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Brain atrophy and lesion load measures over one year relate to clinical status after 6 years in patients with clinically isolated syndromes

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Abstract

Background Conventional MRI lesion measures modestly predict long term disability in some CIS studies. Brain atrophy suggests neuroaxonal loss in MS with the potential to reflect disease progression to a greater extent than lesion measures.

Objective To investigate whether brain atrophy and lesion load, during the first year in patients presenting with CIS, independently predict clinical outcome (development of MS and disability at 6 years).

Methods Ninety-nine patients presenting with CIS were included in the study. T1 gadolinium-enhanced and T2-weighted brain MRI was acquired at baseline and approximately one year later. Percentage brain atrophy rate between baseline and follow-up scans was analyzed using SIENA.

Results Mean annual brain atrophy rates were -0.38% for all patients, -0.50% in patients who had developed MS at six years and -0.26% in those who had not. Brain atrophy rate ($p=0.005$) and baseline T2LL ($p<0.001$) were independent predictors of CDMS. Whilst brain atrophy rate was a predictor of EDSS score in a univariate analysis, only one-year T2LL change ($p=0.007$) and baseline gadolinium-enhancing lesion number ($p=0.03$) were independent predictors of EDSS score at 6-year follow-up. T1 lesion load was the only MRI parameter which predicted MSFC score at the six year follow-up.

Conclusions The findings confirm that brain atrophy occurs during the earliest phases of MS and suggest that one-year longitudinal measures of MRI change, if considered together with baseline MRI variables, might help to predict clinical status six years after the first demyelinating event in CIS patients, better than measurements such as lesion or brain volumes on baseline MRI alone.

Introduction

Multiple sclerosis (MS) is a chronic disorder of the central nervous system (CNS), characterized pathologically by multifocal areas of inflammatory demyelination that evolve in the CNS over time (multiphasic), and clinically by a variable course, although most patients develop significant locomotor disability 15–30 years after onset.[1-4] In approximately 85% of patients who develop MS, clinical onset is characterized by an acute or subacute episode of neurological disturbance (e.g., optic neuritis, or an isolated brainstem or partial spinal-cord syndrome) due to a single lesion within the CNS, and is known as a clinically isolated syndrome (CIS).[2, 3]

Magnetic Resonance Imaging (MRI) is a well-established investigatory tool with a diagnostic and prognostic role in MS, and is increasingly used to provide outcome measures in therapeutic trials.[5-13] Follow up studies ranging from seven to 20 years investigating the prognostic role of MRI in CIS patients [2] have shown that clinically definite MS (CDMS) develops in approximately 60–80% of CIS patients with abnormal MRI, but in only approximately 10-20% who have normal MRI.[14-16] However, conventional MRI measures have correlated less consistently with future disability.[14, 17, 18]

Brain tissue loss (atrophy) is thought to reflect the underlying permanent neuroaxonal damage in MS, and hence is seen as a plausible measure of disease progression. Brain atrophy occurs in CIS patients [19-21], however, few studies have investigated the relative predictive values of early brain atrophy rates and lesion load measures for longer term clinical outcomes – the development of MS and disability.

The utility of longitudinal rather than single time point MRI measures as predictors of future clinical outcome also warrants investigation. A recent 20-year follow-up study from CIS onset demonstrated significant relationships between the rate of lesion load accumulation and clinical evolution [17] but sampling of MRI data in this study was at relatively long (approximately five-yearly) intervals.

The aim of the present study was to investigate, in a cohort of CIS patients who were followed up at regular intervals with clinical and MRI assessments, whether brain atrophy rate or lesion load measures obtained at baseline and over the first year following presentation were independently predictive of MS diagnosis and disability six years after the first demyelinating event suggestive of MS. In particular, we wanted to investigate whether additional predictive information is provided by: (i) measuring brain atrophy in addition to lesion load measures, and (ii) including longitudinal MRI measures in addition to single baseline time-point measures. This study included a cohort of patients with CIS with longer clinical follow-up than many previous studies (six years after the first demyelinating event).

Subjects and Methods

Subjects

Ninety-nine patients (36 males, 63 females) were identified from a longitudinal clinical and MRI research study of subjects presenting with a CIS suggestive of MS, being undertaken at the Institute of Neurology, University College London, Queen Square, London, United Kingdom between 1995 and 2007. The original prospective study included 178 patients but only patients who had both a baseline and one year scan, and had been followed up clinically at six years were included in the present retrospective analysis. The group of 99 patients selected was not significantly different from the whole cohort with regard to its baseline characteristics (gender, age, presenting symptoms, lesion loads). A CIS was defined as a single event of acute onset in the central nervous system suggestive of

demyelination, for example, unilateral optic neuritis, brain stem and partial spinal cord syndromes.

