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Cognitive change and neuroimaging following immunoablative therapy and hematopoietic stem cell transplantation in multiple sclerosis: A pilot study

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Abstract

Background: Individuals with MS undergoing immunoablative therapy and hematopoietic stem cell transplantation (HSCT) show substantial decrease in brain volume over 2.4 months, presumably from chemotoxic effects, although other mechanisms have also been postulated.

Objective: We examined whether volume loss was accompanied by a concomitant decrease in cognition. White and gray matter volumes, and the effect of stem cell dosage were considered.

Methods: Seven individuals with rapidly progressing MS and poor prognosis underwent high dose immunosuppression and autologous HSCT. Neuropsychological testing and MRI scans were performed at baseline, 2 and 24 months post-procedure.

Results: Cognitive impairment was noted at all times in most participants. Median decline of 1.39% in total brain volume was noted 2 months post-HSCT. By 24 months a further decline of 1.65% was noted. At 2 months significant decline was observed for areas of executive functioning. At 24 months almost no significant declines were noted. No significant correlations were found between cognitive decline and change in imaging variables or stem cell dosage.

Conclusions: Cognition changed in the early period following treatment but with little apparent relationship to volume changes. With temporal distance from the HSCT procedure, cognition returned to baseline levels. With the caution of a very small sample, preliminary results suggest that immunoablation and HSCT may have no lasting deleterious effects on cognition.

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1. Introduction

Multiple sclerosis (MS) is a chronic, progressive disease of the central nervous system leading to degradation of the myelin sheath, axonal and neuronal loss and eventual brain atrophy. Cognitive impairment is seen in up to 70% of individuals with MS with impairment across multiple cognitive domains (Hoffmann et al., 2007). No curative treatment exists and current therapies aim to slow the progression of the disease, with limited success. In an attempt to abolish the autoimmune processes which give rise to MS, a few groups worldwide have adopted a Bone Marrow Transplant (BMT) approach in hopes of establishing long-lasting periods during which disease progression is halted (Pasquini et al., 2010). Because of the intensive nature of the treatment, only a select group of individuals with rapidly progressing MS and with poor prognosis are chosen to participate. Of the 23 individuals to undergo the procedure through the Ottawa Hospital MS Clinic research protocol, no new attacks or MRI lesions have been reported (Freedman, 2007; Freedman, personal communication, 2012). Neuroimaging has revealed, however, that the procedure itself results in brain atrophy occurring at a significantly greater rate than is expected on the basis of natural disease progression.

The Barcelona research team reported that reduction in T2 lesion volume was accompanied by decrease in corpus callosum area of 12.71% at 3 years post-procedure (Saiz et al., 2004). The majority of callosal reduction occurred during the first year. The group speculated that atrophy was due to resolution of edema and inflammation present prior to transplant, such that the procedure itself caused loss of brain volume, a phenomenon termed "pseudoatrophy". An Italian research team measured atrophy with more sophisticated imaging techniques (Inglese et al., 2004) as they attempted to control for "pseudoatrophy" by using one-month post-procedure scans as baseline. The mean yearly percentage normalized brain volume change was approximately 1.9% over 2 years of study. Although the rate is less than that initially observed, it remains twice as high as rates of atrophy in the general MS population. Findings demonstrated that progressive tissue loss can occur independently of inflammation. Inglese et al. (2004) postulated possible explanations: (1) the patients in the study with aggressive disease may represent a sub-population that would have demonstrated faster atrophy rates even without HSCT, (2) atrophy may reflect long-term consequences of previous disease activity on tissue integrity, (3) some changes may still reflect "pseudoatrophy" from reductions in edema, at least during the first year, and (4) neurotoxicity of chemotherapy conditioning may be responsible.

Our BMT group examined atrophy in nine secondary progressive MS patients compared to a patient with non-CNS non-Hodgkin's lymphoma (NHL) who underwent a comparable HSCT procedure (Chen et al., 2006). Volume loss exceeded change in T2 lesion volume by 2- to 20-fold. As such, 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 toxicity of therapy (which among other agents consisted of cyclophosphamide, busulfan, and steroids); a known consequence of such treatment.

The Italian group followed patients for up to a mean of 63 months (Roccatagliata et al., 2007). They found a marked decrease in atrophy rates after the second year (−2.72% between baseline and month 24 compared to −1.17% between month 24 and long-term follow-up). The rate of atrophy after the second year is more than 50% lower and comparable to rates observed in patients with the less aggressive MS. The authors felt that pseudoatrophy was an unlikely cause and that initial atrophy post-procedure may be a "carry-over" from the high level of inflammation pre-treatment (i.e. time to see the consequences from the inflammatory demyelination may take longer than 2 years). They agreed that initial atrophy may be due to toxicity of the conditioning regimen and suggested that repair mechanisms present in the latter part of follow-up (i.e. more pronounced glial activity) may have counteracted the effect of tissue loss on brain volume. Lastly, they suggested that slowing of brain atrophy may simply result from natural evolution of the disease.

Volume loss is associated with concomitant decline in cognition in MS (Amato et al., 2007; Benedict, 2012; Benedict et al., 2002; Roosendaal et al., 2011; Sanfilipo et al., 2006). Thus, it behooves us to examine whether or not accelerated atrophy found in the context of the HSCT procedure is associated with a similar change in cognition. Typically, people with MS who are cognitively impaired decline further, with changes detectable after a two to three year interval (Amato et al., 2007; Denney et al., 2008). Given the accelerated atrophy associated with HSCT, it is possible that cognitive decline may also be hastened. Preliminary work by our group documented a change in cognition over time between baseline and 2 month post-HSCT visits with some areas of cognition declining (Berard et al., 2012). The current study evaluated cognition further at 24-months. Expanding upon earlier work, MRI scans were obtained in order to examine any atrophic changes in white (WM) and gray matter (GM) between these three visits. It was hypothesized that any atrophic changes noted would parallel those areas of cognition which declined.

2. Participants and methods

2.1. Participants

The 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 conventional treatment were enrolled. Of these, seven participated in the cognitive add-on study and completed full neuropsychological batteries. High risk of progression was defined as $\geq$5 relapses in the first two years of disease or attainment of a Functional System (FS) Score of at least 3 (or findings consistent with a FS score of 3) affecting pyramidal/cerebellar subscores within 5 years of onset. If a patient had previously received a cytotoxic agent (Mitoxantrone or Cyclophosphamide) they must have had normal bone marrow morphology and cytogenetics before being considered eligible. The Expanded Disability Status Scale (EDSS) scores at baseline ranged from 3.5 to 6