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Brain atrophy and white-matter hyperintensities are not significantly associated with incidence and severity of postoperative delirium in older persons without dementia

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ABSTRACT

Postoperative delirium is a common complication in older people and is associated with increased mortality, morbidity, institutionalization, and caregiver burden. Although delirium is an acute confusional state characterized by global impairments in attention and cognition, it has been implicated in permanent cognitive impairment and dementia. The pathogenesis of delirium and the mechanisms leading to these disabling consequences remain unclear. The present study is the first to address the potential predisposing role of brain morphologic changes toward postoperative delirium in a large prospective cohort of patients undergoing elective surgery using state-of-the-art magnetic resonance imaging (MRI) techniques conducted before admission. We investigated the association of MRI-derived quantitative measures of white-matter damage, global brain, and hippocampal volume with the incidence and severity of delirium. Presurgical white-matter hyperintensities (WMHs), whole brain, and hippocampal volume were measured in 146 consecutively enrolled subjects, ≥70 years old, without dementia who were undergoing elective surgery. These 3 presurgical MRI indices were tested as predictors of incidence and severity of subsequent delirium. Out of 146 subjects, 32 (22%) developed delirium. We found no statistically significant differences in WMH, whole brain, or hippocampal volume between subjects with and without delirium. Both unadjusted and adjusted (age, gender, vascular comorbidity, and general cognitive performance) regression analyses demonstrated no statistically significant association between any of the MRI measures with respect to delirium incidence or severity. In persons without dementia, preexisting cerebral WMHs, general and hippocampal atrophy may not predispose to postoperative delirium or worsen its severity.

1. Introduction

Delirium is an acute confusional state marked by global impairments in attention and cognition (Inouye et al., 2014a). Common yet underdiagnosed postoperative delirium occurs in 11%–51% of hospitalized older patients (Inouye et al., 2014a) and significantly increases their risk for death, institutionalization, and dementia (Witlox et al., 2010). Mortality rates among hospitalized patients

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who develop delirium are as high as those among patients with myocardial infarction or sepsis (Inouye, 2006).

Despite its clinical impact, the pathophysiology of delirium remains poorly understood. It is believed that brain pathology plays an important role. Preexisting cognitive impairment and dementia are important predisposing factors for delirium. In addition, many precipitating factors leading to delirium, such as electrolyte disturbances, malnutrition, infections, anemia, shock, and psychotropic medications, have been identified (Inouye, 2006; Inouye et al., 2014a). Many cases of delirium are preventable through management of these precipitating factors.

A pathophysiological role for preexisting brain damage with respect to delirium incidence has been hypothesized. The hypothesis is based on the evidence that primary neurologic diseases (e.g., dementia, stroke, and traumatic brain injury) are risk factors for delirium (Inouye, 2006). Neuroimaging studies showing structural and functional magnetic resonance imaging (MRI) abnormalities in subjects with delirium further support this hypothesis (Alsop et al., 2006; Hughes et al., 2012; Lipowski, 1990; Soiza et al., 2008; Trzepacz, 2000). As long as 3 decades ago, brain atrophy was found to be associated with delirium in computed tomographic studies. Koponen et al. (1987), (1989) found that delirious patients had more cortical atrophy, wider Sylvian fissures, and more prominent ventricular dilatation on computed tomography. Global and regional perfusion abnormalities have been also observed on brain imaging of delirious patients (Fong et al., 2006; Siepe et al., 2011). As neuroimaging advanced, technology has become available to characterize the chronology of structural and functional brain abnormalities related to delirium and provided clues to the pathogenesis of delirium and associated cognitive decline (Hughes et al., 2012; Saczynski et al., 2012). MRI-derived measures of global and regional brain atrophy and cerebral white-matter damage have been associated with the occurrence of delirium (for a systematic review, see Alsop et al., 2006). Two small MRI studies found higher cerebral white-matter hyperintensity (WMH) burden in subjects who developed delirium after electroconvulsive therapy (Figiel et al., 1990a, 1990b). A few studies suggested a predictive role for multiple brain infarcts (Otomo et al., 2013) and cerebral white-matter damage, as measured by WMH burden or diffusion tensor imaging (DTI), for delirium incidence after cardiac surgery (Hatano et al., 2013; Root et al., 2013; Shioiri et al., 2010). In addition, recent resting-state functional MRI findings during and after an episode of delirium suggested that changes in cortical and subcortical functional connectivity underlie the pathogenesis of delirium (Choi et al., 2012). Other neuroimaging studies found associations between MRI abnormalities and delirium features, such as duration of delirium and subsequent cognitive impairment (for a review, see Soiza et al., 2008). Recent exploratory research in intensive care unit patients suggests that duration of delirium is associated with brain atrophy, particularly superior frontal and hippocampal, leading to long-term cognitive impairment (Gunther et al., 2012). In a very similar setting, duration of delirium was positively correlated with DTI white-matter tract abnormalities at discharge, which persisted at 3 months follow-up (Morandi et al., 2012).

