NeuroImage: Clinical 12 (2016) 460–465

Contents lists available at ScienceDirect

NeuroImage: Clinical

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

Cerebral blood flow in presymptomatic *MAPT* and *GRN* mutation carriers: A longitudinal arterial spin labeling study☆

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ARTICLE INFO

Article history:
Received 19 January 2016
Received in revised form 25 June 2016
Accepted 1 August 2016
Available online 03 August 2016

Keywords:
Frontotemporal dementia
Arterial spin labeling
Cerebral blood flow
Presymptomatic

ABSTRACT

Objective: Frontotemporal dementia (FTD) is characterized by behavioral disturbances and language problems. Familial forms can be caused by genetic defects in *microtubule-associated protein tau* (*MAPT*), *progranulin* (*GRN*), and *C9orf72*. In light of upcoming clinical trials with potential disease-modifying agents, the development of sensitive biomarkers to evaluate such agents in the earliest stage of FTD is crucial. In the current longitudinal study we used arterial spin labeling MRI (ASL) in presymptomatic carriers of *MAPT* and *GRN* mutations to investigate early changes in cerebral blood flow (CBF).

Methods: Healthy first-degree relatives of patients with a *MAPT* or *GRN* mutation underwent ASL at baseline and follow-up after two years. We investigated cross-sectional and longitudinal differences in CBF between mutation carriers ($n = 34$) and controls without a mutation ($n = 31$).

Results: GRN mutation carriers showed significant frontoparietal hypoperfusion compared with controls at follow-up, whereas we found no cross-sectional group differences in the total study group or the *MAPT* subgroup. Longitudinal analyses revealed a significantly stronger decrease in CBF in frontal, temporal, parietal, and subcortical areas in the total group of mutation carriers and the *GRN* subgroup, with the strongest decrease in two mutation carriers who converted to clinical FTD during follow-up.

Interpretation: We demonstrated longitudinal alterations in CBF in presymptomatic FTD independent of grey matter atrophy, with the strongest decrease in individuals that developed symptoms during follow-up. Therefore, ASL could have the potential to serve as a sensitive biomarker of disease progression in the presymptomatic stage of FTD in future clinical trials.

Abbreviations: FTD, frontotemporal dementia; *MAPT*, *microtubule-associated protein tau*; *GRN*, *progranulin*; ASL, arterial spin labeling; CBF, cerebral blood flow; FDG-PET, positron emission tomography with 18F-fluorodeoxyglucose; MMSE, Mini-Mental State Examination; BDI-II, Beck Depression inventory II (BDI-II); RAVLT, Rey Auditory Verbal Learning Test; VAT, Visual Association Test; TMT, Trailmaking Test; WCST, Wisconsin Card Sorting Test; LDST, Letter Digit Substitution Test; BNT, Boston Naming Test; SAT, Semantic Association Test; AD, Alzheimer's disease.

☆ Funding: This work was supported by Dioraphte Foundation [grant number 09-02-03-00], the Association for Frontemporal Dementias Research Grant 2009, The Netherlands Organization for Scientific Research (NWO) [grant number HCMI 056-13-018] and Netherlands Alzheimer Foundation. S.A. Rombouts is sponsored by a grant from The Netherlands Organization for Scientific Research (NWO) [grant number 016130677]. A. Hafkemeijer is sponsored by a grant from The Netherlands Organization for Scientific research (NWO) [grant number 05613010].

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http://dx.doi.org/10.1016/j.nicl.2016.08.001

1. Introduction

Frontotemporal dementia (FTD) is the second most common form of presenile dementia, characterized by behavioral disturbances and language disorders, which is caused by neurodegeneration of the frontal and temporal lobes (Rascovsky et al., 2011; Seelaar et al., 2011a). Mutations in *microtubule-associated protein tau* (*MAPT*), *progranulin* (*GRN*) and *C9orf72*, and, less frequently, *CHMP2B* and *VCP* can cause an autosomal dominant form of FTD (Renton et al., 2011; DeJesus-Hernandez et al., 2011; Baker et al., 2006; Hutton et al., 1998; Skibinski et al., 2005; Watts et al., 2004). There is currently no therapy available to prevent or cure the disease, but knowledge on the pathophysiological disease process is rapidly growing. As a result, clinical trials with disease-modifying agents are upcoming, urging the need for sensitive biomarkers to evaluate such therapies (Tsai and Boxer, 2014). We have previously shown changes in neuropsychological performance, white matter integrity and functional connectivity in the presymptomatic stage of FTD (Dopper et al., 2014).

Positron emission tomography with 18F-fluorodeoxyglucose (FDG-PET) is often suggested as a useful biomarker for the earliest stage of FTD. Hypometabolism in the frontal and anterior temporal lobes, and subcortical regions, is consistently seen in FTD patients (Ishii et al., 1998; Jeong et al., 2005; Diehl et al., 2004; Grimmer et al., 2004), as well as progression over time (Grimmer et al., 2004). Moreover, presymptomatic *GRN* mutation carriers already showed regional hypometabolism on FDG-PET, supporting its potential to detect functional brain changes in a very early stage (Jacova et al., 2013). However, FDG-PET has several serious disadvantages to be used as a biomarker for FTD, including the high costs, invasiveness, limited availability of PET-scanners and the need for exposure to a radioactive tracer (Wolk and Detre, 2012).

