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Relationship between gray matter volume and cognitive learning in CIS patients on disease-modifying treatment

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ABSTRACT

Background: Repeated administration of Paced Auditory Serial Addition Test (PASAT) results in a considerable learning effect in short- or long-term follow-up studies. However, the relationship between PASAT learning and changes in magnetic resonance imaging (MRI) parameters is yet to be investigated.
Objectives: The aim of this study is to determine if change in brain MRI metrics predicts evolution of PASAT in high functioning clinically isolated syndrome (CIS) patients on disease-modifying treatment (DMT).
Methods: This prospective 48-month observational study examined 128 CIS patients treated with 30 μg of intramuscular interferon beta-1a once a week. The correlation between PASAT and MRI measures was assessed at baseline, at 6 months and then annually over the 48-month follow up. Linear mixed model analysis adjusted for age, gender, education and DMT was used to model the temporal association between MRI measures and PASAT performance.
Results: MRI revealed 2.5% gray matter (GM) volume loss and 4.3 point increase in PASAT score over 48 months. MS patients evidenced significantly greater PASAT score absolute change, had lower loss of GM volume ($p = .008$) but not significant change in cortical ($p = .061$), white matter ($p = .086$) or whole brain volumes ($p = .879$).
Conclusions: The present study reveals a significant relationship between higher PASAT learning effect and less GM atrophy in CIS patients on DMT. These findings suggest that change in PASAT associated more with GM than WM pathology, and that treatment strategies oriented toward GM volume preservation may play an important role in prevention of cognitive deterioration in CIS patients.

1. Introduction

Although less common than in multiple sclerosis (MS), cognitive impairment (CI) is also detected in patients with clinically isolated syndrome (CIS), with prevalence estimates ranging from 11 to 57 % [1–3]. The core domains of memory and information processing speed are affected most often [4–6]. CI is an important determinant of employment status and associated societal costs [7,8], and adversely affects social functioning, coping, quality of life and treatment adherence of MS patients [9].

The Paced Auditory Serial Addition Test (PASAT) is widely used to assess CI in MS clinical trials [10,11]. Learning (or practice) effects on PASAT are well known, even during the first years of cognitive testing [12]. Interestingly, a recent study showed that the learning effect resulting from repeated PASAT administration was increased in patients undergoing disease modifying treatment (DMT) [13,14].

However, cross-sectional designs of previous neuroimaging studies have not allowed the investigation of the relationship between temporal changes in PASAT score and change in volumetric MRI. Therefore, MRI correlates associated with the beneficial effect of DMT on the PASAT learning effect [14] in CIS subjects are still to be elucidated.

In this context, an association between PASAT performance and MRI outcomes was shown in cross-sectional studies in patients with relapse-remitting multiple sclerosis (RRMS) [15–19]; however this relationship has not been reported consistently in CIS patients [20,21].

The objective of this longitudinal study was to investigate the evolution of PASAT performance and its relationship to white matter (WM) and gray matter (GM) pathology in CIS patients treated with DMT.

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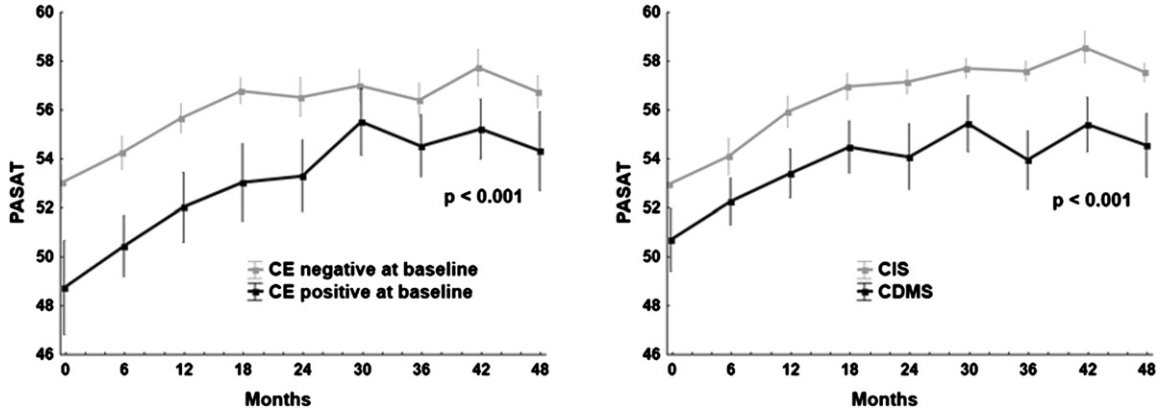

Fig. 1. Temporal changes in Paced Auditory Serial Addition Test scores and score absolute changes by contrast-enhancement positivity at baseline and conversion to clinically definite multiple sclerosis in clinically isolated syndrome patients.

