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Longitudinal change in Paced Auditory Serial Addition Test (PASAT) performance following immunoablative therapy and haematopoietic stem cell transplant in multiple sclerosis

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Abstract

Background: Immediately following immunoablation and hematopoietic stem cell transplantation (IA-HSCT) for MS a median decrease in brain volume of 3.2 % over 2.4 months occurs. After 2 years, rates of atrophy are comparable to normal volunteers. Potential impact of atrophy on cognition was evaluated by examining performance on the Paced Auditory Serial Addition Test (PASAT) pre- and post-IA-HSCT.

Methods: Twenty-three individuals with rapidly progressing/poor prognosis MS underwent high dose IA-HSCT. Individuals completed the 3" PASAT at baseline and 6/12/18/24/30/36 months post-procedure.

Results: Mean decline in performance between baseline and 6-months occurred, though it was not statistically significant. Minor declines were offset by an overall trend for improvement over time. The largest (non-significant) cognitive gains were between months 30 and 36. Neither level of impairment at baseline, nor demographic variables, influenced likelihood of improvement. No relationship between changes in cognition and changes in volumes was detected, likely secondary to small sample size.

Conclusions: While an initial decline in cognition was noted 6 months post-IA-HSCT, there were no lasting negative effects of treatment given the overall trend for improvement. Initial cognitive decline and marked volume loss are likely secondary to acute toxic effects of chemotherapy. Gains in cognition noted over 36 months suggest long-term follow-up is essential.

Keywords: Multiple sclerosis, Cognition, Stem cell, Immunoablation, MRI

Background

Although advances in the therapeutic treatment of MS have improved remarkably over the last several years, current therapies are not curative. Rather, pharmacological treatments simply slow the progression of the disease. Given that MS is an autoimmune disease treatments aim to address the immunological aspects of the illness. Immunoablation and hematopoietic stem cell transplantation (IA-HSCT) has been postulated as a potential tool to treat a number of autoimmune diseases [1, 2]. A few groups of researchers across the globe have initiated the use of IA-HSCT procedures in individuals with MS in hopes of halting disease progression [3, 4]. The treatment is quite aggressive and thus the selection criteria for inclusion in these trials have been restricted to those with rapidly progressing MS and poor prognosis.

The Ottawa Hospital MS Clinic has completed a study evaluating the impact of IA-HSCT on MS. Of the 23 individuals to undergo the procedure, no new attacks or

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MRI lesions have been reported [5, 6]. These individuals have been followed extensively and their progress has been monitored in multiple ways, including neuroimaging studies. This data has revealed that the IA-HSCT procedure results in brain atrophy occurring at a significantly greater rate than is expected on the basis of natural disease progression. For a more detailed discussion on the atrophy observed, please see Lee et al. 2016 [7].

Atrophy has also been noted by other research groups [8–10] and various explanations have been postulated to explain the volume loss including: a selection bias for patients with aggressive disease and potentially faster rates of atrophy; long-term consequences of previous disease activity on tissue integrity; "pseudoatrophy" from reductions in edema (at least during the first year); and finally, neurotoxicity of the chemotherapy conditioning regimen [10]. In an attempt to address this issue our group examined atrophy in 9 secondary progressive MS patients compared to a patient with non-CNS non-Hodgkin's lymphoma (NHL) who underwent a comparable IA-HSCT procedure [11]. Volume loss exceeded change in T2 lesion volume by 2- to 20-fold. Acute atrophy was not explained by resolution of edema. Both the MS group and the NHL patient showed a median 3.2 % volume loss over a median of 2.4 months. The comparable rates of atrophy suggest that volume loss was not related to edema resolution, but rather to the toxicity of therapy (which among other agents consisted of cyclophosphamide, busulfan, and steroids); a known consequence of such treatment.

The impact of this decrease in brain volume on cognition has been evaluated by our group in 7 of the 23 individuals who underwent the IA-HSCT procedure [12]. Results from a large battery of neuropsychological tests (apart from the PASAT results reviewed here) revealed a decline in executive functioning at 2 months post-procedure. However, in those four individuals who completed 24-month follow-up, performance returned to baseline levels. Thus, despite a decline in cognition in the early period following treatment, with temporal distance from the HSCT procedure, cognition returned to baseline levels in those who completed the follow-up. No significant correlations were found between cognitive decline and change in imaging variables or stem cell dosage; although the small sample size may have masked any such relationships. Results from this study, though quite preliminary, are promising and suggest that immunoablation and HSCT may have no lasting deleterious effects on cognition.

