Assessment of Brain Changes with Registered MR Before and After Bone Marrow Transplantation for Chronic Myeloid Leukemia

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PURPOSE: To determine the frequency and nature of changes to the brain resulting from chemotherapy, radiation therapy, and bone marrow transplantation for chronic myeloid leukemia and to compare the sensitivity of conventional and registered MR scans for detecting these changes. **METHODS:** In 15 patients, conventional T1-weighted, T2-weighted, and fluid-attenuated inversion recovery MR sequences, as well as T1-weighted radio frequency spoiled 3-D volume MR scans were performed before, 4 to 6 days after, and up to 339 days after transplantation (13 allografts, two autografts). A subvoxel registration program was used to match the volume images precisely so that small changes could be detected after subtraction of scans. Five healthy adult control subjects were also studied on two occasions 1 month apart. **RESULTS:** Studies performed 4 to 339 days after transplantation showed ventricular enlargement and cortical atrophy in all 13 patients who had allografts. The changes were evident at 4 to 6 days after transplantation and became more obvious during later follow-up examinations. Similar changes were seen in one patient with an autograft but no significant change was seen in the other patient with an autograft or in the five control subjects. Accurately registered volume scans were more sensitive than unregistered conventional scans in detecting early (9/10 versus 0/10), intermediate (12/13 versus 3/12), and late (10/10 versus 4/9) ventricular enlargement on follow-up examinations. The same applied to cortical atrophy (9/10 versus 0/10, 12/13 versus 0/12, and 10/10 versus 0/9.) **CONCLUSION:** The specific cause and clinical significance of these changes are uncertain. Subvoxel registration of serial MR images may reveal changes that are poorly seen or not apparent on conventional scans.

Index terms: Bone marrow transplantation; Brain, magnetic resonance; Leukemia

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Bone marrow transplantation has revolutionized the management of chronic myeloid leukemia and provides the only possibility of cure for this disease (1, 2). Conditioning regimens are essential to the success of transplantation. The aim of these regimens is to eradicate any remaining malignant cells and to suppress the recipient's immune system. The latter is necessary to prevent rejection of the (allogeneic) graft and to permit replacement of the entire hemopoietic and immune systems of the recipient with those of the donor. A typical regimen used for this purpose consists of a cytotoxic drug (eg, cyclophosphamide 60 mg/kg per day for 2 days) followed by total-body irradiation of 1320 to 1440 cGy given in several fractions over 2 to 3 days. This is typically followed by treatment to prevent graft-versus-host disease (GVHD) and viral infection. After bone marrow transplantation for chronic myeloid leukemia in the chronic phase, 50% of patients can expect to be alive at 8 years, and 40% will also be free of disease (3).

Allogeneic bone marrow transplantation carries the risk of significant acute side effects,

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including GVHD, venoocclusive disease of the liver, idiopathic interstitial pneumonia, and late complications such as cataract formation and secondary malignancy. Neurologic complications are unusual, but damage to white matter is well recognized (4–6). The role of chemotherapeutic agents and radiation either individually or in combination in causing brain damage may be difficult to determine. Cytotoxic and immunosuppressive agents, such as methotrexate (7), cytarabine (8), and cyclosporine (9), can cause brain damage. Radiation can also cause damage, but the dose to the brain for conditioning (eg, 1320 to 1440 cGy) is less than that used either in prophylactic cranial irradiation in acute leukemia (eg, 2000 to 4000 cGy) or in treatment of cerebral tumors (eg, 4000 to 6000 cGy). Transplantation patients are not thought to be at particular risk for the typical acute or early delayed complications of radiation treatment, since these are associated with higher doses (10–12). However, it is possible that the combination of cytotoxic or immunosuppressive agents with total body irradiation may be a more potent cause of brain damage than either alone (13). For example, methotrexate and total-body irradiation are particularly associated with white matter damage after treatment of childhood acute lymphoblastic leukemia (14).

To determine the nature and frequency of changes to the brain in patients undergoing chemotherapy, radiation therapy, and bone marrow transplantation, we performed a prospective magnetic resonance (MR) imaging study of 15 patients with chronic myeloid leukemia (13 allografts and two autografts) using conventional pulse sequences and subvoxel registration of volume scans.

Subjects and Methods

All studies were performed with the approval of a Research Ethics Committee and all subjects (patients and volunteers) gave their informed consent.

