Quantitative MRI Phenotypes in Longitudinal Population of MS Patients.

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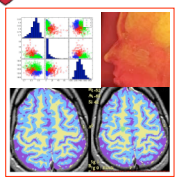

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CLIMB PATHWAYS TO CURING MS

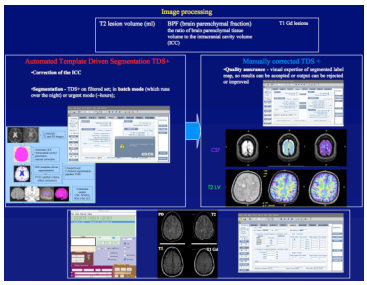
Introduction:

Magnetic Resonance Imaging (MRI) is an important part of diagnostic work-up and treatment monitoring of Multiple Sclerosis (MS) patients[1]. MRI volumetric measurements are widely used as outcome measurements in clinical trials[2,3]. Brain parenchyma fraction (BPF) or volume of brain normalized by intracranial cavity (ICC) represent MRI biomarker of brain atrophy. T2 weighted lesion volume (T2LV) represents MRI biomarker of inflammatory burden of MS disease. Their simultaneous unique combination and rate of change comprise quantitative MRI phenotype of the patient[4,5]. To reveal natural pattern of quantitative MRI phenotypes in longitudinal MS population under CLIMB study observational retrospective analysis was performed.

Methods:

Conventional Head MRI acquired at BWH 1.5T Signa GE scanners. MS legacy MRI protocol for brain segmentation required use of quadrature head coil and included axial dual-echo sequence TR3000/TE30/80ms; slice thickness 3 mm; resulting pixel spacing 0.937mm. MRI analysis (Fig.1) was performed through Oracle Database [6] with semi-automated TDS+ image processing pipeline[7,8,9,10]. Quality control of original MRI and manual correction of automatically generated segmentation maps were performed in 3D Slicer[11]. Intrarater reproducibility $\%COV^{BPF}$=0.1 ; $\%COV^{T2LV,ml}$=3. Expert readers were blinded to clinical status of the patients and MRI protocol. Matlab Statistics Toolbox was used for analysis.

Fig.1. MRI Analysis Work-Flow



Results:

2418 MRI acquired with same protocol of 387 patients with minimum 3 longitudinal timepoints were retrieved from MS Database on 09/09/2014 . Fig.2 shows demographic characteristics of longitudinal MS population.

Using linear fitting (Fig.3) with a separate-slopes model coefficient estimates for volumetric longitudinal trajectories of individual patients in total MS population (Table 1) were retrieved.

Cluster analysis was performed using following parameters: BPF(i,s,p), logT2(i,s,p), ICC(i,s), age at MRI (i,p), age at first diagnosis (i), age at first symptom (i), where intercepts (i), slopes (s), population marginal mean (pmm) estimated value at mean follow-up time 7.4 years.

Fig.2. A) Age of patients (colormap in RGB scale, years): 1. Age at first symptom; 2. Age at first diagnosis; 3. Age at baseline MRI; 4. Age at MRI follow-up time (ppm);

B) Histogramm of MRI follow-up time distribution in MS population.

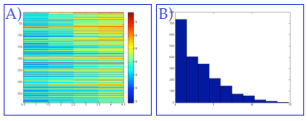


Fig 3. A) Prediction individual trajectory BPF curves (the fitted line) with confidence intervals (the dashed lines) for random individual patient at follow-up time from baseline MRI;

B) Analysis of covariance interactive graph of the per-patients quantitative longitudinal MRI biomarkers: BPF , logT2LV, ICC ml at follow-up time from baseline MRI;

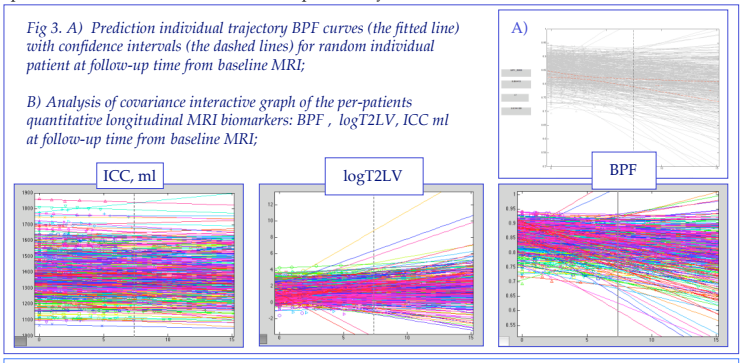


Table 1. Longitudinal MRI biomarkers of MS disease

Term	Estimate	Std. Err.	T	Prob>|T|	Term	Estimate	Std. Err.	T	Prob>|T|
LogT2LVi	1.342	0.008	162.968	0.000	BPFi	0.853	0.000	3052.010	0.000
LogT2LVs	0.027	0.004	6.061	0.000	BPFs	-0.004	0.000	-24.397	0.000

Results:

Dendrogramm of cluster tree (Fig.5) revealed natural grouping in MRI volumetric measurements of MS population, which was reduced to maximum 3 clusters (Table 2).