Ethical approval for the longitudinal study was obtained from the Joint Medical Ethics Committee of the Institute of Neurology and National Hospital for Neurology and Neurosurgery, University College London, and the Moorfields Eye Hospital Ethics Committee. In addition, written informed consent was obtained from all study participants and all patients underwent appropriate clinical and laboratory investigations to exclude alternative diagnoses.

At baseline 76 patients presented with optic neuritis, 13 with a brain stem syndrome, nine with a spinal cord syndrome and one with a visual field defect due to an optic tract lesion. The age at baseline ranged from 18 to 51 years with a median age of 32 years. All patients had a clinical follow-up approximately six-years from baseline (median 6.5 years, range 3.6-10.2) when they were evaluated for a diagnosis of clinically definite MS (progression from CIS).[7, 22] If patients were diagnosed with MS, the time that they were diagnosed was also determined (months from baseline). Patients had additionally been assessed at intermediate time-points (3 months, 1-year and 3-years from baseline) as part of the prospective study, which aided in this task. The median time to conversion to CDMS was 12 months (range 2-120), with 21 patients converting to MS before the 1 year scan. Only two of these patients started disease-modifying treatment before the 1-year MRI scan. The Expanded Disability Status Scale (EDSS) [23] and the Multiple Sclerosis Functional Composite (MSFC) [24] were also recorded at six year clinical follow-up in order to assess disability. Whilst all the patients were scored with the EDSS while only 64 patients were scored with the MSFC.

MRI acquisition

All patients had T1- and T2-weighted brain MRI at baseline and approximately one year later (median 12 months; SD, 3.06; range 10-25). Baseline MRI was performed within 12 weeks of symptom onset in

patients with CIS (median 4.5 weeks; SD, 2.9; range 1-12). MRI was acquired on a 1.5 Tesla GE Signa Horizon Echospeed scanner (General Electric Medical Systems, Milwaukee, WI, USA). Axial T1-weighted images were acquired post-Gadolinium-DTPA (Gd) (0.1mmol/kg) using a conventional spin echo sequence with acquisition parameters TR=600ms, TE=17ms, matrix 256x256, flip angle 90°, FOV 240x180mm, resulting in 46 contiguous 3mm thick slices. In addition axial dual echo PD and T2-weighted images were acquired using a fast spin echo sequence with acquisition parameters TR=3200ms, TE=19/95ms, matrix 256x256, flip angle 90°, FOV 240x180mm, resulting in 46 contiguous 3mm thick slices.

MR data analysis

Images were transferred to a SUN workstation (Sun Microsystems, Inc., Santa Clara, CA) for brain atrophy analysis. Percentage brain volume change (PBVC) between baseline and one year was estimated from T1-weighted images with SIENA (Structural Image Evaluation, using Normalisation, of Atrophy [25]), part of FSL (www.fmrib.ox.ac.uk/fsl). Median control scan-rescan error in SIENA measurements has been reported to be 0.15%. [25] SIENA starts by extracting brain and skull images from the two-timepoint whole-head input data. [26] The two brain images are then aligned to each other [27, 28] (using the skull images to constrain the registration scaling); both brain images are resampled into the space halfway between the two. Next, tissue-type segmentation is carried out [29] in order to find brain/non-brain edge points, and then perpendicular edge displacement (between the two timepoints) is estimated at these edge points. Finally, the mean edge displacement is converted into a (global) estimate of percentage brain volume change between the two timepoints. T1-weighted images did not always include full coverage of the brain, sometimes excluding the vertex. Thus, in order to correct for small differences in the portion of the brain imaged, a standard-space based limit of +60 along the Z-axis was used for each image pair.

In the cohort analysed in this study, the initial automated brain and skull extraction was optimized by using the robust brain centre estimation function. Subsequently, the brain extractions were checked, and manual editing was performed when non-brain regions were still included around the optic nerves, eyes and temporal lobes. Manual editing was performed using the DispImage image analysis package (D. Plummer, University College London Hospitals NHS Trust, UK) [30] by a single operator (MDF) who was blinded to subject identity. Thirty-five patients required manual editing, of which 24 required manual editing on both baseline and repeat scans. The final SIENA output was assessed for all subjects by another expert operator (VMA) who was blinded to subject identity, and who rated scan pairs according to the quality of the scans and registration of images.

