MRI protocol

The following sequences were acquired using a 3T GE Discovery MR750 scanner (GE Medical Systems, Milwaukee, WI) as described previously in detail: 15

1. Pre- and post-contrast (gadolinium) Sagittal 3D T1: GE BRAVO sequence, FOV 256mm, Slice thickness 1mm, TE 2.7ms, TR 7.2ms, Flip angle 12°, Pixel spacing 1mm. Acquisition Matrix (Freq.× Phase) is 256×256, which results in 1mm isotropic acquisition voxel size. The reconstruction matrix is 256x256.
2. FLAIR CUBE; GE CUBE T2 FLAIR sequence, FOV 240mm, Slice thickness 1.2mm, Acqui- sition Matrix (Freq.× Phase) 256×244, TE 163ms, TR 8000ms, Flip angle 90°, Pixel spacing 0.47 mm. The reconstruction matrix is 512x512.
3. Whole brain diffusion-weighted images using a spin echo, 64 directions, FOV 256 mm, Acquisition Matrix (Freq.× Phase) 128×128, slice thickness 2mm, TE 83ms, TR 8325ms, b0=1000 s/mm2 (number of acquisitions – 2). The reconstruction matrix is 256x256.

MRI image pre-processing.

The baseline T1-weighted imaging was realigned to AC-PC (anterior commissure-posterior commissure) orientation in MrVista package (Stanford University). Using FLIRT (FSL, FMRIB Software Library), follow-up T1 image was co-registered to baseline AC-PC space by applying transformation matrices derived from linear co-registration between baseline AC-PC aligned brain and follow-up native T1 brain images.

Diffusion MRI was corrected for motion and eddy-current distortion in FSL, then EPI susceptibility distortion was minimized by applying deformation maps generated from nonlinear co-registration between DWI b0 brain image and T1-weighted imaging at each time-point using ANTS (Advanced Normalization Tools).

Subsequently, tensor reconstruction was performed in MrDiffusion (MrVista, Stanford University). Baseline and follow-up tensor images were then linearly co-registered to corresponding T1 AC-PC images. Diffusivity measurements were analysed in patient’s and timepoint-specific AC-PC space.

Statistical analysis.

Shapiro-Wilk test was used to test all variables for normal distribution. Pearson correlation coefficient was used to measure statistical dependence between two normally distributed variables, while Spearman correlation coefficient was used for non-parametric variables. If not additionally specified in a text, all partial correlations (both parametric and non-parametric) were adjusted for age, gender, and disease duration. P < 0.05 was considered statistically significant. Comparisons between groups were made using Student *t*-test. Longitudinal changes were assessed using paired two-sample *t*-test. Shapiro-Wilk test was used to test for normal distribution.

A Univariate General Linear Model was applied to analyse the potential effect of various factors on brain atrophy. PBVC was used as a dependent variable. Only individual variables significantly associated with brain atrophy were included in the model.