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Mobility impairment is associated with reduced microstructural integrity of the inferior and superior cerebellar peduncles in elderly with no clinical signs of cerebellar dysfunction

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ABSTRACT

While the cerebellum plays a critical role in motor coordination and control no studies have investigated its involvement in idiopathic mobility impairment in community-dwelling elderly. In this study we tested the hypothesis that structural changes in the cerebellar peduncles not detected by conventional magnetic resonance imaging are associated with reduced mobility performance. The analysis involved eighty-five subjects (age range: 75–90 years) who had no clinical signs of cerebellar dysfunction. Based on the short physical performance battery (SPPB) score, we defined mobility status of the subjects in the study as normal (score 11–12, n = 26), intermediate (score 9–10, n = 27) or impaired (score <9, n = 32). We acquired diffusion tensor imaging data to obtain indices of white matter integrity: fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD) and radial diffusivity (RD). Using a parcellation atlas, regional indices within the superior, middle, and inferior cerebellar peduncles (ICP, MCP, SCP) were calculated and their associations with mobility performance were analyzed. Subjects with impaired mobility showed reduced FA and AD values in the ICP and SCP but not in the MCP. The ICP-FA, ICP-AD and SCP-FA indices showed a significant association with the SPPB score. We also observed significant correlation between ICP-FA and walk time ($r = -0.311$, $p = 0.004$), as well as between SCP-AD and self-paced maximum walking velocity ($r = 0.385$, $p = 0.003$) and usual walking velocity ($r = 0.400$, $p = 0.002$). In logistic regression analysis ICP-FA and ICP-AD together explained 51% of the variability in the mobility status of a sample comprising the normal and impaired subgroups, and correctly classified more than three-quarters of those subjects. Our findings suggest that presence of microstructural damage, likely axonal, in afferent and efferent connections of the cerebellum contributes to the deterioration of motor performance in older people.

1. Introduction

Mobility impairment is a common disabling clinical problem which occurs with aging and increases the risk of falls, injuries and even death (Tinetti et al., 1988). Although there are known neurologic (e.g., Parkinson's disease, stroke, peripheral neuropathy), non-neurologic (e.g., musculoskeletal, joint diseases) and pharmacological (Leipzig et al., 1999) causes of impaired mobility, in a significant fraction of older individuals the underlying etiology remains unclear (idiopathic). In these subjects an association between gait impairment and the extent of brain white matter (WM) damage, visible as T2-weighted white matter hyperintensities (WMH) upon upon on magnetic resonance imaging (MRI), has been reported (Baezner et al., 2008; Baloh and Vinters, 1995; Briley et al., 1997; Camicioli et al., 1999; Guttmann et al., 2000; Masdeu et al., 1989; Sachdev et al., 2005; Starr et al., 2003; Wakefield et al., 2010). Such abnormalities are a common finding in the elderly population and

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are thought to represent cerebro-microvascular damage (Pantoni, 2010) including abnormal permeability of the blood brain barrier (Wardlaw et al., 2003).

While lesions in the brain stem have been reported and analyzed in association with mobility (Starr et al., 2003) imaging studies have thus far focused on the supratentorial white matter where WMHs mostly occur. In addition, subjects enrolled in these studies showed no clinical or MRI signs of cerebellar and brainstem pathology.

The cerebellar peduncles are the communication portals to and from the cerebellum and therefore critical components of the neural network underpinning balance and coordination in voluntary motor activity.

Diffusion tensor imaging (DTI), an established advanced in vivo imaging technique that enables the characterization of anisotropic water diffusion in white matter fibers (Pierpaoli et al., 1996), has shown sensitivity to white matter changes in areas not affected by focal WMH on T2-weighted images (Werring et al., 1999) and is therefore well-suited to probe the microstructural integrity of these previously unexplored but potentially informative regions. The DTI parameters reflecting WM structural integrity are the following: fractional anisotropy (FA), a sensitive but not specific index of overall white matter tracts' integrity; mean diffusivity (MD), a general indicator of tissue water accumulation; axial diffusivity (AD), representing diffusivity parallel to the fiber tracts and an index regarded as a more specific marker for axonal injury; and radial diffusivity (RD), a parameter representing diffusivity perpendicular to the fiber tracts and considered more specific for damage to the myelin sheath. To date, a clear interpretation of the relationship between these indices and the underlying microstructural tissue properties is still lacking and therefore it requires caution. However, there is wide evidence in DTI literature (Alexander et al., 2007) that WM damage, which leads to increase in water molecule diffusion, generally is reflected in local decrease of FA and increase of MD (O'Donnell and Westin, 2011). The AD and RD indices can further help to distinguish between axonal degeneration (decrease of AD) or myelin loss (increase in RD) as primary mechanism of damage to the WM tracts (Budde et al., 2007; Song et al., 2002).

