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Brain regional lesion burden and impaired mobility in the elderly

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Abstract

This study investigated the relationship of brain white matter (WM) lesions affecting specific neural networks with decreased mobility in ninety-nine healthy community-dwelling subjects ≥75 years old prospectively enrolled by age and mobility status. We assessed lesion burden in the genu, body and splenium of corpus callosum; anterior, superior and posterior corona radiata; anterior and posterior limbs of internal capsule; corticospinal tract; and superior longitudinal fasciculus. Burden in the splenium of corpus callosum (SCC) demonstrated the highest correlation particularly with walking speed ($r = 0.4$, $p < 10^{-4}$), and in logistic regression it was the best regional predictor of low mobility performance. We also found that independent of mobility, corona radiata has the largest lesion burden with anterior (ACR) and posterior (PCR) aspects being the most frequently affected. The results suggest that compromised inter-hemispheric integration of visuospatial information through the SCC plays an important role in mobility impairment in the elderly. The relatively high lesion susceptibility of ACR and PCR in all subjects may obscure the importance of these lesions in mobility impairment.

Keywords: Aging; Mobility; Brain; White matter; White matter hyperintensity; Splenium of corpus callosum; Corona radiata; Magnetic resonance imaging

1. Introduction

Mobility impairment occurs in 14–50% of those between 65 and 85 years (Odenheimer et al., 1994) and has social and economic consequences as it is a cause of falls and dependence. While mobility impairment in the elderly is multifactorial, brain WM damage has been identified as one pathogenic mediator (Briley et al., 1997; Sachdev et al., 2005; Starr et al., 2003). Prevalence of WM hyperintensities (WMH) in healthy elderly ranges between 27 (Breteler et al., 1994) and 90% (de Leeuw et al., 2000) depending on the defining criteria. In addition to mobility impairment, WMH is also linked to cognitive decline (Charlton et al., 2006; Garde et al., 2000; Mungas et al., 2002; Prins et al., 2005; van den Heuvel et al., 2006) and urinary dysfunction (Sakakibara et al., 1999). Data suggests an ischemic origin of the WMH (Pantoni and Garcia, 1997) with large studies, e.g., Framingham study (DeCarli et al., 2005), Rotterdam study (de Leeuw et al., 2001), Austrian Stroke prevention study (Schmidt et al., 1999, 2005) supporting the link of WMH to vascular disease (Ikram et al., 2006; Prins et al., 2005). Risk factors associated with WMH include hypertension (Dufouil et al., 2001) as well as metabolic factors, e.g., diabetes, homocysteine, hyperlipidemia, and C-reactive protein (Longstreth et al., 1996). Balance during standing conditions and dynamic movement relies on timely processing of vestibular, visual, and tactile-proprioceptive inputs to produce a coordinated motor response that maintains or restores body alignment with the base of support. Failure to rapidly compensate destabilizing forces results in poor balance and falls. Although for the majority of cases there are identifiable pathologies causing mobility impairment, e.g., CNS degenerative disease, arthritis, and deconditioning, for

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a significant fraction no link to a specific disease can be identified. Several cross-sectional studies on elderly subjects have demonstrated a relationship between brain WMH and lower extremity motor function (Masdeu et al., 1989; Baloh et al., 1995; Briley et al., 1997; Longstreth et al., 1996; Camicioli et al., 1999; Guttmann et al., 2000; Baezner et al., 2008). This relationship has been observed also in longitudinal analyses that showed worsening mobility to be associated with increasing WMH (Whitman et al., 2001; Baloh et al., 2003; Wolfson et al., 2005). However, the role/s and progression of regional brain WMH in mobility decline in the elderly population remain to be defined. We hypothesize that WM damage compromises areas of the brain required for sensorimotor integration underlying motor control. Accordingly, we will attempt to define the role of regional lesion burden in mobility impairment, utilizing a prospective study involving ninety-nine healthy old individuals stratified by age and mobility. We report here the results of the cross-sectional analysis on baseline mobility status with regional distribution of WMH. We assessed WM damage in areas containing motor control pathways (corticospinal tracts, internal capsule), mediating inter- and intra-hemispheric integration of visual and other sensory inputs (corpus callosum, superior longitudinal fasciculus), and periventricular regions containing afferent as well as efferent corticospinal connections (corona radiata), and characterized the association of these regional burdens with mobility performance.