Larger prospective studies with high power for detecting association between baseline WMH and delirium while controlling for important covariates are lacking. In most studies, sample sizes were small and importantly without baseline pre-delirium imaging performed (Alsop et al., 2006; Soiza et al., 2008). In addition, a number of study participants had diagnosed degenerative dementias or other known structural brain diseases confounding the interpretation of imaging abnormalities (Alsop et al., 2006; Soiza et al., 2008).

Given these limitations, there remains a gap in our knowledge on the relationship between preexisting neuroanatomic changes and delirium. Our study aims to fill this gap using state-of-the-art MRI techniques within a prospective study of postoperative delirium in older persons without dementia. We investigated the association of presurgical MRI measures of total WMH volume, global brain atrophy, and hippocampal volume with the incidence and severity of postoperative delirium. Our study extended the previous work by using state-of-the-art imaging and analysis methods, cognitive and delirium assessments, in a large well-characterized clinical cohort of older individuals without dementia.

2. Methods

2.1. Study design and cohort assembly

Our study population is a subsample of the Successful Aging after Elective Surgery (SAGES) study, a 5-year prospective observational study of postoperative delirium being conducted at Beth Israel Deaconess Medical Center, Brigham and Women's Hospital, and Hebrew SeniorLife in Boston, MA, USA. The study design and eligibility criteria have been reported in detail previously (Schmitt et al., 2012). Briefly, the elective surgeries included in the study were total hip or knee replacement, laminectomy, lower extremity arterial bypass, open abdominal aortic aneurysm repair, and colectomy. SAGES subjects were recruited through regular review of operating room schedules. Inclusion criteria included age $\geq$70 years old, English speaking, and undergoing elective surgery at Beth Israel Deaconess Medical Center or Brigham and Women's Hospital. Exclusion criteria included diagnosis of dementia as assessed by initial medical record screening or reported by the patient during telephone recruitment or enrollment interview; cognitive impairment as defined by a score $\leq$69 or its education-adjusted equivalent on the Modified Mini-Mental State Examination (3MS) during the baseline interview (Teng and Chui, 1987); terminal disease; total blindness; severe deafness; and alcohol intake $>$5 drinks per day (men) or $>$4 drinks per day (women). A subset of approximately one-third of the enrolled SAGES study participants was recruited to undergo MRI 1 month before surgery. Additional exclusion criteria for the nested cohort MRI study included contraindications to 3-T MRI, such as pacemakers and certain stents and implants. All study procedures were approved by the institutional review boards at the 2 surgical sites (Beth Israel Deaconess Medical Center and Brigham and Women's Hospital) and Hebrew SeniorLife, the coordinating center. All subjects gave written informed consent.

2.2. Baseline measures

All the study participants completed a baseline interview about 2 weeks before surgery. During the baseline interview, the 12-item Short-Form (Ware et al., 1996), 3MS, complete neuropsychological test battery (described subsequently), and the confusion assessment method (CAM) (Inouye et al., 1990) were administered. We also assessed presence of depression using the Geriatrics Depression Scale, which yields a score from 0 to 15 (15 being most depressed). We dichotomized this variable at 5 with an accepted threshold of $\geq$5 as possibly having depression. Demographic information such as age, gender, vascular comorbidities, ethnicity, years of education, and type of surgery planned (orthopedic, vascular, and gastrointestinal) were collected.

2.3. Outcome measures

The outcomes of interest were postoperative delirium incidence and severity during the hospital stay. To enhance sensitivity, we used multiple methods to detect delirium. We used both the CAM and chart review to detect delirium for each patient. If both or either of the 2 methods indicated that the patient had delirium,