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ADC mapping of the aging frontal lobes in mild cognitive impairment

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Abstract Normal aging, leukoaraiosis (LA) and vascular disease particularly involve the human frontal lobes. We decided to investigate a population of elderly patients referred for neuroimaging because of progressive minor cognitive deficits but no dementia. They underwent conventional Magnetic resonance imaging (MRI) using axial T1 and T2-weighted imaging as well as coronal FLAIR sequences in addition to the axial diffusion-weighted MRI. MRI allowed us to differentiate patients with leukoaraïosis (LA+) from those without it (LA-) and mapping of the apparent diffusion coefficient (ADC) to investigate local tissular water motion. We observed an increase in the ADC in all investigated patients with increasing age ($r = 0.326$, $p = 0.002$). This increase was observed in both patients groups (LA+ and LA-) . In addition, the LA+ group had significant higher ADC values than the LA- group after controlling for age ($p < 0.0001$).

Keywords Diffusion imaging · Magnetic resonance imaging · Cognitive impairment · Dementia · Aging

Introduction

With the general increase of the aging population, there is a growing demand for neuroimaging evaluations of patients presenting with minor cognitive deficits and no dementia. Very often it is very difficult clinically and radiologically to assess whether these patients suffer from a primary degenerative disease of the nervous system or if it is secondary to a vascular disease. Indeed small-vessel disease and carotid arteriosclerosis are causes of recognized hypoperfusion affecting the frontal lobes. Leukoaraiosis (LA) also frequently affects the frontal lobes. Moreover the white matter in the frontal lobes contain various neuronal circuits and pathways which are believed to be involved in most of cognitive deficits in normal aging, in pathology, and in patients with LA. Until now these patients had been assessed radiologically by either Computed tomography or Magnetic Resonance Imaging (MRI) using mainly T2-weighted sequences. A new modality, diffusion-weighted MRI (DWI) should be helpful since it allows to demonstate and quantify water motion; diffusion imaging is a modification of an NMR pulse sequence with two diffusion pulses placed around the 180 degree inversion pulse of a standard spin-echo sequence: this provides us with the DWI showing tissular water movement; quantification of the diffusion observed can be done by additionally performing measurements of the apparent diffusion coefficient (ADC) [1, 2, 3], which is done by performing the simultaneous acquisition of a T2-weighted b0 image. Diffusion imaging is well established in imaging and investigation of stroke and brain development [4, 5], but a few reports have surfaced speculating its usefulness in investigating the aging brain

[6, 7, 8, 9, 10, 11, 12, 13, 14]. Using DWI and ADC mapping, we wanted to assess whether there were changes in aging in the frontal white matter of patients with and without LA (respectively LA+ and LA- groups). We used low-field MR technology, [15] due to its increased patient comfort and we chose to focus on the frontal lobes since they harbor most of brain circuits affected in patients with minor cognitive deficits without dementia [16].

Materials and methods

A total of 87 consecutive patients were included in this study, aged between 25 and 83 years of age; Thirty normals that were below the age of 60 (25 to 59 years of age) were added to the study in order to construct a slope for the graph; however, of these only 12 were below the age of 50. Patients were referred for Magnetic Resonance Imaging of the brain from the medicine and geriatric medicine departments of our institution. The referral reason was new minor cognitive deficits but no DSM IV criteria for dementia. The patients underwent a standard MRI protocol including axial T1 and T2 weighted MR images as well as coronal FLAIR images. The patients did not have any other suspected neurological diagnosis such as ischemic or hemorrhagic stroke or primary or metastatic brain tumors. They were examined by a neurologist specialized in the assessment of dementia and underwent a clinical examination including neuropsychological assessment. Patients with clinical criteria for vascular dementia of the State of California Alzheimer's Disease Diagnostic and Treatment Centers (ADDTC) were excluded.

The patients were examined on a 0.23 T open system (Philips Outlook): for each patient a total of 12 ten millimeter thick slices were acquired with b values of 0 and 700s/mm^2. The following parameters were used: FOV: 300 mm; matrix: 216 x 216 pixels, TR: 1440ms, TE: 110ms, NEX: 1. A rotating diffusion gradient was used and the diffusion gradient was applied in the z axis only. ADC values were automatically generated by the console software using a pixel-to-pixel analysis.