The current study aims to further examine patterns of cognitive change in all 23 individuals from the Ottawa Hospital MS Clinic who underwent the IA-HSCT procedure. Whereas only the small subset of 7 individuals completed full neuropsychological batteries, all 23 participants underwent serial evaluation with the Paced Auditory Serial Addition Test (PASAT). As such, we were able to evaluate the impact of IA-HSCT on information processing speed (IPS) and working memory (WM) using the PASAT. Testing took place at baseline (i.e. before the IA-HSCT procedure) and every 6 months for a period of 3 years.

The PASAT is the only cognitive measure in the Multiple Sclerosis Functional Composite (MSFC) [13]. Although there are clear limitations to the PASAT [14] and alternative measures such as the Symbol Digit Modalities Test have been discussed, [15, 16] the PASAT remains a measure that is highly sensitive to cognitive impairment and has become widely used in MS research. It has become a common outcome measure in clinical trials and, in particular, has become a useful tool to monitor cognitive change over time. Longitudinal change in PASAT scores do not correlate with change in EDSS scores, [17] but PASAT performance does correlate with imaging parameters such as DTI measures, [18] MTR in normal appearing white matter, [19, 20] brain activation using fMRI, [21, 22] atrophy, [23] and gadolinium enhancement (a marker of active inflammatory activity), [24] as well as electrophysiological measures such as P3 ERP [25]. Thus, this measure is an easily administered clinical tool that can be a marker for underlying disease progression. Higher scores on the PASAT are associated with better quality of life outcomes, demonstrating that it also has relevance to outcomes important to people suffering from MS [26, 27]. Rosti and colleagues (2007) [28] found that the PASAT was able to detect deterioration in cognition after only 1 year, but this phenomenon was found only in those individuals with MS who were already cognitively impaired at baseline (i.e., cognitively intact individuals with MS did not change over that time interval). One of the complications when using the PASAT in serial testing is its susceptibility to practice effects [13, 28]. Nonetheless, this can be controlled statistically (see below).

Given our previous work which documented cognitive decline immediately post-IA-HSCT in some individuals, [12] it was hypothesized that a similar decline in PASAT scores would be found at the 6 month mark with improvement expected at all other time points. MRI scans were obtained in conjunction with the cognitive testing to examine the potential correlation between volume loss and cognition. Our past preliminary work has shown little relationship between volume and cognitive variables early after transplant, but the current study evaluated this potential relationship over a longer follow-up interval [12].

Methods

Participants

This study was approved by the Ottawa Hospital Research Ethics Board and informed consent was obtained.

Twenty-three individuals with rapidly progressing MS who failed to respond to routine therapy (i.e. progression or continued relapses or worsening MRI after at least 1 year of therapy with interferon-β1, glatiramer acetate, mitoxantrone, or other conventional dose immunosuppressive drug therapy) were enrolled. High risk of progression was defined as ≥5 relapses in the first 2 years of disease or attainment of a Functional System (FS) Score of at least 3 (or findings consistent with a FS of 3) affecting pyramidal/cerebellar subscores within 5 years of onset. If a patient had previously received a cytotoxic agent (mitoxantrone, cyclophosphamide, etc.) they must have had normal bone marrow morphology and cytogenetics before being considered eligible for this study. MRI brain scans satisfied the MRI criteria of Paty or Fazekas for the diagnosis of MS. None of the subjects had evidence of hepatic inflammation or fibrosis. In the 23 subjects enrolled baseline EDSS ranged from 1.5 to 6.5 (mean = 4.87 (1.40)). Education ranged from high school to graduate school with the median value being equivalent to college level. Age ranged from 23 to 44 years (mean = 32.65 (5.82) years). Of the 23 subjects, 12 were diagnosed with relapsing-remitting MS and 11 with secondary progressive MS. Those with primary progressive MS were excluded.

Procedure and measures

The study was a tri-center phase II efficacy study of the role of intensive immunosupression and autologous HSCT on the natural history of MS. Participants underwent stem cell mobilization with IV cyclophosphamide (4.5 g/m^2) and 10 days of granulocyte colony-stimulating factor (10 μg/kg/day) followed by stem cell collection using peripheral vein leukopheresis. All stem cell grafts were CD34 selected and cryopreserved until transplantation. Immunoablation was accomplished using cyclophosphamide (200 mg/kg), dose-adjusted IV busulfan (maximum 16 mg/kg) and IV rabbit antithymocyte globulin (5 mg/kgSolumedrol was administered concurrently with ATG to reduce the risk of hypersensitivity reactions. Participants did not receive further MS-disease modifying drugs or experimental therapy after IA-HSCT.