2. Methods

2.1. Subjects

Ninety-nine community-dwelling subjects 75–90 years old were recruited for a 4-year prospective study defining the relationship between mobility impairment, brain changes, and cardiovascular risk factors. Subjects were recruited through multiple methods. Newspaper articles in the Hartford Courant and New Britain Herald generated the largest response, and were supplemented by presentations at senior centers, retirement communities, civic organizations and health fairs. Advertisements were placed in community newsletters, apartment buildings, and recruitment packets were sent to all Hartford faith-based organizations. A research volunteer database was utilized and geriatricians at the University of Connecticut Health Center were asked to refer patients. Exclusion criteria included: systemic conditions (e.g., severe arthritis) and neurologic disease (e.g., neuropathy, Parkinson's disease) compromising mobility, medication impairing motor function, cognitive impairment (Mini-Mental State Exam, MMSE <24), corrected distance vision >20/70, unstable cardiovascular disease (e.g., myocardial infarction within 6 months, unstable angina), pulmonary disease requiring oxygen, inability to walk 10 m independently in <50 s, lower extremity amputation, weight >114 kg, claustrophobia, pacemaker or other metallic devices/implants, excessive alcohol intake and expected lifespan <4 years. Phone screening was completed on 312 people. All eligible persons were invited to an orientation session and were fully informed and provided consent before further screening of medical history, MMSE and mobility. Of the 164 still eligible, 117 returned for a physical exam performed by the senior investigator (LW) who also administered the remaining exclusion criteria. Seventeen subjects were excluded due to exam findings, arthritis and claustrophobia, and one due to a clinically silent cerebellar meningioma found on MRI. To ensure study compliance MRIs were reviewed by an on-site radiologist and by a neuroradiologist (PGH) at the neuroimaging core. Study population images were carefully reviewed for co-morbidities including cerebral infarction, and intracranial mass lesions. Subjects were enrolled by age and mobility to fill a 3×3 stratification matrix (Table 1). The Institutional Review Boards of participating institutions approved the protocol.

2.2. Mobility assessment

Mobility was measured by one of the authors (JAS), using the short physical performance battery (SPPB) (Guralnik et al., 1994), which rates performance by comparison to a standardized sample with one point for each quartile (best = 4). SPPB is the summed performance on three components: standing balance (SB) during tandem, semi-tandem and side-by-side stance; five chair rises (CR); and time to walk 2.5 m (WS). We defined three categories of normal (SPPB = 11–12), mildly impaired (SPPB = 9–10) and moderately impaired (SPPB <9) mobility, hereafter called normal (SPPB: 11.3 ± 0.4; median: 11), intermediate (SPPB: 9.7 ± 0.4; median: 10), and impaired (SPPB: 6.6 ± 1.5; median: 6.5).

2.3. MR imaging

High-resolution MR images of the head were acquired at the Institute of Living (Hartford, Connecticut) using three MR sequences on a 3-Tesla Siemens Allegra scanner (Erlangen, Germany): T1-weighted Magnetization Prepared Rapid Gradient Echo (MPRAGE) (176 contiguous 1-mm thick axial slices, TR/TE = 2500/2.74 ms, TI = 900 ms, matrix size = 256 × 208, in-plane pixel spacing = 1 mm × 1 mm); 3D-Fast Spin Echo (T2) (176 contiguous 1-mm thick sagittal slices, TR/TE = 2500/353 ms, matrix size = 256 × 220, in-plane pixel spacing = 1 mm × 1 mm), and Fluid Attenuated Inversion Recovery (FLAIR) (128 contiguous 1.3-mm thick sagittal slices, TR/TE = 6000/353 ms, TI = 2200 ms, matrix size = 256 × 208, in-plane pixel spacing = 1 mm × 1 mm). Pre-processing included correction of magnetic field-related signal inhomogeneities (Sled et al., 1998) and linear affine registration of FLAIR and T2 series to the MPRAGE series (Jenkinson and Smith, 2001).