The patients consisted of eight men and seven women, 18 to 56 years old (mean, 37 years). The clinical details are summarized in the Table. The diagnosis of chronic myeloid leukemia was established by examination of the peripheral blood and bone marrow. All were positive for Philadelphia chromosome. Before bone marrow transplantation, all patients had received treatment with hydroxyurea and/or interferon alfa. Fourteen patients were in the chronic phase of the disease at the time of bone marrow transplantation; one patient (F.F.) had evidence of lymphoblastic transformation in bone marrow and cerebrospinal fluid. For the patients undergoing allogeneic bone marrow transplantation, donors were related to the recipient in five cases and unrelated in eight. Eleven donor-recipient pairs were HLA-identical. One patient (F.F.) received a 1-HLA antigen mismatched transplant from his father; another patient (M.E.) received a 2-HLA antigen mismatched transplant from an unrelated donor.

The conditioning regimen for the 13 allograft patients consisted of cyclophosphamide 60 mg/kg per day for 2 days followed by total-body irradiation of 220 or 240 cGy (for related and unrelated donors, respectively) in two daily fractions for a total dose over 3 days of 1320 or 1440 cGy. This was followed by transplantation of donor bone marrow. Prophylaxis against GVHD consisted of cyclosporine (5 mg/kg intravenously on the third day before bone marrow transplantation and, subsequently, 2.5 mg/kg intravenously daily until gastrointestinal function recovered sufficiently to allow initiation of equivalent oral cyclosporine therapy). Methotrexate (8 mg/m^2 intravenously) was given on days 2, 4, 8, and 12 after transplantation. Campath-1G was administered intravenously in a dose of 10 mg daily during the 5 days before and 5 days after transplantation to all eight patients receiving unrelated transplants as well as to one patient undergoing sibling transplantation (A.M.), and one receiving a 1-antigen mismatched transplant from his father (F.F.). Because of lymphoblastic crisis, conditioning for the latter patient also included 25 mg of intrathecal methotrexate in two divided doses given before the first scan and two further intrathecal injections before the scan on the sixth day after transplantation. This patient's leukemia relapsed 170 days after his transplant; before the final scan on the 231st day after transplantation, he received further intrathecal methotrexate (a total of 37.5 mg) and busulfan 8 mg/kg.

Prophylactic antibacterial, antifungal, and antiviral medication was given to all patients. Antiviral prophylaxis with ganciclovir (5 mg/kg intravenously five times per week) was given after engraftment (neutrophils $> 0.5 \times 10^9$/L) in seven patients at high risk for cytomegalovirus infection. Infections were treated with broad-spectrum antibiotics and antifungal medications as required. A variety of corticosteroids were used: dexamethasone for prevention of vomiting, hydrocortisone to prevent allergic reactions to blood and platelet transfusions, and methylprednisolone and prednisolone for the treatment of GVHD. In the text that follows, total steroid dosage is expressed as milligrams of prednisolone based on the following conversions: 1 mg dexamethasone = 6.7 mg prednisolone, 1 mg hydrocortisone = 0.25 mg prednisolone, and 1 mg methylprednisolone = 1.25 mg prednisolone. GVHD was graded by conventional criteria (15).

Two patients had autografts. Their conditioning consisted of oral busulfan (4 mg/kg per day) for 4 days before reinfusion of bone marrow. They did not receive total body irradiation or GVHD prophylaxis but did receive phenytoin while taking the busulfan.

Whenever possible, MR examinations were performed before conditioning and transplantation, in the early

follow-up period (4 to 6 days) after transplantation, in the intermediate follow-up period (2 to 4 months) after transplantation, and in the late follow-up period (6 to 11 months) after transplantation, depending on the patient's well-being. All studies were conducted on an HPQ Vista (Picker, Ohio) scanner operating at 1.0 T. Conventional two-dimensional multisection T1-weighted (720/20 [repetition time/echo time]) spin-echo sequences, mildly T2-weighted (2500/20) spin-echo sequences, heavily T2-weighted (2500/80) spin-echo sequences, and fluid-attenuated inversion recovery (FLAIR) (7500/120,2100) sequences were obtained, with a thickness of 7 mm and a matrix of 128 × 192.