Participants underwent MRI scans with pre- and post-gadolinium enhanced T1-weighted and dual spin-echo (Proton Density/T2-weighted) sequences at baseline and then serially every 6 months until 36 months post-IA-HSCT. T1-weighted pre-contrast scans were used to calculate volumes of GM, WM, and regional structures. At the same time points as the MRI, subjects completed the 3" PASAT. Note that a run-in procedure was not used for the PASAT. However, see below for the manner in which this was controlled statistically. Two participants did not complete the follow-up interval past 18 months as they underwent an unproven therapy for disease progression against the advice of their treating neurologist, and inclusion of their data would have made it more challenging to interpret findings in the context of the treatment of interest.

Data analysis

The GM and WM volumes, normalized for subject head size, were calculated with FSL-SIENAX (cross-sectional variation of Structural Image Evaluation, using Normalisation, of Atrophy) [29]. Subcortical gray matter structures were segmented and their volumes were calculated with FSL-FIRST (FMRIB's Integrated Registration and Segmentation Tool: http://www.fmrib.ox.ac.uk/fsl/first) [30]. Volumes of cortical and other subcortical structures were calculated with Freesurfer v5.1 (http://surfer.nrm.mgh.harvard.edu/) [31, 32].

Because group comparisons of tests scores can mask significant individual differences (as can practice effects due to prior task exposure), the reliable change index (RCI) (corrected for practice) was calculated for the PASAT in order to assess an individual's change over time. A variation of the RCI was used that included an adjustment for practice effects that result from serial testing [33]. Note that practice effects were accounted for up to 12 months given that research has shown stability in practice after the third PASAT retest session [14, 34].

$$RCI = \left(\frac{(time\ 2 - time\ 1) - practice}{SE_{Diff}}\right)$$

SEdiff is the standard error of the difference which represents the spread of distribution of change scores expected had no change occurred. Given that, to the best of our knowledge, there is no published data for the 3" PASAT which provides means and standard deviations for multiple administrations, the *practice effect* was calculated by taking the mean difference between the second and first administration of the 3" PASAT (as well as between the third and second administration) for a group of healthy controls (from a different study in our lab) who received multiple administrations up to a week apart. For a more specific examination of the demographics of this control sample, please see Walker et al. 2012 [35]. The RCI scores were considered to be statistically significant and reliable at 90 % confidence intervals if the degree of change fell outside ±1.64.

Chi-square analysis was conducted to determine if those who were impaired at baseline were more or less likely to show improvement over time compared to those who were not impaired at baseline.

Analysis of variance (ANOVA) was performed to determine if demographic variables (such as age, gender, and education) explained the differences noted between those who show improvement in their performance from baseline to 36 months post-IA-HSCT and those who do not.

Finally, Pearson bivariate correlational analyses were performed to determine if PASAT RCI values (e.g. baseline to 6 months, 6 to 12 months, etc.) correlated with change in brain volume (i.e. difference scores) of the cortical and subcortical structures.

Results

Reliable Change Index (RCI) analyses

Please see Table 1 for RCI values per subject.

On average, there was a decline in RCI values between performance at baseline and performance at 6-month follow-up (mean RCI =−0.13) (see Fig. 1).

This value, although reflective of decline, does not reach statistical significance. An RCI value must exceed +/- 1.64 in order to be considered significant. Following the 6-month mark, a trend for improvement was noted until 24 months, although this trend did not reach statistical significance. There was a decline noted at 30-months but examination of the raw scores revealed a trend for stability, with the mean decline being driven by one outlier who declined significantly. The largest cognitive gains took place between months 30 and 36, but again not to a statistically significant degree.

Chi-square analyses

Subjects' impairment status at baseline (cognitively impaired vs. cognitively intact) did not impact whether they declined, remained stable, or improved over time.