Fig.5. A) Dendrogramm plot of cluster analysis: pairwise distance between objects calculated with the Standardized Euclidean distance function (each coordinate in the sum of squares is inverse weighted by the sample variance of that coordinate). Inner squared distance method (minimum variance algorithm) are used to calculate linkage and create natural hierarchical cluster tree;

B) grouped plot matrix of variables for 3 clusters and histograms along the diagonals;

C) Interactive stepwise regression added BPFi,s; LogT2i,s; ICCi,p as statistical significant terms in a regression for T maxclust=3 partition of the data.

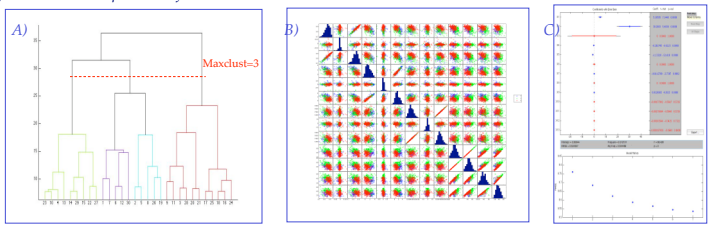


Table 2. Quantitative MRI biomarkers and demographic characteristics in cluster groups: A) baseline ; B) PMM at mean of follow-up time 7.4 years; C) Rates of changes per year

A)	Cluster 1	Cluster 3	Cluster 2
Age at MRI, yr	38(0.7)2	36(0.6)2	50(0.6)13
BPF	0.832(0.004)3	0.878(0.002)12	0.838(0.003)3
LogT2	2.25 (0.10)23	0.8(0.05)12	1.39 (0.07)13
ICC, ml	1352 (12)3	1430 (10)12	1378 (11)3

B)	Cluster 1	Cluster 3	Cluster 2
Age at MRI, yr	41(0.7)2	40(0.6)2	54(0.6)13
BPF	0.814(0.004)3	0.871(0.002)12	0.826(0.003)3
LogT2	2.51(0.09)23	0.84(0.05)12	1.43(0.07)13
ICC, ml	1345(12)3	1428(10)12	1375(11)3

C)	Cluster 1	Cluster 3	Cluster 2
N patients	81	156	150
F/M (%F)	63/18(77%)	112/44(71%)	111/39 (74%)
Age at first Symptom	28(0.7)2	31(0. 6)2	41(0.7)13
Age at first Diagnosis	32(0.7)2	33(0.6)2	45(0.6)13
BPF	-0.005(0.0008)3	-0.002(0.0003)1	-0.003(0.0002)
LogT2	0.084(0.018)23	0.009 (0.007)1	0.013(0.010)1
ICC, ml	-2 (0.3)23	-0.6 (0.2)1	-0.8 (0.2)1

Conclusions:

Our observations highlight distinct quantitative MRI phenotypes in longitudinal population of MS patients. It is unlikely that a single model could explain changes in the brain of MS population. Recent meta-analysis estimated annual rate for average MS patient receiving first generation disease modifying therapy drugs (DMT) or no DMT approximately 0.7% brain volume loss per year (0.1%-0.3% observed in normal aging) [12] . Despite limitations of current analysis (linear modeling, interrater reliability estimation et ctr), trajectories of brain atrophy and MS lesions burden, establish normative reference of quantitative MRI biomarkers in MS population for monitoring effects of neuroprotective treatment.

Quantitative MRI phenotypes can be applicable as surrogate end point in clinical trials including Progressive MS to increase sensitivity to detect changes as well as in defining no evidence disease activity (NEDA) patients. Further research is necessary to account for confounding factors (active lesions, gender) and integration of quantitative MRI phenotypes with clinical and biomarkers data.

References:

1. F. Barkhof (2011); 2. S.Khoury (1994); 3. H.Weiner (2000); 4. Bielekova (2005); 5. C.Guttmann (2006); 6. http://cni-boston.org; 7. S.Warfield 2000; 8. S.Wells (1996); 9. L.Lew (2005); 10. X.Wei (2002); 11. http://www.slicer.org; 12. Vollmer (2014).

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