A three-dimensional isotropic T1-weighted (21/6) radio frequency spoiled volume scan (35° flip angle, 25-cm field of view, 192 × 256 × 140 matrix, and 1.3-mm^3 voxel size) was obtained in the sagittal plane in 13 subjects and in the transverse plane in two subjects. A registration program involving segmentation of the brain, rigid body translation, and rotation as well as sinc interpolation was used to match successive volume scans to subvoxel dimensions (16, 17). Subtraction of the registered difference images was then performed. This technique reduced misregistration artifacts to the noise level and enabled small changes to the brain to be detected on repeat examinations. The registration technique has previously been validated with the use of phantom data (16) and healthy subjects. Accurate registration of multisection data is not possible with this technique (16, 17), so the conventional 2-D images were not registered.

Conventional and 3-D registered control MR scans were obtained in five volunteers (four men and one woman, 33 to 62 years old) to monitor physiologic changes and to test the stability of the scanning system. These scans were performed 1 month apart. In addition 3-D registered scans were obtained for three male volunteers both before the start of the study and at similar intervals as for the patients during the study. Six scans were obtained in each of these three volunteers. The gradient system was recalibrated during the course of four of the patients' studies. The volume scans were adjusted for the change in gradient strength before comparisons covering this period were made.

The conventional scans (T1-weighted, T2-weighted, and FLAIR) as well as the registered volume and subtraction images derived from them were analyzed by three observers using a five-point scale in which 0 = no change, 1 = equivocal, 2 = mild, 3 = moderate, and 4 = marked change. All grades were assessed in conference by consensus. The registered volume and subtraction images were assessed both in the original scan planes and after reformatting into the sagittal or transverse planes.

Results

No significant changes were observed among the control subjects (Fig 1). Clinical data and imaging findings for the patients are summarized in the Table. One patient (P.F.) declined to have conventional scans.

In eight patients who received allografts, grades 1 to 2 acute GVHD of skin and/or gut developed at intervals between 14 and 85 days after transplantation. Grade IV hepatic GVHD developed on day 20 in one patient (M.E.) with a history of manic-depressive illness. While receiving high-dose (1 g per day) methylprednisolone therapy, this patient suffered an acute psychosis with catatonia; this syndrome resolved with improvement in his liver function and reduction in his steroid dose. This was the only instance of neuropsychiatric disease in the series. Fatal septic shock occurred shortly after chemotherapy and radiation therapy in one patient (M.K.). Two patients (A.M. and F.F.) died of relapse of the leukemia at 4 and 8 months, respectively, after bone marrow transplantation.

On the conventional scans, ventricular enlargement was not observed on any of the early follow-up scans; it was seen on only three of 12 intermediate follow-up scans and on four of the nine late follow-up scans. No cortical atrophy (0 of 14 patients), meningeal thickening, or white matter changes were observed with the T1-weighted spin-echo, T2-weighted spin-echo, or FLAIR sequences on early, intermediate, or late follow-up scans.

The registered volume and subtraction images showed ventricular enlargement in nine of the 10 patients who had early follow-up scans, in 12 of the 13 patients who had intermediate follow-up scans, and in each of the 10 patients who had late follow-up scans. Cortical atrophy was also seen on nine of 10 early follow-up scans, on 12 of 13 intermediate follow-up scans, and in 10 of 10 late follow-up scans. Meningeal thickening of some degree was seen at some stage in 14 of 15 cases.

Ventricular Enlargement

The ventricular enlargement was manifest as a dark line on the subtraction image (Fig 2). In each of the cases in which the change was apparent on the initial scan after transplantation it became more obvious on the later follow-up scans. When no initial follow-up scan was performed (four cases), obvious changes were seen on the intermediate and late follow-up scans.