Table 1 RCI values per subject

Subject	Baseline - 6m	6m - 12m	12m - 18m	18m - 24m	24m - 30m	30m - 36m	Baseline - 36m
1	2.23	-1.26	1.53	0.31	0.35	-0.16	3.76
2	0.12	-0.94	-0.35	0.94	-1.76	2.35	0.23
3	-0.7	-1.26	0	1.57	0.12	1.26	1.06
4	-0.47	0	-1.17	1.73	0	0.16	1.17
5	-0.94	0.16	-0.47	1.1	-0.47	1.1	0.35
6	-0.12	0.78	0.23	-0.47	1.29	-1.57	0.94
7	-0.82	-1.41	0.82	-1.26	*	*	-1.76
8	-0.47	*	*	*	*	-0.31	-0.35
9	-0.59	0.16	-0.47	0.94	-0.23	0.94	0.7
10	*	*	0.12	0.94	0.47	-0.12	0.47
11	-0.23	0.63	0	-0.63	0.59	1.41	0.47
12	0	0	0.35	0.31	*	0.94	1.42
13	-2.47	1.1	0.82	-0.16	*	*	*
14	-0.23	0.78	0	-0.16	0.12	-0.16	0.7
15	0.47	1.1	-0.12	-1.26	-0.12	1.41	1.64
16	1.41	-1.26	0.82	0.47	-0.47	1.1	2.47
17	0.12	0.16	0.12	0.63	0.23	-0.16	1.41
18	-1.29	0.16	0.47	*	*	*	*
19	-0.35	0.16	0	-0.16	0.12	*	*
20	-0.12	0.94	-0.23	-0.16	*	*	*
21	0.47	0.16	-0.12	0.16	-0.12	*	*
22	2.11	0.94	-0.23	0.63	-0.59	*	*
23	-0.70	0.47	0.59	*	*	*	*

* missing data

RCI significant improvement

RCI significant decline

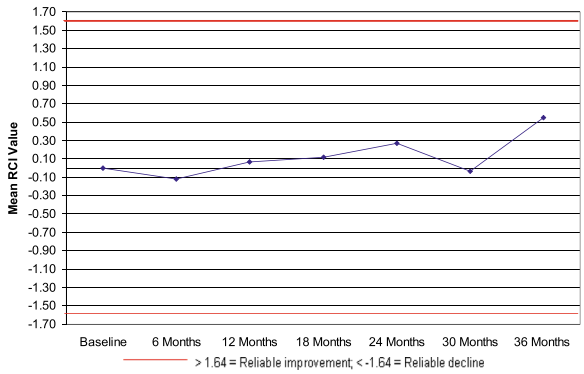

Fig. 1 3″ PASAT Mean RCI Values Over Time

Analysis of variance

There were no differences in demographics (age, gender, education) between those who showed reliable improvement and those who did not.

Correlational analyses

Change in PASAT performance did not correlate significantly with the change in percent normalized brain volume (PNBV), percent cortical grey matter volume (PGMV), or percent white matter volume (PWMV) at any time point (see Table 2 for mean percent normalized brain volumes over time).

Similarly, there was no relationship between change in PASAT performance and change in any of the cortical and subcortical structure volumes at any time point. For a more comprehensive examination of the observed MRI changes please see Lee et al. 2016 [7].

Discussion

Consistent with the hypothesis, we were able to document a slight trend toward the expected decline in PASAT performance in the initial period post-IA-HSCT given that there was a mean RCI decline between baseline and 6 months. Similarly, there was a much more encouraging trend for improvement over the longer follow-up interval. It is important to note however, that these findings did not reach statistical significance when group means were considered. The lack of significance cannot be attributed to changes associated with practice effects given that the RCI analyses take this into account; nor are these findings likely to be attributed to small sample size given that these analyses were at the level of the individual. Six individuals demonstrated significant improvement during at least one of the time periods evaluated but several more exhibited more subtle improvements. The lack of statistical significance overall suggests that the changes in WM and IPS experienced post-IA-HSCT are subtle. This is consistent with others who describe only subtle changes in cognition associated with chemotoxicity and the resolution of initial declines as time progresses post-treatment [36, 37]. In our previous report, we outline why we believe that chemotoxicity played a significant role in the increased rate of atrophy [11]. The neurotoxic effects of chemotherapy have been well documented in the literature [36, 38] and thus, in addition to the atrophic changes, this is also likely the reason for the initial transient decline in cognition noted here. Current findings mirror what was documented by our group when examining performance on a subset of participants on a full neuropsychological evaluation [12]. Indeed, it was found that cognition declined briefly in the initial period post-procedure and returned to baseline levels by the 24-month follow-up. The current study evaluated cognition at more frequent time intervals, and examination of the mean RCI values (see Fig. 1) suggests that cognition returns to baseline levels by 12 months. Thus, the latter half of the first year post-IA-HSCT appears to be a critical period with regard to cognitive gains. The IA-HSCT procedure did not differentially impact cognition based upon cognitive status before the procedure, nor did demographic variables influence outcome.

