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Featured Article

Free water determines diffusion alterations and clinical status in cerebral small vessel disease

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Abstract

Introduction: Diffusion tensor imaging detects early tissue alterations in Alzheimer's disease and cerebral small vessel disease (SVD). However, the origin of diffusion alterations in SVD is largely unknown.

Methods: To gain further insight, we applied free water (FW) imaging to patients with genetically defined SVD (Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy [CADASIL], n = 57), sporadic SVD (n = 444), and healthy controls (n = 28). We modeled freely diffusing water in the extracellular space (FW) and measures reflecting fiber structure (tissue compartment). We tested associations between these measures and clinical status (processing speed and disability).

Results: Diffusion alterations in SVD were mostly driven by increased FW and less by tissue compartment alterations. Among imaging markers, FW showed the strongest association with clinical status (R^2 up to 34%, $P < .0001$). Findings were consistent across patients with CADASIL and sporadic SVD.

Discussion: Diffusion alterations and clinical status in SVD are largely determined by extracellular fluid increase rather than alterations of white matter fiber organization.

Keywords: Small vessel disease; Vascular cognitive impairment; Structural imaging; Diffusion tensor imaging; Free water; Processing speed; Disability; White matter hyperintensities; Lacunes; Brain atrophy

1. Introduction

Cerebral small vessel disease (SVD) is the major cause of vascular cognitive impairment and an important contributor to cognitive decline in patients with Alzheimer's disease [1,2]. SVD typically manifests with widespread brain

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changes detectable by magnetic resonance imaging (MRI) [3]. Diffusion tensor imaging (DTI) has emerged as a key method for studying SVD [4]. By quantifying diffusion properties of water in tissue, DTI is highly sensitive in detecting early and subtle tissue alterations. The typical pattern in SVD is an increase in the extent of water diffusion (increased mean diffusivity [MD]) and reduced directionality (decreased fractional anisotropy [FA]). Moreover, DTI alterations are strongly associated with clinical deficits, both in cross-sectional [5,6] and longitudinal studies [7]. In fact, DTI-based markers typically outperform other MRI measures with respect to clinicoradiological correlations [8].

Despite the wide use of DTI, little is known about the structural underpinnings of diffusion alterations in SVD, in part because DTI measures are not specific to a single pathology [9,10]. The prevailing interpretation is that the increased MD and reduced FA result from microstructural tissue damage, such as axonal degeneration and subsequent loss of white matter fiber organization [11]. However, recent data from experimental models and neuroimaging studies offer alternative explanations for altered water diffusion in SVD, such as edema caused by blood brain barrier damage [12,13] or vacuolization within myelin sheets [14]. The ability of the conventional DTI model to distinguish between these options is limited [15].

Recent advances in diffusion MRI modeling enable more detailed insight into DTI alterations. Of specific interest for SVD is the free water (FW) diffusion MRI model [16]. This technique enhances DTI by explicitly modeling a FW compartment, in addition to a tissue compartment (Fig. 1).

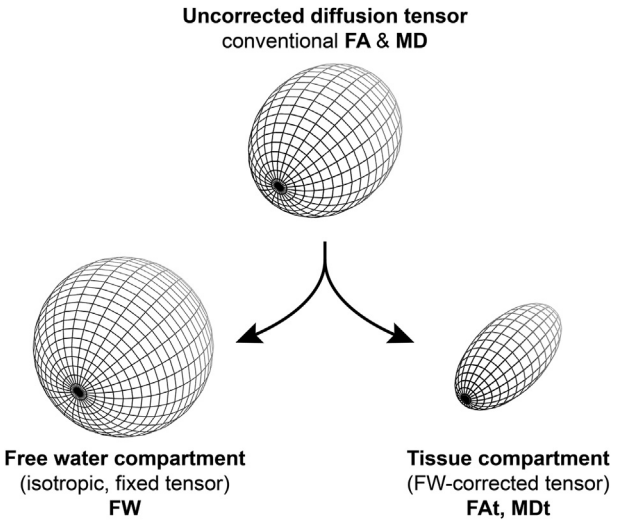

Fig. 1. Free water imaging principle. Free water (FW) is modeled by an isotropic tensor with fixed diffusion coefficient of freely diffusing water at 37°C. The fractional volume of FW is used for quantification. After removal of the FW contribution, the tissue compartment is modeled on the remaining signal by a second tensor. The tissue compartment measures (FAt and MDt) are calculated from this second tensor. Abbreviations: FAt, tissue compartment FA; FA, fractional anisotropy; MDt, tissue compartment MD; MD, mean diffusivity.

The FW compartment represents water molecules that are not restricted or directed. It is modeled by a tensor that is isotropic and has a fixed diffusion coefficient of water at 37°C. The tissue compartment represents all remaining water molecules, that is, water molecules within or in close proximity to cellular structures. This includes intracellular water as well as extracellular water affected by physical barriers, such as axon membranes and myelin. Hence, the tissue compartment reflects white matte fiber organization. Although FW imaging was initially developed to correct the diffusion signal for cerebrospinal fluid contamination [17], the approach has recently been applied to study brain tumors [16], psychiatric disorders [18,19], and neurodegenerative diseases [18,20,21]. These studies indicate that FW imaging increases the sensitivity of DTI to identify clinically relevant microstructural alterations [19,22]. Interestingly, in patients with Alzheimer's disease, alterations in the tissue compartment were found already at early disease stages and were associated with conversion to dementia [22].

In this study, we used FW imaging to obtain deeper insight into the underpinnings of diffusion alterations in SVD. We first explored the contribution of FW and the tissue compartment measures to diffusion alterations in SVD. We then analyzed the association between clinical status and both FW and tissue compartment measures. To minimize confounding from age-related pathologies, we evaluated young patients with the genetically defined SVD Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL), which is caused by mutations in *NOTCH3*. We further studied a large sample of patients with sporadic SVD to validate our findings obtained in CADASIL and to address their generalizability toward sporadic SVD.

2. Subjects and methods

2.1. Subjects

CADASIL patients (n = 57) and healthy control subjects (n = 28) were recruited through an ongoing, prospective, single-center study in Munich [8]. CADASIL was confirmed by molecular genetic testing (identification of a cysteine-altering mutation in the *NOTCH3* gene by Sanger sequencing) or ultrastructural analysis of a skin biopsy (detection of pathognomonic granular osmiophilic material on the surface of vascular smooth muscle cells). Control subjects met the following criteria: (1) No history for neurological or psychiatric disease, (2) no cognitive complaints and no cognitive deficits on neuropsychological testing, and (3) absence of confluent white matter hyperintensities (WMH) on MRI (Fazekas scale score $\leq$ 1).

Patients with sporadic SVD (n = 444) were included from the Radboud University Nijmegen Diffusion tensor and Magnetic resonance imaging Cohort (RUN DMC) study.