toward more patients with diabetes and more treated with psychotropics in the delirium group. There were significant differences among the 3 groups in the following measures: APACHE II, MMSE, CAM, DI, Barthel index, IQCODE, and modified IADL according to the expected clinical characteristics of each group (Table 2). However, the raised IQCODE in the delirium without dementia group may indicate that respondents had difficulty separating the cognitive decline associated with delirium from the premorbid state.

The delirium and acute illness groups had similar acuity of illness on the APACHE II. The dementia and delirium groups had similar cognitive decline on the IQCODE, although the MMSE was lower in the delirium groups than in AD and acute illness, cognitive decline being a feature of both. The delirium groups scored more highly on both measures of delirium, the CAM and DI, than other groups.

On univariate analysis mean, systolic and diastolic FV was lower in the DSD group compared with the acute illness group (mean differences—mean: 14.8 cm/s; 95% CI 8.0–21.6; $P < .001$; systolic: 29.0; 95% CI 16.0–41.9; $P < .001$ and diastolic: 8.9; 95% CI 2.5–15.3; $P = .003$). The DSD group was also significantly lower on mean and diastolic FV than the AD (mean: 13.1 95% CI 0.7–25.5; $P = .040$ and diastolic: 10.9;