Cerebellum plays a major role in voluntary motor control and its three peduncles are a relevant and anatomically well-defined target for assessing with DTI the integrity of critical parts of the neural networks, i.e. afferent and efferent connections, involving the cerebellum. The cerebellar peduncles have been investigated using DTI in various clinical conditions affecting motor functions such as ataxia (Alcauter et al., 2011; Della Nave et al., 2011), Parkinsonian syndromes (Nicoletti et al., 2006, 2008) and multiple sclerosis (Anderson et al., 2011). However, to our knowledge there are no similar studies on the idiopathic mobility impairment in community-dwelling older subjects.

In this report we describe the findings of a cross-sectional study we undertook with the goal of assessing the relationship between poor performance in mobility tests and reduced microstructural integrity of the cerebellar peduncles.

2. Methods

2.1. Subjects and study design

The subjects included in this analysis represent a subset from a cohort of ninety-nine elderly subjects enrolled in a 4-year prospective study on the relationship between brain changes, cardiovascular risk factors and mobility on which we have reported previously (Moscufo et al., 2011; Wakefield et al., 2010; White et al., 2011). Data for the present cross-sectional analysis included eighty-five subjects who had DTI data of sufficient quality acquired at baseline. Recruitment methods and eligibility criteria have been described in Wakefield et al. (2010). Subjects were included if they were 75 to 90 years old and were enrolled according to a balanced 3×3 matrix based on age (75–79, 80–84, ≥85) and mobility (short physical performance battery (Guralnik et al., 1994), SPPB scores: 11–12 = normal; 9–10 = intermediate; <9 = impaired). Briefly, the following exclusion criteria were applied: systemic conditions (e.g., severe arthritis) or neurologic disease (e.g., neuropathy, Parkinson's disease) compromising mobility, medication impairing motor function, cognitive impairment (Mini-Mental State Examination, 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, and evidence of cerebral infarction or intracranial mass lesions on MRI. All the subjects were evaluated with a battery of mobility performance tests and MRI of the brain. The following variables, as indicators of cerebrovascular risk, were included in our analyses: history of hypertension and/or diabetes mellitus, average 24-h systolic (SBP) and diastolic blood pressure (DBP), and serum lipoproteins (total, HDL, LDL cholesterol). The 24-h ambulatory blood pressure monitoring was conducted with the Oscar II BP device (Suntech Medical Instruments, Morrisville, NC) and obtained every 15 min from 6 AM to 10 PM and every 30 min from 10 PM to 6 AM (Campbell et al., 2010); the data were analyzed as previously described (White et al., 2011). Neurologic examination was performed on each subject by the senior investigator (LW) in order to determine the presence of diseases compromising mobility (study exclusion criteria). The exam included evaluation of sensory function (touch, pin position sense and vibration) and motor function (strength, tone, coordinated/rapid alternating hand movements, finger to nose, heel-knee-shin tests and observation of gait/balance). Although minor findings were occasionally encountered, there was no consistent clinical evidence of cerebellar dysfunction. The review board of the involved institutions approved the study protocol, which included a written informed consent.

2.2. Mobility assessment

Mobility assessment was carried out at the Balance and Gait Evaluation Laboratory, University of Connecticut Health Center, by trained expert investigators (Panzer et al., 2011). SPPB, Tinetti and mobility lab testing were done on different days for most subjects. Instruction and demonstration were provided prior to testing and subjects practiced and rested as needed then performed the requested tasks. The assessment included the SPPB (Guralnik et al., 1994), usual walking velocity (velocity, meters/second) and self-paced maximum walking velocity (SPMV, meters/second) (Panzer et al., 2011), as well as Tinetti gait and balance (Tinetti, 1986). The SPPB is a composite score representing the quartile distribution (worse = 1, best = 4) of the mobility performance on the following three timed sub-scores: time to walk a course of 2.5 m (walk time, seconds); five chair rises from an erect sitting position on an unpadded armless chair set at 41 cm (average height in the community) with arms crossed below the sternum to a stand up position with knees and hips fully extended; standing balance consisted in side-by-side, semi-tandem, and tandem stands for ten seconds each. On the basis of the total SPPB score, subjects were assigned to the following three categories defining mobility status: normal (SPPB score = 11–12, n = 26), intermediate (SPPB score = 9–10, n = 27) or impaired (SPPB score < 9, n = 32). To obtain the gait velocity, subjects were asked to walk at preferred ('usual'—performed twice) or as-fast-as possible ('max'—once) pace. The test was performed from a static start on a force-measuring platform (AMTI, Waltham, MA; sample rate 200 Hz) on an enclosed walkway (out and back, 8.1 m total, with turn). Average velocity was calculated for each performance and the faster of the two preferred pace performances (usual velocity) and the single self-paced max pace (SPMV) values were used for the analyses (Panzer et al., 2011) (for methodology review see Graham et al. (2008)). Tinetti gait and balance scores are from the Performance-Oriented Mobility Assessment (Tinetti, 1986). Tinetti gait testing included initiation of gait, step height, step length, step symmetry, step continuity, path deviation, trunk stability, walk stance, and turning