Neurobiology of Aging 70 (2018) 247–253

Contents lists available at ScienceDirect

Neurobiology of Aging

journal homepage: www.elsevier.com/locate/neuaging

The association between brain volume, cortical brain infarcts, and physical frailty

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ARTICLE INFO

Article history:
Received 14 February 2018
Received in revised form 29 May 2018
Accepted 25 June 2018
Available online 30 June 2018

Keywords:
Physical frailty
Aging
Neurodegenerative brain changes
Neurovascular brain changes
Magnetic resonance imaging

ABSTRACT

Physical frailty is an age-associated syndrome of decreased reserve leading to vulnerability to physiological stressors and associated with negative outcomes. The underlying structural brain abnormalities of physical frailty are unclear. We investigated the association between brain volume, cortical brain infarcts, and physical frailty. In this multicenter study, 214 nondemented participants were classified as frail (n = 32), prefrail (n = 107), or nonfrail (n = 75) based on the Fried frailty phenotype. The associations between frailty and brain volumes and cortical brain infarcts were investigated by linear or logistic regression analyses. Participants in the frail group showed a lower total brain volume (−19.67 mL [95% confidence interval −37.84 to −1.50]) and lower gray matter volume (−12.19 mL [95% confidence interval −23.84 to −0.54]) compared to nonfrail participants. Frailty was associated with cortical brain infarcts [frail 16% [n = 5], prefrail 11% [n = 12], and nonfrail 3% [n = 2]). Reduced total brain volume and gray matter volume and increased cortical brain infarcts seem therefore to be part of the structural substrate of the physical frailty phenotype.

1. Introduction

Frailty is defined as an age-associated biological syndrome of decreased reserve that leads to a vulnerability to physiological stressors (Clegg et al., 2013; Fried et al., 2001). Frail individuals have an increased risk of adverse events, such as hospitalization, falls, institutionalization, and complications after surgery including postoperative delirium (Brown et al., 2016; Fried et al., 2001). Frailty is most often described using the physical frailty phenotype (Buta et al., 2016; Fried et al., 2001). This phenotype is assessed with 5 frailty components: slowness, weakness, exhaustion, weight loss, and a low level of activity (Fried et al., 2001). A combination of 3 or more of these components classifies an individual as frail.

Previous studies showed that physical frailty is associated with an increased risk of cognitive decline and dementia (Avila-funes et al., 2012; Buchman et al., 2014; Solfrizzi et al., 2013). These findings may suggest that neurodegenerative or neurovascular changes are the structural substrate of the physical frailty phenotype. However, only few small studies have assessed the underlying structural brain magnetic resonance imaging (MRI) correlates of physical frailty. These studies have shown that signs of neurodegenerative or neurovascular changes, that is, lower global or regional brain volume, a higher number of cerebral microbleeds, and a higher burden of white matter hyperintensities of presumed vascular origin (WMH), were related to frailty in older individuals (Avila-funes et al., 2012, 2017; Chen et al., 2015; Chung et al., 2016; Del Brutto et al., 2016; Jung et al., 2014; Newman et al., 2001; Siejka et al., 2017). These studies were however limited to community-

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0197-4580/
https://doi.org/10.1016/j.neurobiolaging.2018.06.032

dwelling individuals and included only a low number of frail individuals. Knowledge on the biological basis and development of physical frailty could lead to strategies to prevent dependence and eventually reduce the burden on an economic, societal, and individual level. To date, it is unknown if brain alterations are already present in prefrail individuals. Furthermore, the association between cortical brain infarcts and physical frailty has never been investigated.

The aim of the present study was to investigate differences in brain volumes, WMH, and cortical brain infarcts in physical frail, prefrail, and nonfrail older nondemented individuals who were scheduled for elective surgery. In addition, we studied the relation between these brain markers and individual frailty components.

2. Methods

2.1. Study design and participants

This investigation is part of the BioCog consortium study: an ongoing multicenter prospective cohort study performed in the Charité Universitätsmedizin Berlin and the University Medical Center Utrecht. The general aim of the BioCog study is to identify determinants of perioperative neurocognitive disorders (Winterer et al., 2018). For the BioCog study, participants were included who were (1) scheduled for major elective surgery of a minimum of 60 minutes, (2) at least 65 years of age, (3) able to undergo cognitive tests (no blindness, deafness, neurological or psychiatric diseases) and MRI scanning, and (4) had a Mini–Mental State Examination (MMSE) score of 24 or higher. The present study uses data from the first n = 400 participants of the BioCog consortium study. All participants signed an informed consent form, and all procedures were approved by the medical ethics committee of both centers under ethical approval number EA2/092/14 (Berlin) and 14-469 (Utrecht).

