Serial MRI in Epidemiology: Seasonal Occurrence of New MS Lesions

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INTRODUCTION

The use of serial MRI for studies of epidemiological scope is explored on the example of measuring seasonal variation of multiple sclerosis (MS) disease activity. New T2 lesion occurrence was measured in an untreated cohort of MS patients over a one-year period and used to build a likelihood function for the seasonal modulation of MS disease activity. Several plausible theories for such seasonal modulation exist, including evolutionary predetermined changes in immune system reactivity, vitamin D fluctuations from solar radiation, or season-specific exposure to viral and bacterial antigens. Only three studies thus far exist that investigated seasonal effects [1-3]. Only one of them found significant variation in MRI activity, but may be subject to significant observational bias due to limited follow-up and the use of contrast enhancing lesions (CEL) as surrogate for disease activity[1]. From a methodological standpoint, we hypothesize that the use of serial MRI, particularly PD/T2-weighted, provides better sensitivity and less susceptibility to observation bias from infrequent sampling than contrast enhanced MRI. Serial T2 MRI provides an integrated view of disease activity, whereas CEL are present for 2-3 weeks only or less [4, 5].

METHODS

Weekly to monthly MRI was obtained from 44 MS patients over one year (876 exams total). The MRI protocol comprised an axial dual echo protocol (PDw/T2w, TE 30/80 ms, TR 3000 ms, 0.93x0.93x3 mm^3 nominal voxel size), followed by a T1-weighted conventional spin-echo, after injection of a 10 ml intravenous bolus of 0.5M Gd-DTPA (TE=19ms, TR=600ms, 0.93×0.93×4 mm^3 nominal voxel size), acquired on a 1.5-Tesla machine (GE Signa, General Electrics, Milwaukee, WI). Cohort characteristics are summarized in [6]. New T2 activity was detected visually from coefficient of variation maps of temporal MR intensity change, derived from methods described in [7]. A seasonal likelihood function was calculated by distributing each lesion count according to the length of the follow-up interval (1-4 weeks). Several forms of normalization and validation were applied to scrutinize against observational or selection bias. For statistical comparison between seasons, a Monte-Carlo simulation was employed to assign a unique date to each new lesion observation based on the associated follow-up interval.

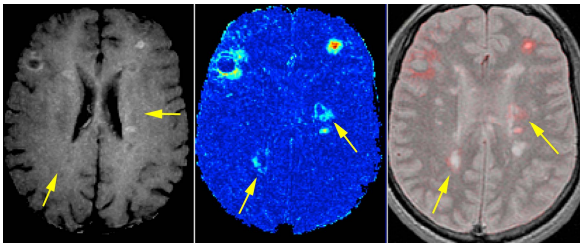

Fig.1: Example shows maximum intensity projection of all activity over 3 months with Gd-DTPA (left) and PD-weighted change (center & right) with monthly intervals. Several activity loci missed by the contrast scan are captured by the PD change.

RESULTS

T2-change showed better sensitivity for the detection of change than contrast-enhancing lesion counts (Fig.1). The likelihood function of new lesion rate and active scan rate showed marked peaks during the summer months (Fig.2). The peaks persisted when splitting the cohort randomly, validating against significant selection bias in the result. Results of 300 Monte-Carlo simulations showed robust and significantly higher level of activity in spring and summer compared to fall and winter (Kruskal-Wallis, p=0.01). The number of CEL, on the other hand, did not show the same modulation (Fig.3).

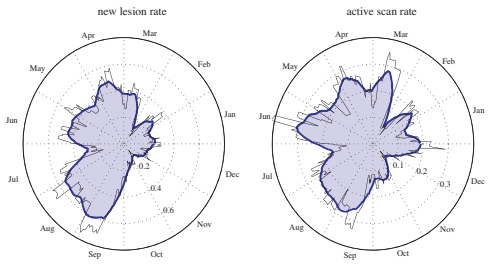

Fig.2: Polar plots of seasonal likelihood for new lesions and active scans. Significantly higher rates of disease activity in spring/summer compared to autumn/winter are apparent. "active scan" rates reflect relative counts of exams with one or more new lesions

DISCUSSION

A significantly increased levels of MS disease activity during spring and summer, as observed here, agrees with findings from clinical variables [8, 9]. This is the first time to our knowledge where a clear seasonality of MS disease activity has been demonstrated on non-contrast MRI, which advocates the use of T2 change as a more robust surrogate for disease activity rather than CEL counts, because it provides sensitivity that is both higher and not as dependent on follow-up interval length. We believe the observed T2 change is a preferable contrast for epidemiological questions with a longitudinal component, because new T2 lesions leave a residual hyperintensity that can be observed several weeks to months after the initial event, thereby providing a variable that is less subject to observation bias. These results hold important implications for the design and interpretation of clinical trials assessing treatment efficacy with MRI-visible activity as outcome measure, which are common-place in MS. Particularly, using CEL as surrogate for disease activity may result in biased outcomes depending on the timing of the trial and control arms relative to the seasons. The use of new T2 lesions in lieu of CEL holds considerable advantages and should be seriously considered in its application to clinical trials [10, 11].

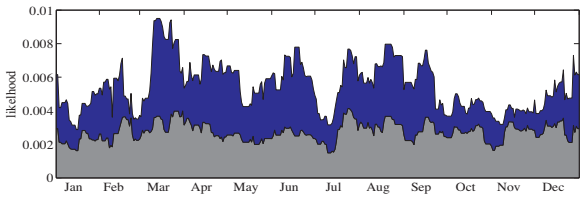

Fig.3: Comparison of likelihood functions for disease activity, derived from contrast-enhancing lesion counts (gray) and new T2 activity (blue). Only the T2 activity did provide sensitivity to isolate the seasonal effects.

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