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# White matter magnetic resonance imaging hyperintensity in Alzheimer's disease: correlations with corpus callosum atrophy

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**Abstract** We have previously demonstrated with MRI that as well as marked white matter involvement in late-onset Alzheimer's disease (AD), atrophy of the corpus callosum may also be present. This finding prompted us to study possible correlations between atrophy of the corpus callosum and white matter hyperintensity (WMH) and between white matter lesions and the severity of the disease. We compared the corpus callosum and white matter lesions on MRI from 15 AD patients and 15 controls. The white matter lesions were scored according to the Scheltens' rating scale. We found a significant reduction of the area of the corpus callosum and more severe white matter lesions in AD patients than in controls. Both atrophy of the corpus callosum and the severity of lesions depended mainly on the diagnosis of senile dementia of the Alzheimer type and on age but not on the diagnosis of presenile AD. We demonstrated a negative correlation between white matter lesions scores and areas of corpus callosum in AD patients and no correlation between the white matter lesions and the severity of the disease. We demonstrated that white matter lesions including WMH and atrophy of the corpus callosum are more frequent in AD than in controls. The predominance of white matter lesions in senile AD may be explained by the combination of aging and disease processes.

**Key words** White matter · Magnetic resonance imaging · Alzheimer's disease · Corpus callosum · Signal hyperintensity

## Introduction

White matter hyperintensity (WMH) has been identified on MRI in patients with cardiovascular diseases, diabetes mellitus and hypertension, but also in healthy subjects [1, 6]. Extensive WMH is one of the hallmarks of cerebral autosomal dominant arteriopathy with subclinical infarcts and leukoencephalopathy (CADASIL) [4]. Such white matter changes have also been reported in 40–100% of patients with Alzheimer's disease (AD) [2, 10, 17]. There is no agreement that WMH is more severe in AD patients than in controls [4, 5, 11, 13, 23]. In a previous paper, as part of an MRI study using coronal sections, we provided evidence of atrophy of the corpus callosum in AD [25]. In this study on a new cohort of patients and controls, we investigated the corpus callosum using sagittal sections and examined the relationship between the area of corpus callosum and WMH.

## Patients and methods

### Study population

The demographic data on the 30 subjects included in the study are summarized in Table 1. The diagnosis of probable AD was made in 15 patients according to the criteria of the NINCDS-ADRDA workgroup [16]: 5 patients had early onset (presenile AD, PSAD)

**Table 1** Demographic data and values (SD) of corpus callosum index (*CCi*) and white matter score (*WMS*; *AD* Alzheimer's disease, *MMS* Mini-Mental State Examination, *PSAD* presenile AD, *SDAT* senile dementia of Alzheimer type)

| | *n* | Age (years) | Sex (F/M) | PSAD/SDAT | MMSE | CCi | WMS |
|---|---|---|---|---|---|---|---|
| AD | 15 | 75.6 (9.5) | 11/4 | 5/10 | 13.1 (6.5) | 0.04 (0.02) | 23.2 (13.11) |
| Controls | 15 | 71.6 (12.8) | 9/6 | | ≥ 28 | 0.064 (0.02) | 12.4 (8.67) |

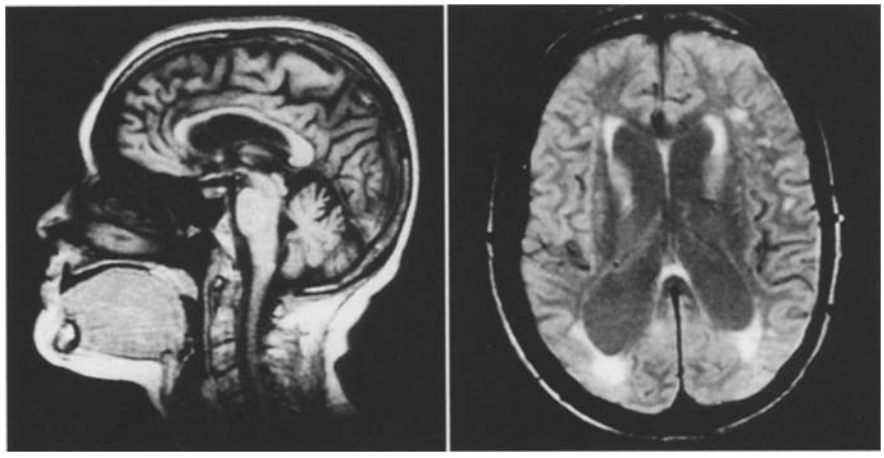

**Fig. 1** Example of atrophy of the corpus callosum on a T1-weighted MRI *(left)* and high-intensity lesions on proton density *(right)* MRI of the brain of a patient with Alzheimer's disease