In addition to brain atrophy rate, T1- and T2-weighted lesion volumes at baseline were calculated, and baseline Gd-enhancing lesion number was determined. T1 hypointense lesions count included both enhancing and non-enhancing lesions. Follow-up brain scans were also utilized to determine T2-weighted lesion volume at one year and thus to calculate the one-year change in T2 lesion volume. All lesions were outlined in DispImage using a semiautomated local thresholding technique or, where necessary, by manual outlining using a mouse-driven cursor. A computer program summed all the individual lesion volumes (calculated as the surface area of each lesion multiplied by the slice thickness (3mm), and total T2 hyperintense and T1 hypointense lesion volumes were generated.

Statistical analysis

Data were analyzed using Stata version 9.2 (Stata Corp, College Station, TX). All PBVC measures were annualized prior to statistical analysis. Differences in variables between patients who had developed MS by six year follow-up and those that remained CIS were examined using unpaired *t*-tests

and Fisher's exact test. In addition, Cox regression analysis of time to MS diagnosis was used to determine which MRI variables were independently related to CDMS development.

Ordinal logistic regression analysis was performed to determine which MRI variables were related to disability at the six year time-point as assessed by the EDSS. EDSS measurements were categorized into five groups as follows: EDSS = 0, EDSS = 1, EDSS = 1.5-2, EDSS = 2.5-3, EDSS greater than 3. These groups were chosen as they were considered to represent different levels of disability. Linear regression analysis was used to determine which MRI variables were related to disability at six year follow-up as assessed by the MSFC.

The following MRI variables were considered for inclusion as potential predictors in all regression analyses: baseline T1 lesion volume, baseline T2 lesion volume, baseline Gd-enhancing lesion number, and T2 lesion volume change and PBVC between baseline and one year. Age and gender were also included as covariates. A manual backwards selection procedure was used to determine which variables were included in the final regression models.

Results

Seven scan pairs were considered to be of unacceptable quality, due to motion artefacts on either the baseline or repeat scans, and were thus excluded from the statistical analysis.

The mean baseline to one-year brain atrophy rate for the remaining group of 92 CIS patients was found to be $-0.39\% \text{ year}^{-1}$ (SD 0.55). The mean T1 and T2 lesion volumes at baseline were, respectively, 337.6mm^3 (SD 868) and 2023.5mm^3 (SD 4015). The mean number of Gd-enhancing lesions in the baseline scan was 1.54 (SD 3.7). Thirty-one patients had at least one Gd-enhancing lesion whilst 61

patients had no Gd-enhancing lesions. The mean increase in T2 LL between baseline and the one year was 1232.3mm^3 (SD 4399).

Relationship between MRI variables and conversion to CDMS.

At the six-year follow-up 49 patients (53.3%) had developed clinically definite MS, while 43 subjects (46.7%) remained CIS. The median EDSS was 1 (range 0 to 8.5) and only 10/92 (11%) had an EDSS>3, indicating significant disability. Of the 49 patients diagnosed with MS, 45 had an abnormal T2-weighted MRI scan at baseline, whilst of the 43 subjects remaining CIS, only 23 had an abnormal T2-weighted MRI scan at baseline (Fisher's exact test $p<0.001$). Mean brain atrophy rates were significantly different between patients who had developed MS and those who had not (respectively, $-0.50\% \text{ year}^{-1}$ (SD 0.63) versus $-0.26\% \text{ year}^{-1}$ (SD 0.42), mean difference $-0.24\% \text{ year}^{-1}$ (95% CI 0.02-0.46), $p=0.035$) (**Figure 1**). Considering only the patients who had an abnormal MRI scan at baseline, mean atrophy rates were $-0.23\% \text{ year}^{-1}$ (SD 0.4) in patients who had not converted to MS, and $-0.52\% \text{ year}^{-1}$ (SD 0.63) in patients who had converted to MS ($p=0.04$, mean difference $-0.29\% \text{ year}^{-1}$ (95% CI -0.01 to -0.57).

