Longitudinal mixed-effect model analysis of the association between global and tissue specific brain atrophy and lesion accumulation in patients with CIS

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TARGET AUDIENCE: Researchers and clinicians interested in brain atrophy, lesion activity, multiple sclerosis, and neuroimaging.

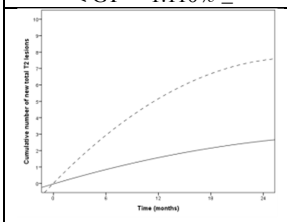
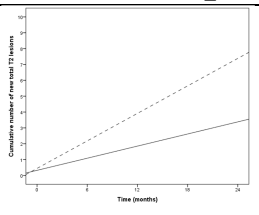
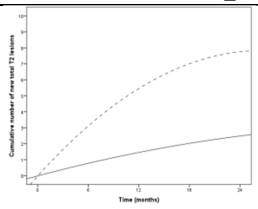
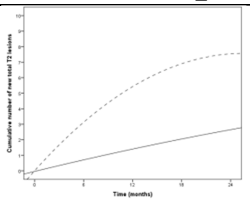
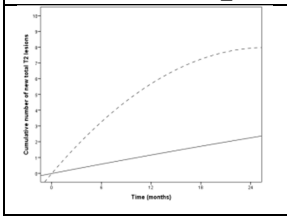
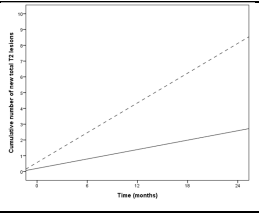
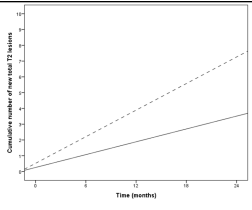
BACKGROUND AND PURPOSE: Atrophy has been shown to occur upon clinical onset, and relates to clinical definite multiple sclerosis (CDMS) conversion.[1] We aimed to investigate the accumulation of new brain lesions and lesion volumes with respect to atrophy of gross brain structures in patients with clinically isolated syndrome (CIS).[2]

METHODS: 216 CIS patients were recruited as part of a multicenter prospective, longitudinal observational study in high risk subjects who were receiving early interferon β1a treatment. Participants were imaged on a Philips 1.5T scanner (Best, the Netherlands) over 2 years with continuous MRI measures at baseline (0), 6 months, 1 and 2 years. Longitudinal linear and quadratic mixed-effect models were performed. Percentage changes in whole brain and tissue-specific compartments (dependent variable) were compared with median cumulative lesion appearance (<2, n=98; ≥2, n=117), lesion volume (<-8.68%, n=102; ≥-8.68%, n=102), and contrast enhancing (CE) lesions as the grouping (independent) variables. Also, based on the cumulative lesion activity, the development of new T2 lesions, lesion appearances, lesion volume, and contrast enhancing (CE) lesions were compared between groups based on median percentage change in whole brain and tissue-specific compartments. All models were adjusted for age, gender, treatment-status, disease-duration, and time until first recorded relapse. Benjamini-Hochberg correction was used to minimize the false discovery rate. After correction, p-values of <.05 were considered significant.

RESULTS: Percent change in whole brain-, lateral ventricle- (LV), grey matter- (GM), and cortical volume (all p<.05) changes were significantly different between groups based on the median number of new T2 lesions. Similar yet stronger results were observed for inverted models (Figure 1) with median percentage of brain volume change as the grouping factor and T2 lesion appearance as the dependent variable (LV-, GM-, and cortical-volume all had p<.001, and thalamic volume was p=.016). No significances were found for mixed-effect models with lesion volume or CE lesions.

DISCUSSION: Lesion accumulation and brain volume changes occur simultaneously from the earliest phases of MS.[3] We used mixed effect model analysis due to its strengths, including all time-points, missing data, covariates, and the possibility to generate an inverted effect. The more robust inverse mixed-effect model results suggest that the level of brain atrophy can explain T2 lesion accumulation better than the T2 lesion can explain accumulation of brain atrophy. We found very strong results for whole brain and all other tissue specific compartments when performing inverse mixed effect model analysis of cumulative total new T2 lesion appearance as the dependent variable with median percentage of brain volume change as the grouping factor. The high number of significant results suggest that atrophy is affected in not one, but a plethora of brain structures, indicating that volume loss is an important factor in the pathophysiological mechanism in CIS, even after adjusting all models for age, gender, medication and disease duration.

Figure 1: Mixed Effect Model Results of cumulative total new T2 lesion number activity split by median global, tissue specific and regional brain volumes over 24 months.

Whole Brain Volume (p=.007)	White Matter Volume (p=.084)	Lateral Ventricle Volume (p<.001)	Cortical Volume (p<<.001)
── < GT = -1.110% ≤ - - -	── < GT = -0.710% ≤ - - -	── < GT = 9.180% ≤ - - -	── < GT = -1.860% ≤ - - -
			
Grey Matter Volume (p<<.001)	Thalamic Volume (p=.016)	Deep Grey Matter Volume (p=.14)	**LEGEND:** LVV = Lateral Ventricular Volume; GT = Grouping Threshold, which is the median value used to separate groups. Values ≥GT were high atrophy / LVV group (dotted line) whereas values <GT were low atrophy / LVV group (solid lines).
── < GT = 1.485% ≤ - - -	── < GT = -2.050% ≤ - - -	── < GT = -1.215% ≤ - - -	
			

CONCLUSION: These results indicate the scientific relevance of brain volume changes from the earliest disease phases, which serves as a good indicative factor of both lesion accumulation and disease activity. This suggests close monitoring of brain volume changes may be relevant for identifying patients at risk for MS as compared to the conventional measurements of T2 lesion volume or CE lesion number.

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