Regions of interest were defined on the system console in the region of the preventricular frontal white matter in both hemispheres and ADC values were measured from the ADC maps.

Two neuroradiologists sat together and interpreted the neuroimaging data with the knowledge that they had been referred to our unit for minor cognitive deficits but no dementia. They visually inspected the images and came to an agreement that the patients had leukoaraiosis or not based on the presence of T2-weighted hyperintensities in the subcortical white matter (LA+) or its absence (LA-). In a second phase a third neuroradiologist performed every patient's ADC measurements blinded to the the fact that the patient had LA or not. The neuroradiologists were also completely blinded to other clinical data.

We performed ADC measurements in the frontal lobes bilaterally by a pixel-by pixel analysis as described previously by Mehdizade (15) whereas mean ADC values in 10 volunteers had been 1.117 x 10^{-3}mm^2/s].

Statistical analysis was performed to compare ADC values and comprised (1) t-tests between groups (LA+ and LA-), (2) ANOVA with age as a covariate, (3) Pearson correlations on the entire sample, with linear regression including a test for differences between groups in the slope of ADC against age.

Results

In our sample, there was a significant correlation of ADC and age ($r = 0.326$, $p = 0.002$). Using our qualitative method twenty patients had frontal lobe LA defined by T2 weighted MRI and 67 did not (Figure 1).

The ADC values in the frontal lobes in the LA+ group was measured between 1.32 x 10^{-3}mm^2/s and 1.59 x 10^{-3}mm^2/s and in the LA- group was: 1.08 x 10^{-3}mm^2/s to 1.31 x 10^{-3}mm^2/s ($t = 12.439$, $df = 85$, $p < 0.0001$). This is shown in figures 3 and 4. We observed an increase of ADC values with age in the two patient groups (Figure 4). The difference between the two groups remained significant after controlling for age (ANOVA, $F(1,84) = 131.56$, $p < 0.0001$). The LA+ group on average had higher ADC values but the change with age was not significantly different from the LA- group ($F(1,83) = 1.046$, $p = 0.309$).

Discussion

We observed an overall increase in ADC values in the frontal white matter with increased aging. This is an

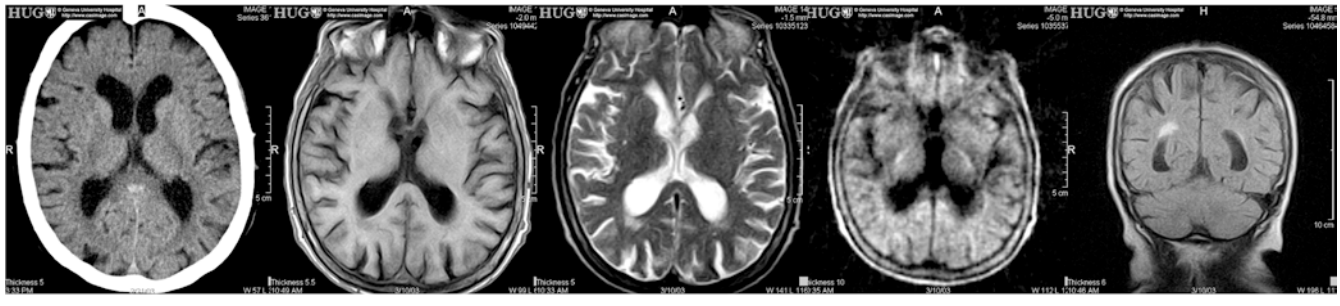


Fig. 1 A 93-year-old woman who was referred for MRI because of mild cognitive impairment. Computed tomography at the level of the ventricles and basal ganglia showed slight age-related atrophy, whereas MRI additional showed signs of periventricular leukoaraiosis, mainly visible on the axial T2-weighted image, and the coronal fluid-attenuated inversion recovery image: this corresponds to the hyperintensities in the white matter posterior to the ventricular atria on both sides (slightly more on the right side). The primary DWI image shows no stroke-related hyperintensity

