Development of Central Atrophy May Lead to Underestimation of Lesion Accrual in Patients with Multiple Sclerosis

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Objective. To quantify the volume of T2 lesions (T2-LV) lost due to central atrophy development over a 5-year period in patients with multiple sclerosis (MS).

Background. Change in brain T2-LV is a commonly used secondary endpoint in MS clinical trials. However, a thorough understanding of the different biological mechanisms affecting T2-LV is critical to the correct interpretation of these changes. In particular, loss of T2-LV due to tissue atrophy clearly does not represent a reparatory process, yet may result in decreased LV measures or underestimation of lesion accrual.

Methods. We investigated the evolution of T2-LV and ventricular enlargement in a group of 38 patients with early relapsing-remitting MS (mean age 32.9+/-9.1 years, mean disease duration 5.1+/-5.3 years and mean EDSS 2.1+/-0.8). Patients received baseline and 5-year MRI examinations, including high-resolution FLAIR and T1-SPGR images.T2-LV masks were created from the baseline and follow-up images via a highly-reproducible edge-contouring technique. Lateral ventricle volume (LVV) was also calculated at both baseline and follow-up using a similar technique. For each patient, all images and masks were placed into the same space via linear co-registration. Baseline lesion masks were then overlaid with follow-up ventricle masks to identify voxels which were classified as lesion at baseline and converted to ventricle at follow-up.

Results. Patients showed a mean increase in T2-LV of 4.7ml+/-8.0ml (96.0%+/-96.3%). Mean increase in LVV was 8.5ml+/-4.2ml. Mean T2-LV lost due to LVV enlargement was 0.5ml+/-0.7ml (3.4%+/-3.7%), and represented an average of 5.6%+/-1.9% of the total change in T2-LV. Some patients lost as much as 17.7% of their baseline T2-LV to LVV enlargement, which also accounted for as much as 79.2% of their overall change in T2-LV over 5 years.

Conclusions. T2-LV measurement alone may be misleading as a secondary endpoint without the additional context of central atrophy measurement.