Application of Lesion Probability Maps to predict progression in primary-progressive multiple sclerosis: a 10-year multi-centre study

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Introduction

Although primary-progressive multiple sclerosis (PPMS) is generally considered to have a poor prognosis, the rate of deterioration has been demonstrated, both clinically and radiologically, to be quite variable. Long-term studies of large cohorts of patients with PPMS have shown that male sex and a shorter disease duration at baseline were associated with a more rapid clinical progression over time [1,2]. Established prognostic indicators gained from magnetic resonance imaging (MRI) are needed to provide patients with indication of their disease course. To date, no convincing evidence of a role played by baseline T2 lesion load in predicting long-term outcome has emerged. The question that remains unanswered is whether the spatial distribution of T2 lesions at baseline, rather than the T2 lesion load, predicts progression in PPMS. To clarify this important issue, we used a novel technique, termed Lesion Probability Map (LPM) [3], and applied it to a large cohort of PPMS patients followed-up over 10 years. This was possible through the pan-European MAGNIMS (MRI in MS) initiative.

Methods

Eighty patients (39 females, mean age 49.6 years, SD 10.1), diagnosed with PPMS according to clinical history, were recruited from Amsterdam, Barcelona, Bordeaux, London, and Milan. At baseline, all patients were scanned and assessed on the day of the scanning with the Expanded Disability Status Scale (EDSS) [4]. Patients were then clinically assessed and scored on EDSS after one, two, five and ten years. For each patient, the time in years taken to reach the need of bilateral constant assistance (i.e. EDSS 6.5) from disease onset was calculated and used as outcome measure.

All MR imaging was obtained at 1.5T, and consisted of T1 and T2 weighted images of the brain (44x3mm contiguous axial slices, in plane resolution 1x1 mm). Lesions were delineated on the dual-echo scans and binary lesion masks were created. The original T2-weighted images were registered to the Montreal Neurological Institute (MNI152) standard space, through a non linear registration which we performed using FNIRT, which is part of FSL (http://www.fmrib.ox.ac.uk/fsl/) [5]. The resulting transformation parameters were then applied to the binarised lesion masks. Voxelwise statistics was performed to produce LPMs, where the probability of a lesion being present in any given voxel is defined by the relative voxel intensity. We then investigated the correlation between the probability of a voxel being lesional and the time taken to reach EDSS 6.5, allowing for age, gender, disease duration and centre, using a linear regression analysis. Correction for multiple comparisons at voxel level ($p<0.05$, $t>1$) was performed by using permutation-based inference. To assess the best independent predictors of the risk to reach EDSS 6.5, we extracted for each patient the number of lesional voxels from the brain regions which resulted significant in the LPM analysis, and entered it in a Cox regression model, together with other covariates (sex, age, disease duration, centre, total T2 lesion load and atrophy measures extracted using SIENAx, [6]), using the time to reach EDSS 6.5 as dependent variable.

Results

At baseline, 23 patients had already reached EDSS 6,5. Twenty-three patients reached the need of bilateral constant between the baseline and year five, and 13 patients reached the endpoint between year five and year ten, Twenty-one patients never reached EDSS 6.5 during the observation period. There was a significant correlation between the probability of baseline lesional voxels being localised in the cortico-spinal tracts (CSTs), from the cortex to the corona radiata, in the longitudinal superior fasciculi and in the right inferior fronto-occipital fasciculus, and the time taken to reach EDSS 6.5 ($p<0.002$ on the right, $p<0.02$ on the left, **Fig.1**). Cox regression analysis showed that the best indipendent baseline predictors of the risk of reaching EDSS 6.5 during the observation period were sex and the number of lesional voxels within the CSTs. In particular, (i) male gender was associated with an increased risk of 61% compared with female gender ($p<0.05$, hazard ratio 1.61, confidence interval 0.96-2.73), and (ii) there was an increased risk of 25% per 100 lesional voxels in the CST ($p<0.07$, hazard ratio 1.0022, confidence interval 0.99-1.00).

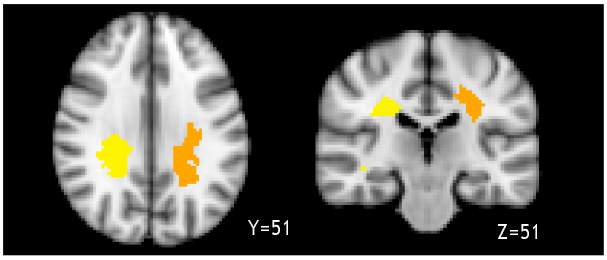

Fig 1. *Regions of significant correlation between the probability of a voxel being lesional at baseline and the time taken to reach EDSS 6.5 .*

Discussion

Our findings suggest that spatial distribution of T2 lesions is relevant in predicting the risk of long-term progression in PPMS. In particular, we showed that lesions localised in the motor and associative tracts at baseline correlated with a more rapid clinical progression over time. Moreover, we confirmed that male gender is significantly associated with a poorer long-term prognosis. In conclusion, spatial distribution of T2 lesions may have an important role as a prognostic indicator of long-term clinical outcome in patients with PPMS.

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