Arterial spin labeling MRI (ASL) provides a non-invasive measure of brain perfusion by magnetically labeling water protons in arterial blood, thereby creating an endogenous tracer of cerebral blood flow (CBF), which is assumed to be tightly coupled to brain metabolism (Wolk and Detre, 2012). ASL studies in patients with FTD have provided highly similar results as FDG-PET studies with hypoperfusion in bilateral frontal lobes, the anterior cingulate cortex, insula, and thalamus compared with controls (Binnewijzend et al., 2014; Du et al., 2006; Hu et al., 2010; Shimizu et al., 2010; Zhang et al., 2011; Steketee et al., 2015). Besides one small study in presymptomatic *CHMP2B* mutation carriers showing widespread hypoperfusion in hippocampus, temporal, parietal, and occipital lobes compared with controls by means of spin echo contrast agent perfusion MRI (Lunau et al., 2012), CBF has not been investigated in the presymptomatic stage of FTD thus far.

In the current study we used longitudinal ASL to study early changes in CBF in presymptomatic carriers of *MAPT* and *GRN* mutations to investigate whether ASL has the potential to serve as a sensitive biomarker to detect FTD and track disease progression in the earliest disease stage.

2. Materials and methods

2.1. Participants

This study is part of a larger project investigating biomarkers in individuals at risk for FTD (Dopper et al., 2014). Healthy first-degree relatives (aged 20–70 years) of patients with FTD due to a *GRN* or *MAPT* mutation were included in this study. Subjects were excluded in case of MRI contraindication ($n = 6$), history of drug abuse ($n = 2$), or other neurologic ($n = 1$) or psychiatric ($n = 1$) disorders. The drug abuse or psychiatric disorders were not related to FTD, since it was either associated with non-carriership or there was no progression of symptoms over time. No subjects from families with the *C9orf72* repeat expansion were included, since this gene defect was not yet identified at the start of this study (2010). DNA of all subjects was screened (Seelaar et al., 2008), resulting in a group of presymptomatic individuals with a *MAPT* or *GRN* mutation and a group of controls without a mutation. All participants were studied at baseline and two-years follow-up. In total, 73 participants underwent baseline and follow-up ASL-MRI scans, however, eight subjects had to be excluded from the analyses because of labeling errors or major artefacts at baseline ($n = 3$) or follow-up ($n = 5$), leaving in total 65 participants. We investigated cross-sectional differences in CBF between mutation carriers and controls at baseline and follow-up. Moreover, we investigated between-group differences in longitudinal CBF changes. All analyses were ran for the entire group of mutation carriers versus controls, and separately for subjects from *MAPT* ($n = 18$) and *GRN* ($n = 47$) families. Subsequently, we evaluated single-subject data. Conversion to symptomatic FTD was diagnosed according to established clinical criteria (Rascovsky et al., 2011; Gorno-Tempini et al., 2011). The local ethics committee approved the study and all participants provided written informed consent.

2.2. Neuropsychological assessment

All participants were screened using the Mini-Mental State Examination (MMSE) (Folstein et al., 1975) the Beck Depression inventory II (BDI-II) (Beck et al., 1996) and an extensive neuropsychological assessment including the Dutch version of the Rey Auditory Verbal Learning Test (RAVLT) (Rey, 1958), Visual Association Test (VAT) (Lindeboom et al., 2002), WAIS III subtests digit span, similarities, and block design (Wechsler, 1997; Wechsler, 2005), Trailmaking Test (TMT) (Battery, 1994), Stroop color-word test (Stroop, 1935), categorical and letter fluency (Thurstone and Thurstone, 1962), modified Wisconsin Card Sorting Test (WCST) (Nelson, 1976), Letter Digit Substitution Test (LDST) (Jolles et al., 1995), Boston Naming Test (BNT) (Kaplan et al., 1978), Semantic Association Test (SAT) (Visch-Brink et al., 2005), ScreeLing phonology (Doesborgh et al., 2003), clock drawing (Royall) (Royall et al., 1998), Ekman faces (Ekman and Friesen, 1976), and Happé Cartoons (Happe et al., 1999).

2.3. Image acquisition

MRI scans were acquired using a Philips 3.0 Tesla Achieve MRI scanner (Philips Medical Systems, Best, The Netherlands) using an eight-channel SENSE head coil. We obtained pseudo-continuous ASL scans using single-shot echo-planar imaging (EPI) with a background suppression scheme, consisting of a saturation pulse directly before labeling and inversion pulses at 1680 and 2830 ms after the saturation pulse. The following acquisition parameters were applied: repetition time = 4020 ms, echo time = 14 ms, label duration = 1650 ms, postlabeling delay = 1525 ms, 17 slices, voxel size = $3 \times 3 \times 7$ mm, 40 pairs of label and control images, total scan duration = 5.5 min. The labeling plane was oriented perpendicular to the carotid arteries. Furthermore, we acquired whole brain T1-weighted images for registration purposes as described previously (Dopper et al., 2014).

2.4. Image analyses

We used in-house developed MATLAB (Matrix laboratory http://www.mathworks.nl/products/matlab/) scripts to convert the raw scanner data to NIfTI files. The remaining analyses were carried out in FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk) (Smith et al., 2004). First the raw ASL images were motion corrected and brain-extracted. Then the perfusion weighted maps, i.e. CBF images, were calculated by pairwise subtraction of control from label images and averaging these images across time. These CBF maps were then registered to the anatomical scans and to MNI-152 (T1 standard brain averaged over 152 subjects; Montreal Neurological Institute, Montreal, QC, Canada) standard space, and smoothed with an isotropic Gaussian kernel of 3.4 mm. The derived CBF images were divided by the mean perfusion in the occipital pole, a region typically spared in FTD (Ishii et al., 1998;