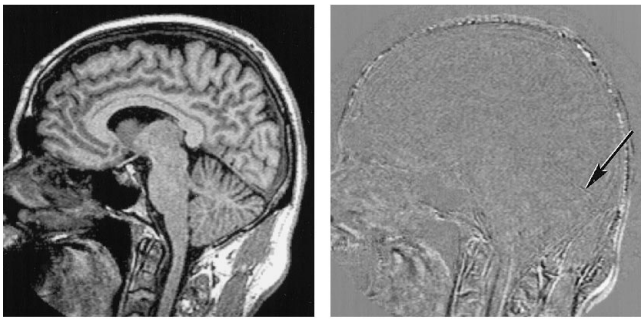
Clinical findings in 15 patients undergoing chemotherapy, radiation therapy, and bone marrow transplantation for chronic myeloid leukemia

Patient	Age, y/Sex	No. of Days Since Transplantation	Weight, kg	GVHD, grade*	Steroids (as mg of prednisolone)		Complications/ Outcome	Findings on Conventional Scans		Findings on Registered Volume and Subtraction Scans		
	Allograft/ Autograft				Dose for 48 hrs before Scan	Total Dose between Scans		Ventricular Enlargement	Cortical Atrophy	Ventricular Enlargement	Cortical Atrophy	Meningeal Thickening
L.F.	42/F	−8	63	. . .	0	. . .	Early relapse	. . .	. . .	. . .	. . .	. . .
	Allograft	4	64	0	50	515		0	0	3	2	0
		64	59	0	0	125		0	0	4	3	0
		237	55	2	30	560		0	0	4	3	1
M.H.	30/M	−6	72	. . .	0	. . .	Well	. . .	. . .	. . .	. . .	. . .
	Allograft	67	68	0	0	650		0	0	3	2	1
		285	71	0	0	0		0	0	3	3	2
E.W.	32/F	−8	52	. . .	0	. . .	Well	. . .	. . .	. . .	. . .	. . .
	Allograft	67	51	2	50	3700		0	0	3	3	1
		298	48	0	0	1500		0	0	3	2	2
S.R.	33/F	−84	56	. . .	0	. . .	Immune	. . .	. . .	. . .	. . .	. . .
	Allograft	4	57	0	25	645	thrombocytopenia;	0	0	3	3	2
		79	56	0	0	375	died on 358th day	0	0	4	4	2
		183	52	0	150	1200		2	0	4	4	1
M.E.	30/M	−8	69	0	0	. . .	Psychosis, persistent	. . .	. . .	. . .	. . .	. . .
	Allograft	4	64	0	0	625	GVHD	0	0	2	2	2
		60	60	4	625	19 525		1	0	4	3	2
A.M.	53/M	−8	80	. . .	0	. . .	Relapse; died on 129th	. . .	. . .	. . .	. . .	. . .
	Allograft	6	77	0	0	605	day	0	0	3	2	0
		84	72	2	200	800		1	0	4	3	1
J.B.	30/F	−8	82	. . .	0	. . .	Well	. . .	. . .	. . .	. . .	. . .
	Allograft	60	66	2	100	1125		0	0	3	3	0
		210	59	0	0	2870		0	0	4	2	1
P.F.	25/M	−8	73	. . .	0	. . .	Well	. . .	. . .	. . .	. . .	. . .
	Allograft	73	62	2	100	1960		. . .	. . .	3	2	0
		339	75	0	0	960		. . .	. . .	3	3	0
F.F.	18/M	−10	101	. . .	0	. . .	Sinusitis, relapse; died	. . .	. . .	. . .	. . .	. . .
	Allograft	6	98	0	25	600	on 247th day	0	0	3	1	1
		84	91	2	12.5	1890		1	0	3	2	1
		231	87	0	25	1950		2	0	4	3	2
P.D.	40/M	−10	73	. . .	0	. . .	Well	. . .	. . .	. . .	. . .	. . .
	Allograft	4	62	2	100	100		0	0	2	1	1
		227	75	0	0	1760		0	0	4	3	1
I.H.	32/M	−8	76	. . .	0	. . .	Well	. . .	. . .	. . .	. . .	. . .
	Allograft	4	69	0	0	425		0	0	2	1	1
		62	68	3	10	1970		0	0	3	3	1
		210	64	0	0	0		1	0	4	4	2
M.K.	36/F	−8	66	. . .	15	. . .	Septic shock; died on	. . .	. . .	. . .	. . .	. . .
	Allograft	4	66	0	40	550	13th day	0	0	3	2	1