2. Methods

2.1. Study population

SET was an investigator-initiated, prospective observational clinical study that involved 8 centers in the Czech Republic (clin.gov # NCT01592474) [19,20]. CIS patients were enrolled between 2005 and 2009 and included subjects between 18 and 55 years of age within 4 months from the initial clinical event, with an Expanded Disability Status Scale (EDSS) [22] score of 3.5 or less, who displayed the presence of two or more T2-hyperintense lesions on diagnostic MR images, and had two or more oligoclonal bands in cerebrospinal fluid obtained at the screening visit prior to steroid treatment [23,24]. The exclusion criteria for the SET study were lack of clinical and MRI follow-up data after baseline, occurrence of a second clinical relapse before the baseline visit, any major disease and pregnancy. Additional exclusion criterion for the SET-PASAT substudy was participation in a previous SET-cognitive substudy that enrolled 81 consecutive CIS patients [1]. Hence the current substudy included 128 CIS patients with clinical visits every 3 months for 48 months. Detailed characteristics of the original study sample are provided elsewhere [23,24]. The study protocol was approved by the local ethics committees in all participating centers, and all patients gave their informed consent.

2.2. Neuropsychological assessment

Participants were tested at disease onset, at baseline, and then every 6 months with the PASAT version that was extracted from the MSFC (Multiple Sclerosis Functional Composite) battery [25]. The PASAT was originally developed by Gronwall [10], and we used the Rao adaptation [26] presented on audiocassette tape or compact disc (CD) to control the rate of stimulus presentation. Series of single digits were presented every 3 s (PASAT-3) and the patient added each new digit to the one immediately prior to it. Subjects were asked to vocalize the result and the test score was the number of correct sums given (out of 60 possible) [10]. The PASAT was administered by a trained and licensed nurse. The first PASAT assessment that was performed at disease onset during acute clinical symptoms was not included in the analysis.

2.3. MRI acquisition and analysis

MRI acquisition and analysis were performed at baseline, 6, 12, 24, 36 and 48 months with a standardized protocol on the same 1.5T scanner (Gyroscan; Philips Medical Systems, Best, the Netherlands). Axial brain acquisitions included fluid attenuated inversion recovery, three-dimensional T1-weighted images, and T1 spin-echo images before and 5 min after a single injection of 0.1 mmol/kg of gadopentetate dimeglumine. The details of the MRI sequences are provided elsewhere [23]. All MRI scans were interpreted in a blinded manner.

Image analyses included a cumulative number and volume of contrast-enhanced (CE) and new and enlarged T2 lesions, T2 lesion volume (LV) and analyses of changes in whole-brain and tissue specific global and regional GM volumes [23]. All 3D T1 images were preprocessed using an in-house developed lesion inpainting algorithm to minimize the impact of WM lesions on tissue volumetry analyses. Percent changes in whole brain (WB) volumes were obtained using the SIENA method [27], while for the GM, WM, cortical and lateral ventricle volume changes we applied a modified SIENAX multi-time point algorithm, as previously described [28]. Percentage volume changes for the total subcortical deep gray matter (SDGM) (defined as the sum of thalamus, caudate nucleus, putamen, globus pallidus, hippocampus, amygdala, and nucleus accumbens) and thalamus at each time point were estimated using FMRIB's Integrated Registration and Segmentation Tool (FIRST) [23].

2.4. Statistical analysis

Statistical analyses were carried out with Statistica 10 (Statsoft, Tulsa, OK), R version 3.0.1 (http://www.R-project.org) and SPSS software version 21.0 (SPSS, Armonk, NY). Normality of the distribution was assessed by using the Kolmogorov–Smirnov method and non-normally distributed variables were log transformed. We applied a linear mixed model design with the outcome being performance of PASAT score and PASAT score absolute change from baseline (PASAT learning effect). Longitudinal uni- and multivariable-linear mixed effect models with a random term for intercept for each patient, adjusted for age, sex, education and DMT status over the 48 months were used to describe temporal associations between MRI measures and both PASAT variables. Considering the previously reported positive effect of DMT [13,14], especially of natalizumab [29] on cognitive performance of MS patients, our models were corrected for the DMT status. Impairment on the PASAT was assessed on the level of 5th percentile (compared with the healthy population), using the regression-based norms adjusted for education. To avoid spurious findings due to multiple comparisons, we considered the nominal p values $\leq .05$ as a trend and as the nominal p value $\leq .01$ as statistically significant.

3. Results

3.1. Patients

Of the 128 CIS patients included in this study, on average 12 (9.1%) patients in each time-point did not undergo cognitive assessment. More details are given in Table 1. CIS patients showed on average 51.7