MRI Metrics of Nonlinear Atrophy in MS Disease Progression

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INTRODUCTION

Global brain parenchymal atrophy, assessed from structural brain MRI, has become established as reliable metric of progression in many neurodegenerative diseases. Uncertainty remains to what extent this measure expresses nonlinearity over time and to what extent current methods are sensitive to capture nonlinear behavior. We tested nonlinearities in BPF change in multiple sclerosis (MS) over time and the impact on predicting disease progression. Clinical disease progression is highly variable and difficult to predict in individual patients with MS. Reliable markers for modeling progression are sparse, and models built on existing markers are often linear. Under the premise that neurodegeneration expressed as brain atrophy is a major contributor to clinical progression and currently untreatable, reliable assessment of early progression and its linear or non-linear relationship to later atrophy rates becomes critical for therapy choice and assessment.

METHODS

26 patients with early relapsing-remitting MS underwent frequent MRI during 1 year and a 3-5 year follow-up, with at least 20 MRI exams per subject in the first year [1]. BPF was measured from an automated
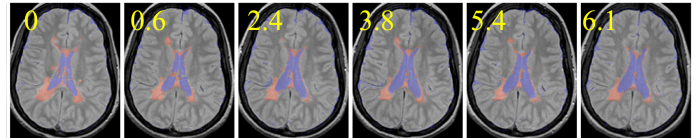

Fig.1. MRI series of an MS patient followed over 6 years (yellow), with superimposed segmentation of CSF (blue) and lesion (red). BPF is a normalized measure of CSF and dominated by ventricular enlargement. The corresponding BPF series is shown in the center plot of Fig.2.

segmentation [2] and calculated as BPF=1-CSF/ICC, with CSF and ICC as volumes of cerebrospinal fluid and intracranial cavity, respectively (Fig.1). We studied the nonlinearity in atrophy progression by measuring how well linear atrophy models predict progression from 1-year follow-up. Linear and nonlinear models of BPF change were also compared. Nonlinear modeling applied a robust least-squares regression using a reflective Newton algorithm, employing a 3-parameter model for BPF change with time (t): $BPF(t)=a+bt^c$. Adjusted R^2 was used to compare fit quality for both models. We also measured how well linear atrophy models predicted progression from 1-year follow-up. Relations of baseline BPF, progression rates, and nonlinearity to clinical markers of disability (EDSS), clinical phenotype and disease duration (from 1st symptom) were also examined.
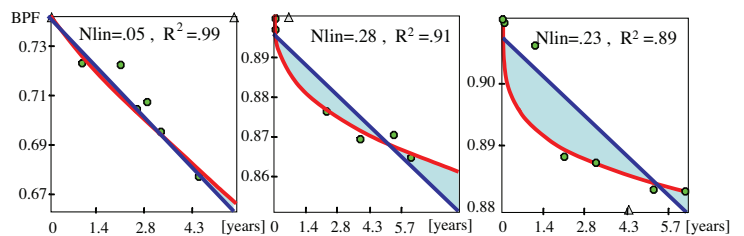

Fig.2: Examples of nonlinearity observed in BPF from serial MRI (green), ranging from almost perfectly linear to strongly nonlinear behavior. The area (cyan) between a linear (blue) and nonlinear (red) regression fit was used as a metric for the level of nonlinearity (Nlin). R^2 reports quality of the nonlinear fit. The MRI series for the subject in the center plot is shown in Fig.1.

RESULTS

Linear models over 1 year showed serious overestimation (range 0.003-0.14, absolute BPF value) of atrophy at 3-5 year follow-up, which, relative to the largest expected change in BPF, accounts for 20%±19% (2-57%) error. Atrophy rates were overestimated in all cases, i.e. a significant reduction in atrophy rates was observed. Nonlinear models achieved significantly better fits than linear (robust) regression (p<0.01) (Fig.1).

A greater atrophy rate in the first year was associated with a higher number of attacks (r=0.4, p=0.048) (Fig.3). Interestingly those patients with accelerated atrophy showed a particularly strong nonlinearity in the progression, i.e. the BPF at 4-year follow-up was substantially greater than predicted by a first-year linear regression model, whereas for patients with fewer or no attacks this initial acceleration was not observed. We observed a positive correlation between the deviation (measured as standard error SE) from a linear atrophy progression and the number of attacks observed (r=0.5, p=0.035, N=21).

DISCUSSION

Strong nonlinearities in atrophy progression can lead to significant overestimation when extrapolating from 1-year data. The substantial individual differences in early atrophy rate and the association with attacks suggest that appropriate models of MRI morphometry may carry potential to identify patients at risk for more aggressive disease progression. Implications arise for trials/studies with linear BPF rates as outcome measure and follow-up intervals long enough for nonlinearities to express.
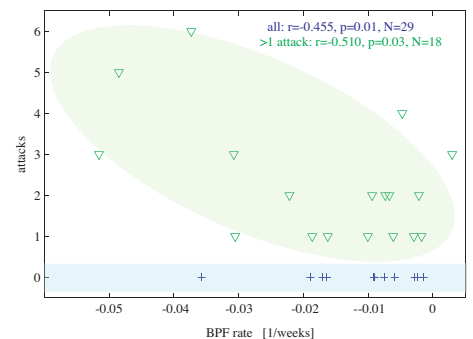

Fig.3: Relation between BPF rates and number of attacks recorded. A significant correlation between faster BPF rates and higher number of attacks is apparent. Those subjects with higher number of attacks also showed particularly strong nonlinearity in their atrophy progression, i.e. a more rapid initial BPF decline.

REFERENCES

1. Weiner HL *et al.*; J Neuroimmunol; 2000:104
2. Warfield S *et al.*; Academic Press; 1999