HIGH LIGHT

Brain atrophy after immunoablation and stem cell transplantation in multiple sclerosis

Abstract—The authors measured brain atrophy in nine patients undergoing immunoablation and autologous hematopoietic stem cell transplantation for multiple sclerosis. From baseline to 1 month after treatment, atrophy was 10 times faster than before treatment. A patient with non-CNS lymphoma showed comparable acute brain atrophy after analogous therapy. These observations suggest that brain atrophy after immunoablation may not be due entirely to the resolution of edema but may be related to chemotoxicity.

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Brain atrophy occurs at a faster rate than normal in patients with multiple sclerosis (MS) and may be accelerated in the year after initiation of immunomodulatory therapy[1]—a phenomenon that is often attributed to the resolution of edema.

To explore the nature of the changes in brain volume after anti-inflammatory therapy, we measured global brain volume changes on MRI scans of patients with aggressive MS being treated with immunoablation and autologous hematopoietic stem cell transplantation (AHSCT). We also measured brain volume changes on MRI scans of a patient with lymphoma that did not involve the CNS and who was undergoing a similar treatment.

Methods. We studied nine secondary progressive (SP) MS patients with active disease who were participating in a tricenter phase II trial of immunoablation followed by AHSCT.[2]

Stem cell mobilization was achieved with IV cyclophosphamide (4.5 g/m^2) and 10 days of granulocyte colony-stimulating factor (10 μg/kg/day). Immunoablation was accomplished using IV cyclophosphamide (200 mg/kg), dose-adjusted oral busulfan (maximum 16 mg/kg) and rabbit antithymocyte globulin (5 mg/kg).[2] Solu-Medrol was administered for 4 days during the conditioning regimen.

A 54-year-old man with non-Hodgkin lymphoma and no CNS involvement was followed up after chemotherapy (IV busulfan: 12.8 mg/kg [total = 845 mg]; IV cyclophosphamide: 120 mg/kg [total = 7,920 mg]; dose-adjusted IV methotrexate: 45 mg/m^2 [total = 76 mg]; cyclosporine: 1.5 mg/kg every 12 hours from day −1) and allogeneic bone marrow transplantation (BMT).

MRI scans included T1-weighted and dual spin-echo (PD/T2-weighted) sequences acquired at baseline and serially after treatment as previously described.[3] In two cases, the earliest baseline scans were performed more than 12 months before the last baseline scan because of delays in the study.

The rate of brain atrophy was calculated using SIENA[4] (http://www.fmrib.ox.ac.uk/fsl). Gadolinium-enhancing lesions were segmented manually, and T2-weighted lesion volume (T2LV) was quantified automatically using a Bayesian classifier followed by manual correction. A simplified estimation of T2-relaxation maps were calculated based on a single-exponential fit of the image intensities of the dual spin-echo sequence.

Results. The patient demographics and rates of atrophy at baseline and 1 month after AHSCT are shown in the table. Atrophy (brain volume loss) is reported as a positive percentage change. The entire therapy (stem cell mobilization, immunoablation, and AHSCT), resulted in a decrease of brain volume by a median value of 3.2% (interquartile range [IQR] = 2.6 to 3.4%/year, n = 5) during a median time interval of 2.4 months, which represents a median annualized rate of atrophy of 15.1%/year (IQR = 12.9 to 16.4%/year, n = 5) which is higher than baseline ($p < 0.001$). During the same interval, on average there was either no significant change or slight increases in the simplified estimated T2-relaxation times. The rates of atrophy after the acute period were slightly slower than but not significantly different from baseline (figure).

Relation of atrophy to inflammation. Brain atrophy after treatment exceeded concurrent decreases in T2LV by 2- to 20-fold, suggesting that resolution of edema in lesions was not solely responsible for the acute brain atrophy.

To assess a possible direct toxic effect of the immunoablation on the brain, we measured brain volume change in a patient with lymphoma without CNS involvement who underwent analogous treatment. Baseline measurements in this patient were stable. During the treatment interval (baseline to 3 months after immunoablation and transplantation), the patient showed an annualized rate of atrophy of 6.0%/year, which was within the range of atrophy measurements in the MS patients during a similar treatment interval. This patient continued to show a high rate of brain atrophy during the subsequent 3 to 6 months, which again was similar to atrophy measured in the MS patients during a similar interval.

Discussion. We found that substantial brain atrophy (median 3.2% over median 2.4 months) occurred acutely after immunoablation and AHSCT in patients with MS and BMT in a patient with lymphoma without preexisting CNS disease.

Decreases in brain volume can be associated with a decrease in the volume of cellular components or a loss of water without tissue loss, often called "pseudoatrophy." Dehydration associated with acute

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Table *Subject demographics*

Demographics	
Age, mean (range), y	32 (26–40)
Sex, F:M	5:4
EDSS, median (range)	6 (4–6)
Disease duration, mean (range), y	6 (2–10)
MRI at baseline	
Volume of T2-weighted lesions, mean (range), cc	36.87 (13.84–84.40)
Number of patients with Gd^+ lesions	4
Number of Gd^+ lesions, median (range)	10 (0–23)
Volume of Gd^+ lesions, cc, mean (range)	0.76 (0–5.72)
Rate of atrophy, annualized median (interquartile range), (%)y	1.4 (−1.3 to 1.6)
MRI after treatment	
Number of patients with Gd^+ lesions	0
Rate of atrophy from pretreatment to 1 mo after AHSCT, annualized median (interquartile range), (%)y	15.1 (12.9–16.4)

AHSCT = autologous hematopoietic stem cell transplantation; EDSS = Expanded Disability Status Scale; Gd+ = gadolinium-enhancing.