TABLE: Continued

Patient	Age, y/Sex	No. of Days Since Transplantation	Weight, kg	GVHD, grade*	Steroids (as mg of prednisolone)		Complications/ Outcome	Findings on Conventional Scans		Findings on Registered Volume and Subtraction Scans		
	Allograft/ Autograft				Dose for 48 hrs before Scan	Total Dose between Scans		Ventricular Enlargement	Cortical Atrophy	Ventricular Enlargement	Cortical Atrophy	Meningeal Thickening
M.O.	48/F	−8	63	. . .	0	. . .	Otitis externa, Well	. . .	. . .	. . .	. . .	. . .
	Allograft	4	61	0	0	500		0	0	2	0	0
		60	59	1	20	2100		0	0	3	2	0
		225	59	0	10	1410		1	0	3	2	1
P.D.	56/F	−8	76	. . .	0	. . .	Mastoid infection, Well	. . .	. . .	. . .	. . .	. . .
	Autograft	73	65	0	0	125		0	0	3	2	2
J.W.	52/M	−8	95	. . .	0	. . .	Well	. . .	. . .	. . .	. . .	. . .
	Autograft	6	93	0	0	0		0	0	0	0	0
		112	93	0	0	20		0	0	0	0	1

* A grade of 0 indicates no change; 1, equivocal; 2, mild; 3, moderate; and 4, marked change.



A B

Fig 1. Healthy adult male control subject.

Initial T1-weighted volume scan is shown in *A*. A follow-up scan was performed 1 month later, and the registered difference image produced by subtracting the first image from it is shown in *B*. On this precisely registered difference image, the signal from the brain is reduced to the general noise level apart from some structure in the straight sinus (*arrow*). This may be due to a change in its size. The skull and scalp show differences caused by a change in the distribution of blood and soft-tissue deformation.

Cortical Atrophy

Cortical atrophy was manifest as dark regions around the gyri and over the brain on the registered subtraction images. It was present in all the early follow-up scans and became more obvious when intermediate and late follow-up scans were obtained (Fig 2).

Meningeal Change

Meningeal change was manifest as a white line on the registered subtraction image (Fig 3). It followed the contour of the dura mater (parallel to the inner table of the skull) rather than that of the pia mater along the surface of the brain. This feature became more obvious on subsequent follow-up scans in seven cases, was the same in three cases, and became less obvious in one case.

In seven cases the bone marrow increased in signal intensity. Changes in the scalp were seen, but these were difficult to evaluate, since changes in the scalp were seen with differences in patient position.

Of the two patients who underwent autografting, one (P.D.) showed similar changes to those of the allograft patients, but the other who received an autograft (J.W.) showed no ventricular enlargement or cortical atrophy and only very mild meningeal change on one of his late follow-up scans.

Discussion

The detection of changes to the brain in patients undergoing conditioning and allogeneic bone marrow transplantation is a matter of considerable interest, as is the fact that these changes appeared early, increased in extent, and were still present up to 11 months later. The relationship of these findings to intellectual performance is uncertain at present, but cognitive impairment after bone marrow transplantation has been described (18, 19).

The ventricular enlargement and cortical atrophy seen on the registered volume and subtraction scan occurred early and increased over several months. It did not have the imaging