2.2. Procedure

All participants were invited before surgery for a visit that included questionnaires, a frailty assessment, and an MRI scan. Trained researchers collected data on age, gender, body mass index (BMI), diabetes, smoking, and history of cardiovascular events. All participants were assessed with the MMSE (Folstein et al., 1975) to determine preoperative cognitive status. An MMSE score of 24 or higher was considered as absence of severe dementia. The American Society of Anesthesiologists classification was assessed in a preoperative interview by an anesthesiologist (in training) (Dripps et al., 1961).

2.3. Frailty assessment

Frailty was assessed by trained researchers based on a modified version of the Fried frailty phenotype by Rockwood et al. and consisted of 5 frailty components: slowness, weakness, exhaustion, weight loss, and a low level of activity (Fried et al., 2001; Rockwood et al., 2007); see Supplementary Table A for a detailed description of these components. Participants who had a combination of 3 or more components were considered frail, participants who had a combination of 1 or 2 components were considered prefrail, and participants who had none of these components were considered nonfrail.

2.4. MRI scans

Participants were scanned on a Siemens Magnetom TrioTim MRI scanner (Berlin) or a Philips Achieva 3T MRI scanner (Utrecht). The MRI scanning protocol was standardized and consisted of a 3-dimensional (3D) T1-weighted sequence (voxel size $=1.0 \times 1.0 \times 1.0$ mm^3; Berlin: 3D T1 magnetization-prepared rapid acquisition gradient echo sequence, repetition time [TR]/echo time [TE] = 2500/4.77 ms; Utrecht: TR/TE = 7.9/4.5 ms) and a fluid-attenuated inversion recovery (FLAIR) sequence (Berlin: TR/TE/inversion time = 4800/388/1800 ms; voxel size = $0.49 \times 0.49 \times 1.00$ mm^3; Utrecht: TR/TE/inversion time = 4800/125/1650 ms; voxel size = $1.11 \times 1.11 \times 0.56$ mm^3).

2.5. MRI processing steps and analysis

A robust approach to brain segmentation of multicenter data was used (Heinen et al., 2016; Mendrik et al., 2015). 3D FLAIR images were registered to the 3D T1-weighted images by using statistical parametric mapping software (SPM12, Wellcome Institute of Neurology, University College London, UK, http://www.fil.ion.ucl.ac.uk/spm/doc/), running on Matlab R2013a (Mathworks, Natick, MA, USA). WMH segmentations were performed on the FLAIR scans by the lesion prediction algorithm (Schmidt, 2017) as implemented in the Lesion Segmentation Toolbox version 2.0.15 (www.statistical-modeling.de/lst.html) for SPM12. All resulting WMH segmentations were visually checked for segmentation errors by trained researchers (I.M.J.K., and E.A.) and in doubt by a radiologist (J.B.) with 10 years of experience in brain segmentation. WMH segmentations were thresholded on a 0.5 probability, and WMH volumes were calculated using the Lesion Segmentation Toolbox. Lesion filling was performed on the 3D T1-weighted images by using the WMH segmentations. The resulting "lesion filled" 3D T1-weighted images were subsequently segmented in the CAT12 toolbox for SPM12 (Gaser and Dahnke, Jena University Hospital, Departments of Psychiatry and Neurology, http://www.neuro.uni-jena.de/cat/index.html#About). This resulted in segmentations of gray matter, white matter, and cerebrospinal fluid. Intracranial volume (ICV), total brain volume, gray matter volume, white matter volume, and cerebrospinal fluid volume were calculated by the SPM12 option "tissue volumes." All scans were checked by a neuroradiologist (J.B.) for presence of cortical brain infarcts and major artifacts that might hinder accurate segmentations. Subsequently, all brain tissue segmentations were visually checked for segmentation errors (e.g., registration errors, wrong classification of tissue) by a trained researcher (I.M.J.K.). All cases that contained errors were discussed in a consensus meeting with an expert neuroradiologist (J.B.). All final decisions on exclusion of MRI data were made in this consensus meeting. All scans that contained cortical brain infarcts over 1.5 cm were excluded from the WMH and brain volume analysis because of segmentation errors. We have used the threshold of 1.5 cm based on the standards for reporting vascular changes on neuroimaging (STRIVE) criteria for large subcortical infarcts (Wardlaw et al., 2013). Brain surfaces were estimated by a fully automated method that estimates cortical thickness and the reconstruction of the central surface in 1 step (Gaser and Dahnke, 2012). To allow intersubject analysis, a spherical map was plotted and images were smoothed by a 15-mm Gaussian kernel.

2.6. Statistical analysis

Demographic variables were compared between the 3 groups (frail, prefrail, and nonfrail) by a one-way ANOVA or chi-square test depending on the type of variable. For analysis of brain volumes, participants with cortical brain infarcts over 1.5 cm were excluded. To study differences in brain volumes (total brain volume, gray matter volume, white matter volume, and WMH volume) between frail, prefrail, and nonfrail participants, linear regression analyses were performed adjusted for age, gender, ICV, and study center. Analyses of WMH volume were additionally corrected for vascular risk factors (hypertension, hypercholesterolemia, smoking, BMI,