illness or medication could cause acute reversible brain volume change. We do not believe that atrophy in our patients was secondary to water shifts, because patients were in dedicated transplant centers that carefully maintained nutritional and hydration status during the acute phase of their treatment, and changes in body weight during the acute period were not consistently associated with the magnitude of acute changes in brain volume. In addition, simplified estimates of T2-relaxation times did not show the decreases that would be expected with loss of tissue water. To explore whether the resolution of edema in lesions might be the explanation for the brain volume changes observed,[5] we compared the change in T2LV during the acute interval with the change in brain volume. Brain volume loss exceeded the change in T2LV by 2- to 20-fold. Therefore, resolution of focal edema associated with lesions is not likely to explain the acute atrophy observed. We also considered the possibility that resolution of diffuse inflammatory edema involving normal-appearing brain tissue could result in pseudoatrophy. The average change in simplified estimates of T2-relaxation times in normal-appearing brain tissue during the acute interval did not show the decreases that would be expected with resolution of diffuse inflammatory edema. In addition, we obtained MRI scans from a patient with lymphoma without CNS involvement, before and after immunoablation and allogeneic bone marrow transplantation. This patient showed acute brain atrophy comparable to that in the transplanted MS patients. This suggests that the brain volume change observed in the MS patients also may not be simply related to the resolution of edema; toxicity of the therapy, which included cyclophosphamide and busulfan (as well as steroids and other concomitant medications), likely contributed. Cerebral toxicity of chemotherapy is a known complication of such therapy.[6-9]

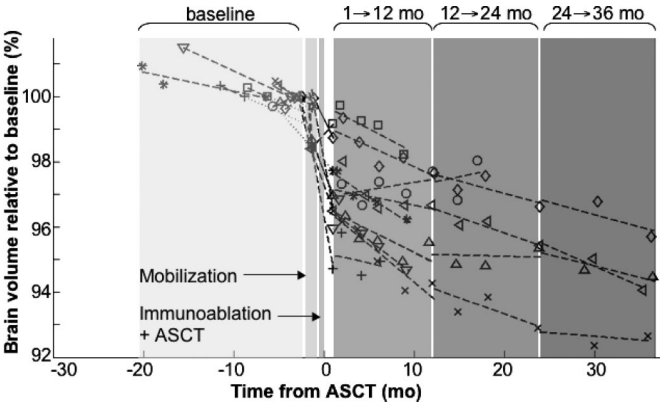

Figure. The evolution of brain atrophy from baseline until 3 years after transplantation. Brain volume and time expressed relative to last baseline MRI. Dashed lines represent linear least-squares fit of the data at baseline, 1–12 months, 12–24 months, and 24–36 months. Dotted lines at the linear extrapolation of the baseline fit to the start of stem cell mobilization. The rates of atrophy after the acute interval were not significantly different from baseline (1–12 months: median = 1.6%/year, interquartile range [IQR] = 0.7 to 1.9, n = 9; 12–24 months: median = 0.9%/year, IQR = −0.1 to 1.1, n = 5; 24–36 months: median = 0.8%/year, IQR = 0.5 to 1.2, n = 4). Because of the staggered entry in the trial, full MRI follow-up is not available for all patients. ASCT = autologous stem cell transplantation.

The observation of rapid brain atrophy from baseline to 1 month after immunoablation suggests that yearly measurement of brain atrophy may not be optimal for assessing brain volume changes after therapeutic intervention. Measurements early after therapeutic intervention can distinguish treatment-related changes and establish a new baseline for ongoing atrophy.

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Neuro*Images*

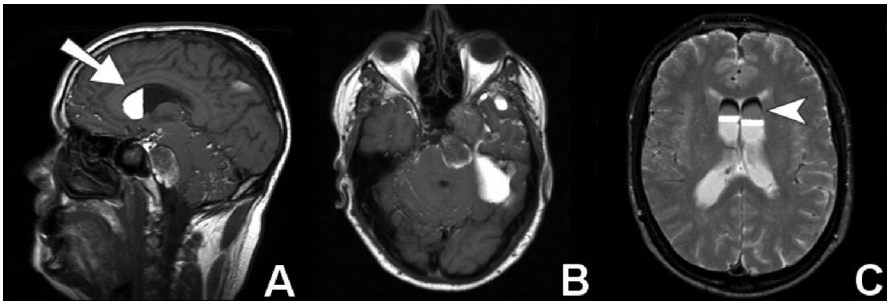

Figure. (A) Sagittal and (B) axial T1-weighted imaging (WI) demonstrate the mass to be heterogeneously hyperintense. Multiple focal areas of T1 shortening are present within the subarachnoid space. Note the presence of a fluid-fluid level into the ventricles (arrow). (C) Axial T2-WI shows a prominent chemical shift artifact (arrowhead) that confirms lipid content.

Intracranial dermoid cyst rupture with subarachnoid and intraventricular fat dissemination

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A 53-year-old man presented with an abrupt onset of depressive syndrome with atypical features (depersonalization, derealization, and occasional disorientation). Neurologic examination revealed mild sensory loss in the first left trigeminal division and diminished swallowing reflex. Cranial MRI showed a ruptured left cerebello-pontine angle dermoid cyst extending to the middle cranial fossa (figure).

A retrosigmoid craniotomy allowed resection of the posterior fossa cyst, and pathologic analysis confirmed the diagnosis. Despite initial treatment with an external ventricular drainage, the patient developed hydrocephalus and finally needed a ventriculoperitoneal shunt. Six months after initial treatment, the patient has no psychotic symptoms and follows treatment with antidepressant drugs and valproate due to left temporal irritative activity. CT images of fat dissemination still persist.

Dermoid cysts account for 0.04 to 0.25% of all intracranial tumors. Their rupture is relatively rare.[1]

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