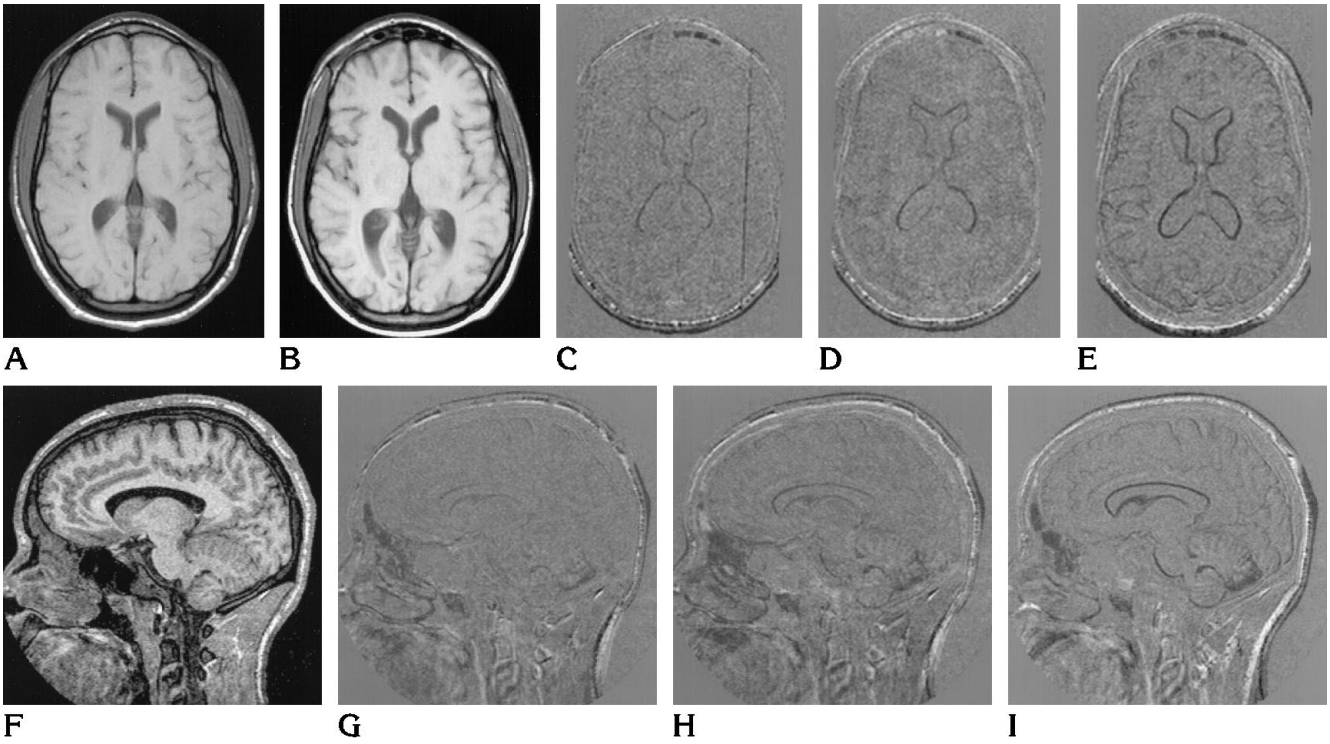


Fig 2. Ventricular enlargement and cortical atrophy in patient F.F.

Transverse T1-weighted (720/20) spin-echo images before (*A*) and 231 days after (*B*) transplantation.

Transverse difference image obtained 6 days after transplantation minus image obtained before transplantation (*C*), 84 days after minus the before image (*D*), and 231 days after minus the before image (*E*).

Initial sagittal volume image obtained before transplantation (*F*) and difference images obtained 6 days after transplantation minus image obtained before transplantation (*G*), 84 days after minus the before image (*H*), and 231 days after minus the before image (*I*). A change in ventricular size can just be seen by comparing *A* with *B* (the difference was graded as 2). Progressive increase in ventricular size is readily recognized as a dark line around the ventricles on images *C*, *D*, and *E* (graded as 3, 3, and 4, respectively). Changes involving the cortex are just seen in *C* and *D*, and become obvious in *E*. The vertical line on *C* is an artifact. The sagittal difference images (*G*, *H*, and *I*) confirm the progressive ventricular enlargement and show equivocal (*G*), mild (*H*), and moderate (*I*) changes in the cortex. Bone marrow changes are noted on the difference images.

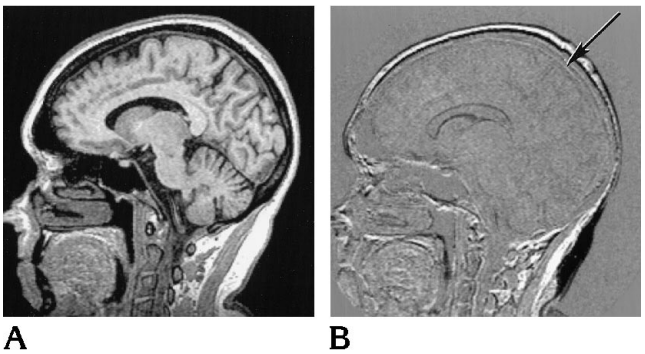


Fig 3. Meningeal change in patient P.D., who received an autograft.

T1-weighted volume image (*A*) and difference image (*B*) produced from image obtained 73 days after transplantation minus image obtained before engraftment. Meningeal changes are seen as a faint white line (*arrow*). The ventricular enlargement and cortical atrophy are noted.

characteristics of acute radiation injury, which produces cerebral edema and in any case should have resulted in a decrease in ventricular size and obliteration of sulci. The radiation dosage was also low for this complication.