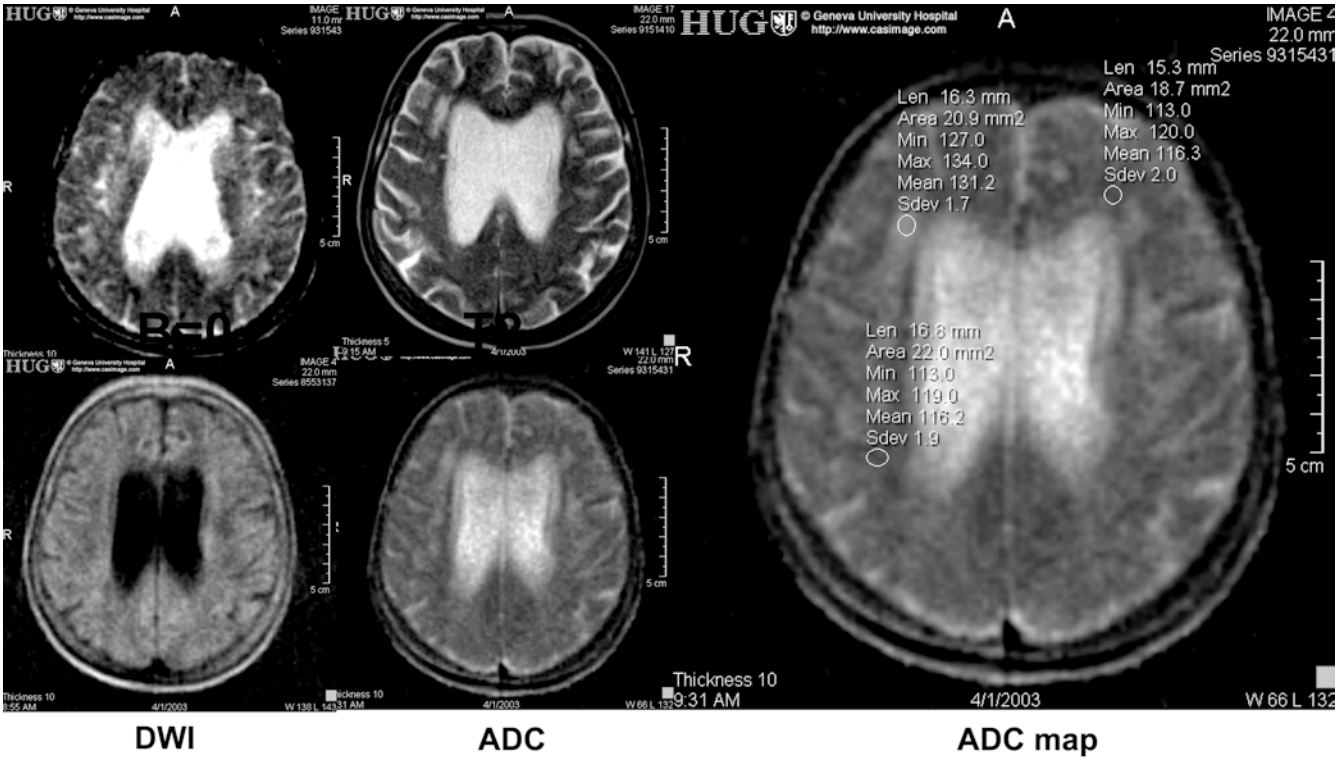


Fig. 2 An 83-year-old woman with recent development of cognitive changes: the T2-weighted images in the upper left corner (*far left:* b = 0 image; *middle:* T2-weighted spin-echo image) demonstrate frontal leukoaraiosis with little atrophy. The DWI image shows no acute stroke (*far left*) and the calculated ADC map again shows the bifrontal hyperintensities in the same areas. When measuring ADC measurements we found that the highest values in the leukoaraiosis on the right (1.31×10^{-3} mm^2/s) showed mean values higher than in the non-affected normal brain either in the less affected left hemisphere (1.16×10^{-3} mm^2/s) or in the parietal white matter (1.16×10^{-3} mm^2/s)

overall phenomenon found in both populations, both those suffering from radiologically diagnosed leukoaraiosis and those not. This seems to be a sign of progressively wasting brain substance with aging.