and 10 late-onset of senile dementia of Alzheimer type (SDAT). There were 15 age-matched controls. Patients with evidence of other neurological diseases were excluded. Each subject had a Hachinski score of 3 or less [9]. None of the patients or controls suffered from hypertension, diabetes or cardiac disease. The Mini-Mental State Examination (MMSE) score was higher than 27 in controls and the mean score was 13.1 in the demented group [8]. None of them had a definite family history of AD but 3 had a first-degree relative suffering from dementia, without sufficient data available for a diagnosis of AD to be made.

MRI technique

MRI was performed on an MR-max machine (General Electric) with a superconducting magnet operating at a field strength of 0.5 T. The area of the corpus callosum was assessed on sagittal sections using T1-weighted spin echo sequences (TE 22 ms, TR 300 ms). The hemispheric white matter changes were rated using proton density and T2-weighted spin echo sequences (TE 60 ms, TR 2000 ms, section thickness 6 mm, 25% interslice gap) on axial sections. In all cases axial images were obtained with an inplane resolution of 1.0 × 1.6 mm.

The assessment of the corpus callosum was performed as follows: the MRI slices were digitized and boundaries of the corpus callosum were delineated with a mouse-driven cursor. The images of the slices were processed with an image analysis program (IMAGE 1.35 from W. Rasband, NIH Research Services Branch). For comparison, we used an index: the corpus callosum index (CCi) was defined as the ratio between the area of the corpus callosum and the area of the skull at the same level. The WMH was separately rated by three of us (P.V., J.R., M.H.), blinded to the clinical diagnosis and age; the Scheltens' rating scale was used [22]. For each subject, the white matter score (WMS) was defined as the mean of scores given by each observer and as the summation of four subscores as defined by Scheltens et al. [23]: periventicular hyperintensity score (PVH), white matter score in the four lobes (WMLH), basal ganglia hyperintensity (BGH) and infratentorial foci of hyperintensity (ITFH).

Statistical analysis

Differences in the CCi and the WMS between the AD patients and controls were tested using the non-parametric Mann-Whitney U-test. Spearman's non-parametric rank correlation test was used to investigate possible correlations between CCi and the WMS or the subscores described above and the MMSE scores. A multiple linear regression was performed using a model including age (years), the presence of PSAD (1 = yes, 0 = no), the presence of SDAT (1 = yes, 0 = no) as dependent variables and CCi or WMS as independent variables. The level of interobserver agreement was measured by the κ statistic using the Fleiss method [7]. It has been suggested that a κ value between 0.40 and 0.80 can be considered moderate to substantial [24]. Data were analysed using the statistical SAS package. We regarded $P$ values <0.05 as significant.

## Results

The CCi values were significantly smaller in AD patients than in controls, with a high variance in both groups ($U = 46.5$, $P < 0.01$) (Table 1). The WMS was significantly higher in AD patients than in controls ($U = 57.5$, $P < 0.05$). Most of these hyperintensities are found in periventricular and deep white matter regions. Very few subjects in either group had hyperintensities in the basal ganglia (2 patients and 1 control) and infratentorial regions (1 patient). The interobserver study provided κ values of 0.58 and 0.54 for CCi and WMS respectively.