Cox regression analysis gave brain atrophy rate and baseline T2 lesion volume as the only independent risk factors for MS diagnosis. The risk (hazard) of diagnosis with MS was reduced by 33.8% (95% CI 12.0% to 50.2%, $p=0.005$) for each SD lower (i.e. less negative) atrophy rate, and increased by 45.6% (95% CI 18.2% to 79.4%, $p<0.001$) for each SD higher baseline T2 lesion volume.

Relationship between MRI variables and disability measures at 6 years.

All patients had EDSS measurement at six year follow-up while only 64 patients had been assessed on all the individual components of the MSFC. Although univariate ordinal logistic regression gave

baseline to one year PBVC as a significant predictor of EDSS score at six years, with 41% ($p=0.008$) reduced odds of higher EDSS per SD lower atrophy rate (**Figure 2**), multiple ordinal logistic regression showed that PBVC did not predict EDSS independently of other MRI measures; baseline to one-year change in T2-lesion load and baseline Gd-enhancing lesion number were the only independent predictors of EDSS score at six years. The odds ratio of having a higher EDSS score was 2.21 for each SD higher T2 lesion volume change over the first year (95% CI 1.23 to 3.97, $p=0.007$), and was 1.73 for each SD higher Gd-enhancing lesion number at baseline (95% CI 1.05 to 2.84, $p=0.030$). When patients were divided into only three subgroups according to the degree of disability (“none” (EDSS 0, $n=27$), “minimal” (EDSS >0 and <3 , $n=78$), and “significant” (EDSS ≥ 3 , $n=22$)) univariate regression analysis showed that PBVC remained a significant predictor of disability ($p=0.005$). In the subset of 64 patients who were scored with the MSFC, univariate regression analysis showed that baseline to one year PBVC was not a significant predictor of either MSFC at six years ($p=0.309$) or its single components (25-foot timed walk, $p = 0.340$; nine-hole peg test, $p = 0.567$; PASAT, $p = 0.931$). However, in this same subgroup of 64 patients, brain atrophy rate was no longer a significant predictor of EDSS score at six year follow-up ($p=0.08$). T1 lesion load was the only MRI parameter which was found to be predictive of MSFC score at six year follow-up ($p=0.005$).

Discussion

Our study confirms that brain atrophy occurs early in patients with MS, and that it is an independent prognostic factor for the development of CDMS in patients with CIS. Although brain atrophy rate was a significant predictor of disability after six years in patients presenting with a CIS, this was not independent from the other MRI measures taken into account. However, another longitudinal MRI measure, the change over one year in T2 lesion volume, was an independent predictor of subsequent disability in this cohort of CIS patients, together with the baseline number of Gd-enhancing lesions,

suggesting that longitudinal measures of MRI change, if considered together with measurements from baseline MRI, may better predict clinical outcome for patients presenting with a CIS.

Development of clinically definite MS

Our results confirm previous studies showing that brain atrophy rates are higher in those CIS patients who subsequently develop MS compared with those who remain CIS. [14, 20, 21, 31, 32] In the placebo arm of the ETOMS (early treatment of multiple sclerosis) trial the mean PBVC in over 100 patients with CIS was found to be -0.83% during the first year.[33] In the same study a difference in median annual PBVC was found between patients who developed CDMS versus patients who did not (-0.92% and -0.56%, respectively).[33] Although the atrophy rates in that study are slightly higher than those found in our study, one possible explanation is that all subjects in the ETOMS trial had a positive baseline brain MRI scan (at least four T2 lesions or at least three T2 lesions if at least one was infratentorial or enhancing after Gd injection), compared with our unselected cohort of CIS patients. However, analysis of only those patients with four or more lesions in the current study, gave atrophy rates that were still noticeably smaller than those in the ETOMS study (data not shown). This may be the result of different image acquisition methods and different standard-space limits for the brain in the SIENAX analysis.

A new finding in the current study was that brain atrophy emerged as an independent predictor of MS development (in addition to T2 lesions). Thus, inclusion of both brain atrophy and lesion load measures in therapeutic trials that aim to prevent the evolution from a CIS to CDMS may provide complementary and relevant information. Future studies of atrophy following CIS might usefully investigate changes in grey matter specifically, since there is evidence that most of the brain atrophy seen following a CIS and in early relapsing remitting MS occurs in grey matter.[21, 34, 35]

Development of disability

To date, few studies have investigated the relative predictive value of lesion load and brain atrophy measures for disability in CIS patients with a relatively long clinical follow-up. Therefore a key focus of our study was to investigate the relationship of MRI measures, including atrophy rate, with subsequent disability, measured six years after the first clinical episode. In the current study, despite the univariate association of brain atrophy rate with EDSS score, when considering other MRI lesion measures in addition, it did not predict disability independently from these variables. The change over one-year in T2 lesions load and baseline Gd-enhancing lesions number were found to be the only independent predictors of EDSS score at six years in our cohort of CIS patients. This result suggests that longitudinal but still relatively early (one year) measures of MRI lesion load change, representing a “dynamic” parameter of disease evolution, might predict disease progression and disability better than single baseline lesion measures alone.