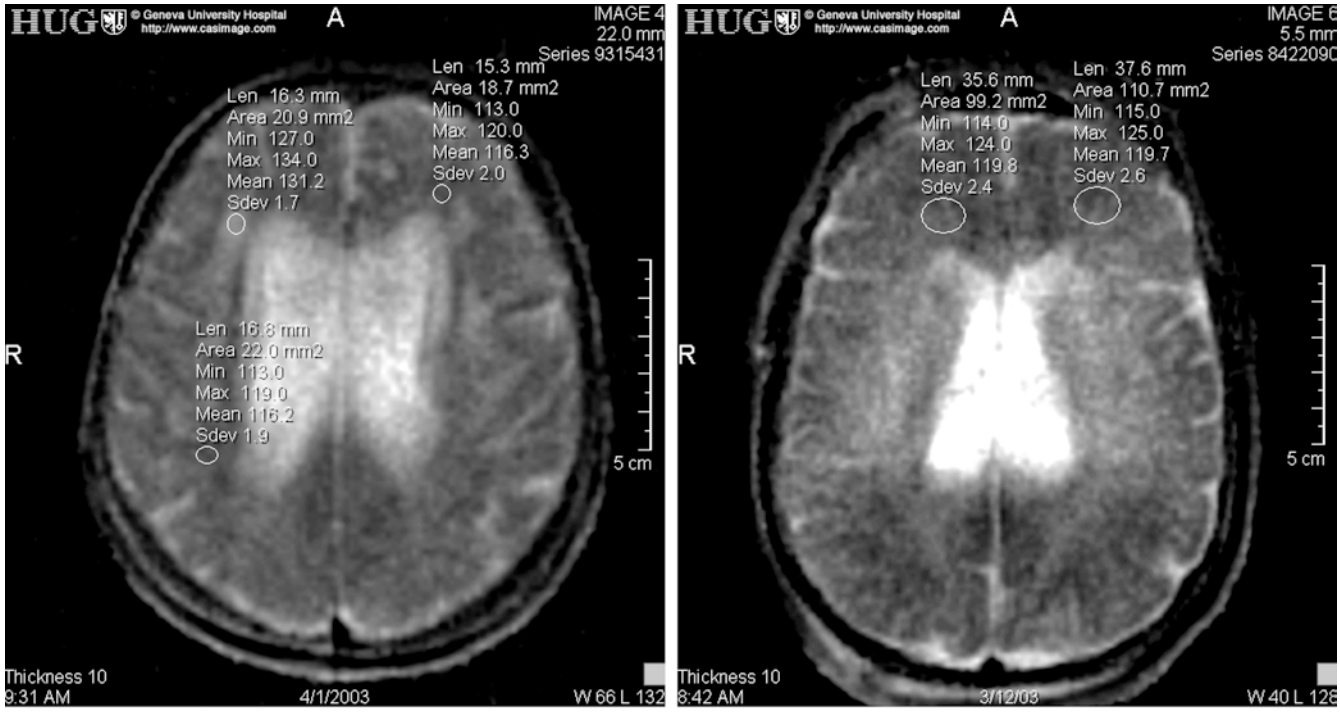
Diffusion-weighted MR imaging, which allows the imaging of tissular water motion, is applied increasingly in clinical neuroscience imaging [3]. Besides its very well-established use in the acute imaging of stroke, it has found acceptance in the investigation of the developing infant brain. While DWI is used primarily for the investigation of stroke by using the strong sensitivity to ischemia, the ADC maps that can be generated from the same image sets seem to contain further information regarding tissular pathophysiology: indeed this has been demonstrated in both animal and now in human models of stroke where the ADC seems not just to reflect the presence or absence of a lesion but to correlate with the underlying hemodynamic pathophysiology [2].

Overall studies seem to agree that there is an increase of diffusion in the brain as reflected by increasing ADC values with age. Interestingly, we observed changes that are the opposite of those found in the neonatal period: with increased myelination and brain development there is a decrease in the ADC in the neonatal brain; therefore, indirectly the ADC seems to correspond to the state of development or degeneration of the brain which occurs naturally in the neonatal and aging brains.

In a study of diffusion tensor imaging in the elderly, Pfefferbaum and Sullivan [6] found that, depending on the region of interest, trace diffusitivity increased with age ($r = 0.24$–0.58) and fractional anisotropy decreased with age ($r = -0.29$ to -0.79). The flip angle was inversely correlated with trace, even when controlling for age.