Cerebral atrophy has been described as a consequence of long-term administration of steroids, and reversibility of this finding may follow a decrease or cessation of steroid use (20). The appearance of atrophy is typically described with long-term steroid use (6 months to 5 years) and cumulative doses of 4000 to 58 000 mg of prednisone (20). Assessing the potential effect of steroids is complex. All 15 patients in our study had steroids at some stage in their illness. The total dosage for allograft patients varied from the equivalent of 100 mg to 20 250 mg of prednisolone. The two patients who received autografts had totals of only 125 mg and 20 mg prednisolone, respectively. The

patient with the lowest dose of steroids (autograft) showed no ventricular enlargement or cortical atrophy.

In the allograft patients, ventricular enlargement either remained the same (three patients) or increased (nine patients) on follow-up studies. Three patients received no steroids (for 148 to 222 days) between their intermediate and late follow-up scans. In one of these the ventricular size remained the same; in the other two patients it increased. Thus, there was no evidence of reversibility of ventricular size in any patient. This might have been expected in patients in whom steroid treatment was reduced or stopped. Overall, the onset of brain changes occurred at the same time as treatment with steroids, cyclophosphamide, and total-body irradiation, but there did not appear to be a particular association with steroids given in the previous 48 hours. There was no evidence of reversibility when steroids were reduced or stopped.

Reversible cerebral atrophy has been described in patients with anorexia nervosa (21, 22), and some of the patients in this study had clinical features similar to those of anorexia nervosa, in particular, substantial weight loss. At the last follow-up examination, 11 had lost weight, one had retained the same weight, and two had increased weight. Changes in the brain did not reverse in these latter three patients. Of the two patients who had autografts, the patient who lost 11 kg showed brain changes while the patient who lost only 2 kg showed no change.

Dehydration might account for the early brain changes. Seven patients who had early follow-up scans lost weight (2 to 11 kg) between their baseline and early follow-up scans, one remained the same, and three gained weight. One patient (J.W., autograft), who lost weight, showed no change in the brain. The other patients, who both lost and gained weight, all showed ventricular enlargement and cortical atrophy. In general, acute disturbances of the fluid balance would be expected to revert to the pretransplant state on late follow-up studies.

The toxicity associated with cyclosporine is relatively specific (9) and involves hypertension, severe visual disturbances, and occipital lobe changes. These complications were not seen in this study.

It is possible that some other drug besides steroids and cyclosporine may have caused the MR changes. High-dose methotrexate has been associated with cerebral atrophy in late follow-up scans when it was used for treatment of osteosarcoma (7). However, the dosage was much higher than in the cases described here. Neuronal loss may be a cause of atrophy in this context, but the changes appeared relatively early for this complication.

The cortical atrophy followed a time course similar to the ventricular enlargement. Many of the remarks made about ventricular enlargement also apply to cortical atrophy. In fact the change overall could be regarded as one of cerebral atrophy. This view is supported by the changes seen in the brain stem and cerebellum in Fig 2H and I.

The meningeal thickening was of interest. "Duropathy" has been described in one case after autologous bone marrow transplantation for breast cancer (4). The meningeal thickening may represent an inflammatory response to radiation or reactive changes associated with increased vascularity in the external carotid artery territory as a result of irradiation.

No changes in white matter were seen in this series. A subtle reduction in white matter volume may have been present and manifest as an increase in ventricular and sulcal size rather than as a change in T1 or T2. The conventional T2-weighted and FLAIR sequences that were used are particularly sensitive to changes in T2, and the changes in white matter signal intensity are usually quite obvious.

This study raises a number of questions that could be addressed in further studies. It will be of interest to follow the present group of patients for a further period to see how long the brain changes persist. It will also be of importance to correlate changes in the brain with studies of cognitive impairment. Patients receiving autografts may form a particularly useful control population for assessing the effects of radiation and drugs. The absence of change in the one patient in this series is of considerable interest. Diffusion-weighted imaging, which is particularly sensitive to acute injury, might prove to be more sensitive than the sequences used in this study for detecting changes in white matter. Contrast enhancement may be of value in assessing the significance of the meningeal thickening (23). This feature is important in its own right but it needs to be recognized in the context of suspected infection or spread of disease after transplantation when thickening and/or enhancement might be misdiagnosed as a feature

of disease (infection or malignant infiltration) rather than as a side effect of the treatment.

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