A previous study in patients with established relapsing remitting MS reported that brain atrophy rate over two years was a predictor of disability after eight years.[36] It may be that over time, as the disease duration and disability increase and pathological changes become more widespread and complex, the predictive value of different imaging measures will change. Few patients had acquired significant disability (with an EDSS of more than 3) at the 6-year follow up in our study. A longer period of observing atrophy following a CIS (e.g. 2 or 3 years) may also be informative. Further follow up of our CIS group should help to elucidate this issue.

We did not find any association between brain atrophy rate and either total MSFC score or its single components measuring leg, arm and cognitive functions. However, only a relatively small number of

patients had MSFC measurements at the six-year time point, and the smaller sample size might have negatively influenced the research of a statistical association between the two parameters. This conclusion is also supported by the fact that in the same subgroup of patients, the association between brain atrophy and EDSS score was not significant. These somewhat inconsistent findings also highlight the complexity of factors to consider when investigating the relationship between a global brain atrophy measure and permanent disability in MS. For example, disability evident on clinical assessment may be limited when neuroaxonal damage causing atrophy occurs in clinically silent areas or does not reach a clinically relevant threshold; and cortical reorganization may also reduce disability in spite of neuroaxonal loss. It is also worth noting that a crucial role in the determination of disability might be played by the presence of spinal cord lesions [37] and spinal cord atrophy.[38] Thus, the study of the association between brain atrophy and disability might be further complicated by the presence of spinal cord damage.

Several limitations of the study must be noted. Firstly, due to the nature of prospective studies, not all patients were followed-up clinically at exactly six-years or had their repeat MRI scan at exactly one-year. However, this affected only a minority of patients and we believe that this should not detract from our finding of an association of brain atrophy rate (all brain atrophy measures were corrected for scan interval) with the development of MS at some point in the future. Secondly, some patients (21) were included in the analysis that converted to MS before the one-year repeat scan. However, we feel that exclusion of these patients would have biased the results to those patients who had a less severe disease course. Any bias that may be introduced by including these patients in the analysis is extremely unlikely as both brain atrophy and T2 lesion load plausibly increase at a fairly steady rate during the first year, rather than suddenly changing after conversion. Thirdly, the effect of disease-modifying treatments in limiting the evolution of brain atrophy has been demonstrated [39, 40], whilst steroid

treatment has been shown to decrease brain volume after administration.[41] Although two patients started treatment with a disease-modifying agent before the 1-year MRI scan, this is unlikely to have influenced brain atrophy during this time, or significantly impact on the measurement of brain atrophy rate in the whole cohort of CIS patients. Due to the nature of the study, patients were scanned as close to the initial CIS as possible, and some patients may have been on steroid treatment. This may have resulted in a pseudo-increase in brain volume at follow-up. Indeed 21 patients were found to have an increase in brain volume after one year. A pseudo-increase in volume may also have been due to the presence of Gd-enhancing lesions at one-year follow-up. Conversely, pseudoatrophy may also have been detected due to the presence of Gd-enhancing lesions at baseline, and these factors should always be taken into account when interpreting the results of brain atrophy studies.

In summary, our study indicates that brain atrophy is a feature of CIS patients who develop MS. Measurement of brain atrophy should be a useful supportive endpoint in trials of disease-modifying agents aimed at preventing CDMS development and disability in patients with CIS suggestive of MS. The study also suggests that longitudinal measures of MRI change, such as brain atrophy rate and change in T2 lesion load volume, if considered together with baseline MRI variables, might improve the prediction of future clinical status in CIS patients better than baseline, single time-point MRI measurements alone.

Figure Legends

Figure 1. Box-and-whisker plot showing the median (central line), interquartile range (box), 2.5 and 97.5 centiles (whiskers) and outliers (circles) for baseline to 1-year percentage brain volume change (PBVC) in CIS patients remaining CIS or developing CDMS by six year follow-up.