Rovaris et al. reported significant correlations between subject age and the following variables: number of hyperintense areas in the brain at T2-weighted MR imaging ($r = 0.63, p < 0.001$), mean ADC ($r = 0.34$, $p = 0.001$), ADC peak height ($r = -0.34, p = 0.001$), and fractional anisotropy peak height ($r = -0.57$, $p < 0.001$) [7].

Shenkin et al. [8] found that diffusion anisotropy, which correlates with the ADC, did reflect mental ability and how it was reflected by aging when they performed a series of measurements in the centrum semiovale. The centrum semiovale is also of interest since it contains at least in part watershed areas.



83 y-o with leukoaraiosis **81 y-o without leukoaraiosis**

Fig. 3 Two elderly patients with slight cognitive impairment: on the left side an 83-year-old patient with T2-weighted leukoaraiosis, on the right an 81-year-old patient without leukoaraiosis. When measuring ADC values in the leukoaraiotic areas in the frontal lobes we found that in the high T2-weighted hyperintensity (*right*) there are higher ADC values (1.34×10^{-3} mm^2/s) in the left frontal lobe of the patient with leukoaraiosis than in the less affected areas (contralateral frontal white matter: 1.16×10^{-3} mm^2/s, or homolateral parietal white matter: 1.16×10^{-3} mm^2/s); or compared with the elderly patient of slightly younger age with no leukoaraiosis (1.19×10^{-3} mm^2/s in both the white matter in both frontal lobes)

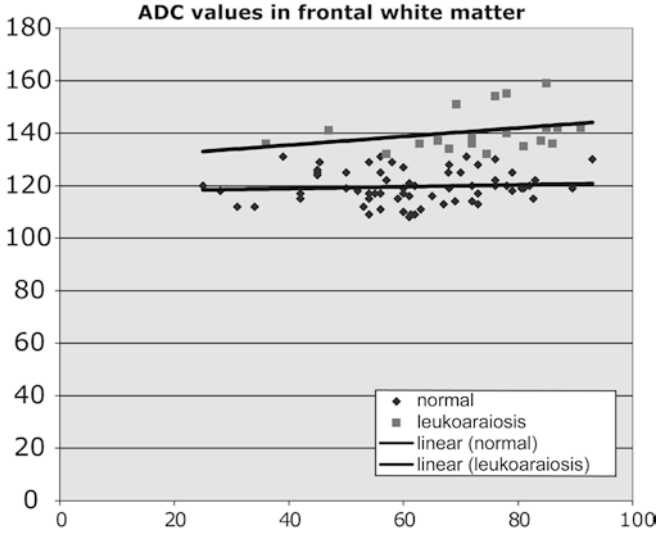


Fig. 4 Graph representing the ADC values in the frontal white matter (y axis) in the series of reported patients, according to age (x axis). There are two patient groups, one with leukoaraiosis as defined by T2 imaging and one without leukoaraiosis. The patients with leukoaraiosis (*squares*) have higher ADC values than those without leukoaraiosis (*diamonds*). The ADC values are $\times10^{-5}$ mm^2/s

In another study of 294 patients Naganawa found a gradual increase with aging of the ADC, slightly more so in the right hemisphere, when they compared their findings with those in five volunteers [10].

Overall, our findings are compatible with those found in the scientific literature; however, further investigations may be warranted to determine if a vascular and therefore treatable cause of the cognitive changes is present [14]. Further studies, including positron emission tomography and single photon emission computed tomography, in order to quantify the underlying vascular flow parameters, are necessary. Indeed, it is necessary to determine whether the changes found in patients with a vascular dementia can be differentiated with security from those with an Alzheimer-type disease [17, 18]. Kantarci et al., for instance, found that hippocampal volume did best reflect Alzheimer's disease [18].

Diffusion-weighted imaging is independent of field strength and DWI imaging on a system such as the one used in the present study and has already been validated in stroke patients and in healthy volunteers.

The main drawback is that, because of the gradients, it is not possible to perform additional perfusion imaging or spectroscopic imaging in these patients, rendering

developments on this system difficult; however, its use for the selection of patients seems promising: indeed patients suffering from a vascular cause of beginning cognitive deficits might be recognized as such, and not as being genetic, with the proper use of adapted neuropsychological tests [19], and the patient will therefore be referred for further investigation of the cerebral circulation with Doppler ultrasound, MR, or conventional angiography. This would allow finding patients that would benefit from possible carotid stenting.

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