Registration and subtraction of 2D-T2SE images in a routine multicentre multiple sclerosis (MS) trial setting

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Introduction

In phase III clinical MS trials MRI indices are used as a secondary endpoint to monitor treatment effect. Detection of new or enlarging T2 lesions on consecutive MRI scans is a labour-intensive process, complicated by repositioning errors and a background of unaltered non-active lesions. The change in overall T2 lesion load is calculated by subtracting the lesion loads of two consecutive time points. This is quite labour intensive and inefficient when the change is relatively small, furthermore the accuracy with which the change can be determined is affected by errors in measuring the two lesion load volumes. Thirdly, overall disease activity may be underestimated as positive and negative disease activity may cancel each other out. Subtracted images provide an alternative that was deemed reliable, time efficient and informative in an earlier study (1) but has not been tested in a multi-centre trial . Our goal is to explore the feasibility and sensitivity of registration and subtraction in detecting active lesions and lesion load change in the setting of a multi-centre trial.

Patients&Methods

Serial MR images were selected from a trial examining the effects of interferon beta-1b on progression from clinically isolated syndromes (CIS) suggestive of MS to clinically definite MS (BENEFIT). 46 pairs of scans were randomly selected from 41 patients, scans originated from 8 different participating sites. This sample was stratified for the number of lesions and enhancement status at baseline. The MRI protocol included 3 mm interleaved dual-echo T2-weighted scans obtained at 3-monthly intervals.

Pre-processing/registration

Several pre-processing steps were implemented to homogenize the quality of the data, including slice-to-slice intensity differences, bias field and global scaling. For each pair of scans, spatial normalization (registration) was performed using a mutual information criterion and images were resliced to the halfway position using an automated intensity-based registration algorithm with a mutual information criterion and spline interpolation (2). Intra-scan intensity normalization (bias field correction) was applied using the non-parametric method N3 (3). Inter-scan intensity normalization (scanner drift correction) was applied based on the method described in (4).

Image Analysis

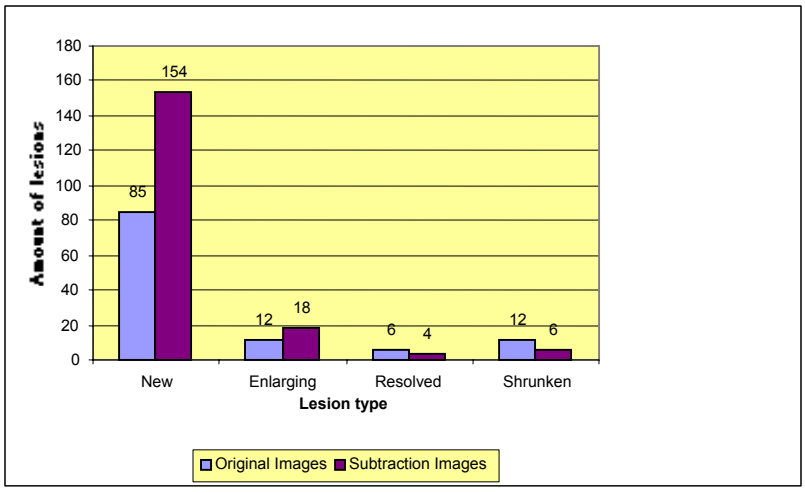
The original baseline, the original follow-up and subtraction images (calculated from registered images) were analyzed by a single observer for active T2 lesions and total lesion loads. To determine the time spent on native space analysis and registered space analysis a handheld stopwatch was used. Lesions were defined as new or enlarging (positive activity) or resolved or shrunken (negative activity). A change of 50% in size was used to define a change in size for enlarging or resolving lesions. Artefacts on the subtraction images were identified by simultaneously viewing registered baseline and follow-up scans (Figure 2).

Results

The number of lesions detected are shown in Figure 1. On the subtracted images 77% more active lesions (positive change) were detected in about two-third of the time (2h15m48s compared to 3h21m30s). The biggest gain was perceived in the detection of juxtacortical lesions especially near the vertex. Negative disease detection was decreased by 56%. The latter might be the result of the limitations of the human eye to discern black spots (negative change) on a dark gray background.

Discussion

Subtraction of registered images is a fast and sensitive technique for depicting positive disease activity in MS. To improve the detection of negative disease activity a two-way colour scheme can be adopted to improve the contrast between lesions and background. A second rater will be added to investigate interobserver agreement that is notably poor using non-registered, non-subtracted images and is expected to be better for the registration/subtraction scheme used here.



References

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2. Maes et al. Med Image Anal 1999;3:373-86
3. Sled et al. IEEE Trans Med Imaging 1998;17:87-97
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Figure 1 (Left). Note the increased detection of positive change (new and enlarging lesions) on the subtracted images

Figure 2 (Below). From left to right the original baseline, the original follow up and the subtracted image (calculated from registered images). Note the 3 new juxtacortical lesions near the vertex.