We found a significant negative correlation between the CCi and the WMS ($r = 0.613$, $P < 0.01$) and between the CCi and the white matter subscores PVH ($r = 0.516$, $P < 0.01$) and WMLH ($r = 0.583$, $P < 0.01$) (Fig. 1). We failed to find any correlation between the CCi and the BGH and ITFH subscores. In the AD group, there was

**Table 2** Regression analysis of CCi and WMS. CCi and WMS are independant variables and age, PSAD and SDAT are dependent variables

| | Intercept | $R^2$ | Global $P$ value | Age (β, SD of β, $P$) | PSAD (β, SD of β, $P$) | SDAT (β, SD of β, $P$) |
|---|---|---|---|---|---|---|
| CCi | 0.45 | 0.434 | 0.0018 | –0.001, 0.003 $P = 0.048$ | –0.004, 0.01 $P = 0.156$ | –0.024, 0.008 $P = 0.008$ |
| WMS | –26.2 | 0.428 | 0.002 | 0.54, 0.187 $P = 0.0079$ | 9.36, 5.19 $P = 0.08$ | 8.28, 4.35 $P = 0.041$ |

also no correlation between WMS or the CCi and the MMSE score ($r = 0.19$ and 0.21 respectively, NS). The regression analysis showed (Table 2) that the CCi depends mainly on the diagnosis of SDAT ($P = 0.008$) and on age variations ($P = 0.048$), but not on the diagnosis of PSAD ($P = 0.156$). The WMS also depends mainly on age variation ($P = 0.0079$) and on the diagnosis of SDAT ($P = 0.041$) but not on the diagnosis of PSAD ($P = 0.08$).

## Discussion

This study using sagittal sections confirms our preliminary finding that there is atrophy of the corpus callosum in AD. Like Bowen et al. [2] and Scheltens et al. [21], we also found more WMH in AD than in controls. Other studies including younger patients [13] or only early-onset cases [5] failed to detect such findings. These differences may suggest that white matter changes are due to the inclusion of old patients. However, our statistical approach demonstrated that both atrophy of the corpus callosum and white matter changes are not only an effect of age but also an effect of the disease.

The corpus callosum is composed of interhemispheric fibres traversing the subcortical white matter. In patients with diffuse radiological abnormalities of the hemispheric white matter, atrophy of the corpus callosum may result from axonal disruption. We found a close correlation between the atrophy of the corpus callosum and the severity of white matter changes. This association is also observed in other diseases with subcortical pathology such as multiple sclerosis [19] or vascular dementia [26]. It is probable that the atrophy of the corpus callosum is due to axonal changes secondary to hemispheric white matter lesions. The area of the corpus callosum may reflect the number of axons. A reduction in the callosal area may, therefore, reflect a loss of axons probably due to wallerian degeneration in subjects free of any vascular disorder [14]. Indeed, in our study, very few subjects had hyperintensities in the basal ganglia, which are known to be probably of a vascular nature. The atrophy of the corpus callosum may be due to the loss of callosal neurons in the neocortex. Therefore, the loss of interhemispheric connections is related to specific neocortical changes. Indeed, it has been proposed that a global cortico-cortical disconnection occurs in AD, leading to a neocortical isolation syndrome that is manifested as dementia [18]. However, linkage between white matter changes and cortical lesions remains hypothetical because the occurrence of the white matter disorder is neither regularly related to the severity nor the regional appearance and accentuation of the cortical Alzheimer process [3]. Our results may also explain why some neuropsychological tasks that specifically evaluate interhemispheric transfer are impaired in AD [12]. The role of incidental advanced periventricular diffuse or patchy white matter changes in the development of cognitive or neurobehavioural impairments remains controversial [1, 15, 20]. In our study, we failed to find any correlations between CCi or WMS and MMSE in the AD group. This suggests that the cognitive decline in AD is more likely to be the consequence of the characteristic cortical lesions. Although the MMSE score is a poor measure of severity of dementia, a mean score of 13.1 implies that the AD patients were severely demented, limiting the validity of our conclusions for mid- to-late- stages of AD. Further radiological and extensive neuropsychological longitudinal studies are needed to establish the contribution of WMH and corpus callosum atrophy to the cognitive decline of AD. Our study is in agreement with the hypothesis of Scheltens and coworkers that the presence of white matter changes might distinguish a subgroup of AD patients with a late onset of the disease [22]. Indeed, our results suggest that the white matter involvement, both atrophy of the corpus callosum and WMH, is a combined effect of aging and the disease in the senile form of AD.

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