Corpus callosum fractional anisotropy predicts clinical progression and cognitive dysfunction in early primary-progressive MS: a 5 year follow-up study

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Introduction

Primary-progressive multiple sclerosis (PPMS) is generally considered to have a poor prognosis, but the rate of motor and cognitive deterioration is quite variable [1]. MRI prognostic indicators are needed to help inform patients of their likely disease course. In a previous cross-sectional study of patients with early PPMS, we demonstrated widespread reduction in white matter (WM) fractional anisotropy (FA), reflecting diffuse WM demyelination and axonal loss, and in grey matter (GM) volume, indicating cortical and deep GM atrophy, compared with controls [2]. We also showed that these abnormalities were clinically relevant. We have now performed a longitudinal study on the same cohort to identify areas of WM and GM which predict the development of motor disability *over* five years and cognitive dysfunction *after* five years.

Methods

We studied 32 patients (13 women, mean age 44.5 yrs, SD 10.3) with definite or probable PPMS within 5 years of symptom onset. All patients were assessed on the day of scanning and five years later with the Expanded Disability Status Scale (EDSS) [3]. EDSS step-changes were calculated to assess disability progression over the follow-up period. Changes in EDSS between baseline and 5 years were estimated using the Wilcoxon Signed Ranks Test. At the 5-year follow-up, a subgroup of 25 patients (11 women, mean age at time of cognitive assessment 51.3 yrs, SD 10.3) and 31 healthy controls matched for age, gender and premorbid IQ, underwent the following neuropsychological tests: (i) the National Adult Reading Test (NART), to estimate each patient's premorbid intellectual functioning; (ii) the Story and Figure Recall tests, to assess the verbal and visual recall memory; (iii) the Paced Auditory Serial Addition Test (3-second version) (PASAT-3) and the Symbol Digit Modalities Test (SDMT), to assess the attention and speed of information processing; (iv) the Hayling Sentence Completion Task and the Brixton Spatial Anticipation Test (BSAT), to explore the executive functions. The raw scores of all the measures, except premorbid IQ, were converted to z-scores referenced to the control group, and these multiplied by -1 when appropriate, so that a lower score always indicated a poorer performance. A z-score ≤ -2 in a test was considered to be abnormal; cognitive impairment was defined when abnormal results emerged on three or more tests. Baseline MR imaging at 1.5T consisted of a dual-echo FSE sequence (TEs=17/92 ms; TR=2000 ms), a 3D inversion recovery fast SPGR (TI=450 ms, TE=4.2 ms, TR=13.3 ms) and a cardiac-gated diffusion tensor (DT) EPI (TE=95 ms, maximum b factor=1000 smm-2, 25 diffusion directions). FA maps were created using dtifit (http://www.fmrib.ox.ac.uk/fsl/), and they were fed into Tract-based spatial statistics (TBSS) [4], to obtain a projection of all subjects' FA data onto a mean FA tract skeleton. To investigate whether FA predicted EDSS step-change and the neuropsychological tests scores, a voxel-wise linear regression analysis was performed, adjusting for age, gender, disease duration and NART (the latter was used for neuropsychological variables only). The analysis was based on permutation-based inference, and corrected for multiple comparisons using Threshold-Free Cluster Enhancement ($p<0.05$). The SPGR volumes were segmented and normalized to obtain GM, WM and CSF using SPM8, according to the VBM protocol [5]. GM images were modulated and smoothed using a 12-mm FWHM Gaussian kernel. Multiple regression analyses, adjusted for the same variables as those used for TBSS, and corrected for multiple comparisons with familywise error rate, were used to investigate the association between regional GM volume and EDSS step-change and neuropsychological measures.

Results

Patients showed progression of disability during the follow-up, as measured by EDSS (median EDSS at baseline = 4.5, at 5 yrs = 6.4, $p=0.001$). At 5-year follow-up, 7 patients were cognitively impaired, 9 showed abnormal results on one or two tests, and 9 showed normal results on all tests. Lower FA in the splenium of the corpus callosum predicted greater EDSS step-change ($p<0.05$) (Fig 1.A), whereas baseline GM volume did not significantly predict EDSS deterioration. Lower baseline FA along the entire corpus callosum (genu, body and splenium) at study entry predicted worse verbal memory ($p<0.01$) (Fig 1.B), worse attention and speed of information processing (PASAT-3 $p<0.01$, SDMT $p<0.05$), and worse executive function (BSAT $p<0.01$) scores at 5-year follow-up. GM baseline volume did not significantly predict any neuropsychological test at five years.

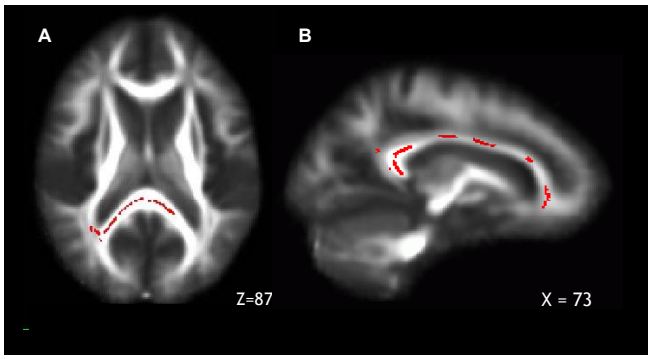

Fig 1. A. Lower baseline FA in the splenium of the corpus callosum predicted a worse clinical progression at five years. **B.** Lower baseline FA along the whole corpus callosum significantly correlated with neuropsychological tests assessing verbal memory.

Discussion

Our findings highlight the importance of damage to the inter-hemispheric callosal pathways in determining disability in PPMS, and suggest that early disruption of the callosal WM pathways, which are crucial in co-ordinating the flow of information between different grey matter regions, results in a disconnection syndrome that may contribute to deteriorating mobility and cognitive function in patients with PPMS. Measuring early damage in the WM seems to be more useful in predicting long-term motor deterioration and cognitive dysfunction than estimating regional GM atrophy.

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