After 12 months, there is a trend for ongoing subtle cognitive gains (with the exception of the outlier influencing performance at 30 months). Does the fact that PASAT values at 36 months follow-up exceed initial baseline levels (after accounting for practice) argue for neuronal repair? Clearly, it is too soon to make a claim like this, but results are promising and warrant further study. If cognition is improved over baseline levels then perhaps the IA-HSCT procedure does not simply halt disease progression, but fosters repair (i.e. the cognitive findings may be a marker for this potential improved pathology). Certainly past research has confirmed that PASAT performance correlates with imaging markers of pathology [18, 19, 21, 22, 24]. Nine of the 23 individuals undergoing this study have demonstrated improvement in neurological function (i.e. EDSS improvement of 1 or more) compared to baseline levels, [6] so this would

Table 2 Mean percent normalized brain volumes over time

	Baseline	6 m	12 m	18 m	24 m	30 m	36 m
Percent Normalized Brain Volume	100.00	97.68 (1.58)	97.44 (1.90)	97.31 (1.72)	97.25 (1.75)	96.26 (2.20)	96.45 (2.57)
Percent Grey Matter Volume	100.00	94.12 (2.59)	94.89 (2.98)	95.28 (2.79)	94.09 (2.71)	93.78 (4.20)	93.50 (5.18)
Percent White Matter Volume	100.00	100.66 (1.90)	99.29 (3.12)	98.97 (2.60)	99.83 (3.62)	98.60 (3.37)	98.59 (3.36)

appear to provide converging evidence for this possibility. Further investigations must occur in order to test this notion and draw any firm conclusions.

The lack of association between PASAT performance and atrophy measures is consistent with our past preliminary findings, [12] but inconsistent with the research literature that typically demonstrates a correlation between PASAT performance and neuroimaging [18, 19, 21, 22, 24]. The primary reason for the lack of relationship is likely that the sample size was insufficient. A larger sample size would garnermore statistical power to detect such a relationship. The small sample size is a function of the nature of this particular study. Enrollment criteria was quite restrictive and was limited to those with rapidly progressive disease who had not responded well to established therapies. Although the current IA-HSCT procedure appears quite promising with regard to halting disease progression and with regard to these preliminary cognitive findings, it remains a procedure that should be considered only after other options have been exhausted given the risks with which it is associated. A multi-centre trial holds the most promise with regard to enrollment of larger numbers, and indeed, discussions are underway. In such a circumstance, greater statistical power may allow us to detect the expected relationship between change in cognition and changes in brain volumes.

An additional limitation of this study is the lack of a control group. Attempts were made to obtain an appropriate control; however, we were unsuccessful. We attempted to approach individuals undergoing bone marrow transplant for other indications besides MS (i.e. haematological cancers). However, recruitment proved to be extremely difficult due to the fact that individuals undergoing such procedures are typically extremely ill. Their motivation to participate in research is low and those who are more motivated are more likely to volunteer for research targeting their own health condition (i.e. they have no impetus to contribute to MS research given that it does not relate to them directly).

Conclusions

The results of this study are clearly preliminary, but hold some promise. Initial subtle declines in cognition post-IA-HSCT are presumably due to chemotoxic effects, but these subtle declines are reversible with scores improving over time and eventually exceeding initial baseline levels. Thus, any negative impact on cognition of the IA-HSCT procedure appears to be only minor and temporary and does not appear to cause any lasting damage to the CNS. Results at 36 months highlight the necessity of long-term follow-up. Future research should attempt to replicate these findings in larger sample sizes via multi-centre initiatives. The question of possible neural repair should also be evaluated.

Abbreviations

ANOVA, analysis of variance; FS, functional system score; IA-HSCT, immunoablation and hematopoietic stem cell transplantation; IPS, information processing speed; MSFC, Multiple Sclerosis Functional Composite; NHL, non-Hodgkin's lymphoma; PASAT, Paced Auditory Serial Addition Test; PGMV, percent cortical grey matter volume; PMWV, percent white matter volume; PNBV, percent normalized brain volume; RCI, reliable change index; WM, working memory

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Availability of data and materials

The data is not publicly available, though may be shared on a case by case basis upon request at the discretion of the first author (Lisa A.S. Walker; lwalker@toh.on.ca).

Authors' contributions

LASW and JAB—data acquisition, analysis and interpretation of data, manuscript preparation and revision, final publication approval. MB—data acquisition, analysis and interpretation of data, manuscript revision, final publication approval. HLA and MSF—study design, data acquisition, interpretation of data, manuscript revision, final publication approval. HL and DA—MRI data acquisition, interpretation of data, manuscript revision, final publication approval.

Competing interests

The authors declare that they have no competing interests. Dr. Mark Freedman is a member of the Editorial Board for the Multiple Sclerosis and Demyelinating Disorders journal.

Consent for publication

Not applicable.

Ethics approval and consent to participate

This study was approved by the Ottawa Hospital Research Ethics Board and informed consent was obtained.

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