Figure 2. Box-and-whisker plot showing the median (central line), interquartile range (box), 2.5 and 97.5 centiles (whiskers) and outliers (circles) for baseline to 1-year percentage brain volume change (PBVC) in CIS patients, according to EDSS score at six-year follow-up.

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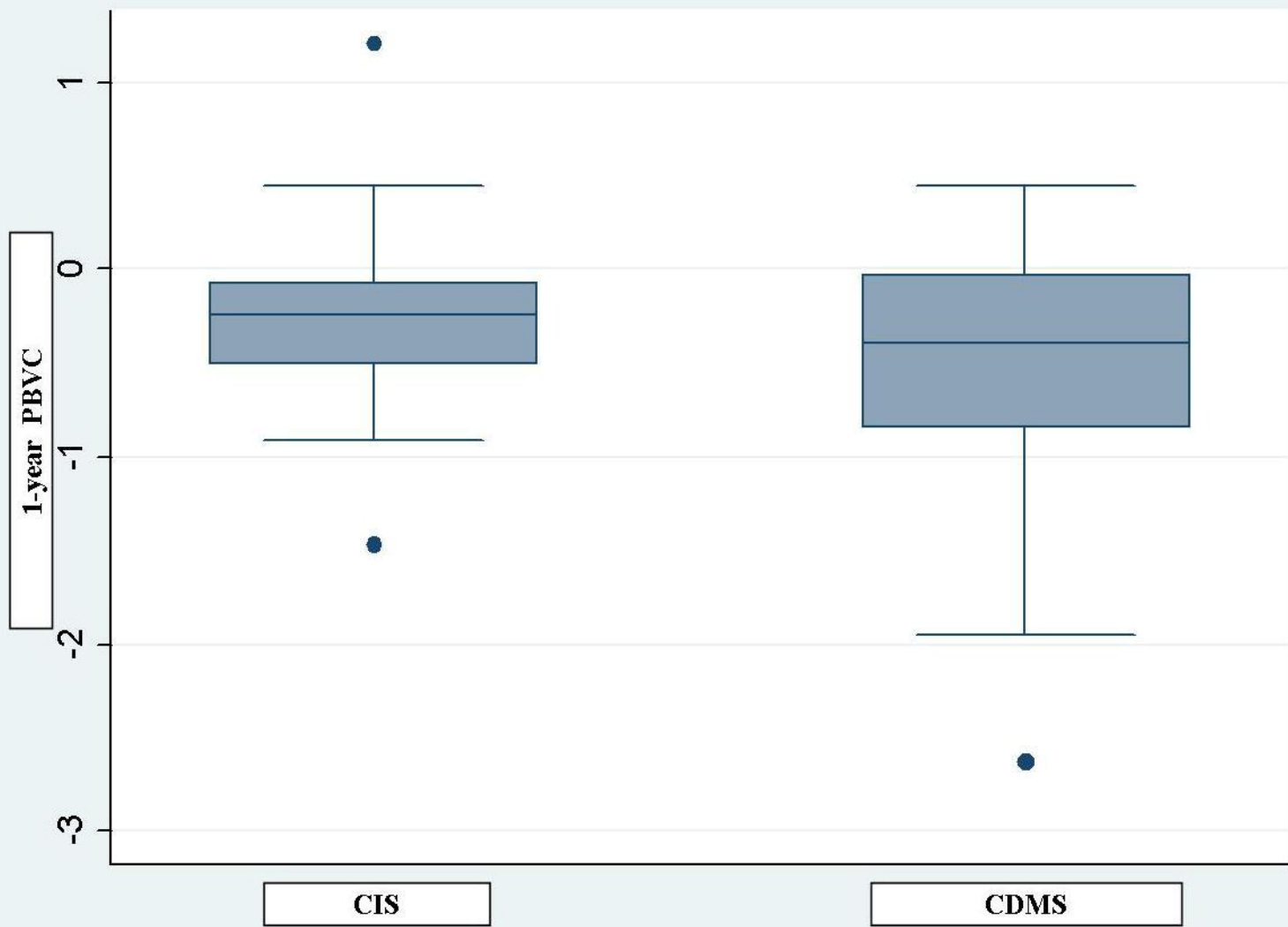
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1-year PBVC

1
0
-1
-2
-3

EDSS=0

EDSS=1

EDSS=1.5-2

EDSS=2.5-3

EDSS > 3

