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The Effect of Human Leukocyte Antigen Disparity on Cyclosporine Neurotoxicity after Allogeneic Bone Marrow Transplantation

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PURPOSE: **We examined the relationship between human leukocyte antigen (HLA) matching and the development of cyclosporine (CyA) neurotoxicity in patients undergoing allogeneic bone marrow transplantation, and determined the frequency and imaging characteristics of CyA neurotoxicity in these patients.**

METHODS: **Records of 87 patients who underwent allogeneic bone marrow transplantation were reviewed. Eight patients who presented with visual disturbance and/or seizures and had MR imaging within 24 hours were identified. Transplant donor relatedness was examined, and patients' imaging studies were reviewed. Clinical parameters, including blood pressure, CyA, creatinine, and magnesium levels, and the presence of graft-versus-host disease were reviewed.**

RESULTS: **CyA neurotoxicity was seen more frequently in HLA-mismatched and unrelated donor transplants. The frequency of CyA neurotoxicity was 4% for patients with a 5/6 or 6/6 HLA match, 13% for matched unrelated donor transplants, and 50% for haplotypic 3/6 or 4/6 transplants. Patients with matched unrelated donor transplants and haplotypic transplants presented earlier in the posttransplant time course and had decreased survival time relative to patients with HLA-matched transplants. Imaging abnormalities most commonly affected the occipital lobes and the posterior cerebral hemispheres; both cortical and white matter involvement was identifiable as T1 hypointense and T2 hyperintense signal with associated gyral swelling and sulcal effacement on the initial MR studies. Hypodensity in the affected areas was noted on CT scans. Contrast enhancement was seen in HLA-mismatched and unrelated transplants only. Follow-up imaging showed interval decreases in subcortical edema; however, residual signal abnormality, primarily affecting the cortex, was present in all cases and seen best on proton density–weighted MR images.**

CONCLUSION: **The frequency of severe CyA neurotoxicity increases with increasing HLA disparity, suggesting that immune factors may play a role. CyA neurotoxicity appears to represent a spectrum of disease processes. Disruption of the blood-brain barrier as well as hypoxic or vasculitic cortical injury resulting in MR-detectable cortical signal abnormalities may occur in severe cases.**

Cyclosporine (CyA) is a potent immunosuppressant used to prevent graft-versus-host disease (GVHD) after allogeneic bone marrow transplantation (BMT) and solid organ transplantation (1). Common side effects include renal dysfunction, electrolyte abnormalities, hypertension, and tremors (2). Severe neurotoxicity, including ataxia and occipital blindness, although rare, have also been reported after CyA use. Recently, a clinical syndrome consisting of seizures and visual disturbances has been described in association with predominantly occipital/posterior cerebral abnormalities on both computed tomography (CT) and magnetic resonance (MR) imaging studies in patients receiving CyA (3–16). The majority of reported cases of CyA toxicity have been described in connection with solid organ transplants; the reported high prevalence of CyA neurotoxicity in liver transplantation may be related to liver failure and preexisting disturbance of the blood-brain barrier (9). Earlier reports have focused on the transient nature of the clinical symptoms and the imaging findings affiliated with this syndrome, the most commonly re-

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ported being white matter edema (4, 6, 7, 12, 17). Several reports have also noted the existence of associated cortical signal abnormalities (13, 18, 19).

CyA neurotoxicity has also been reported in patients undergoing allogeneic BMT (13, 17, 18). One study suggested a relationship between human leukocyte antigen (HLA) disparity and development of CyA neurotoxicity after allogeneic BMT; however, MR findings were described for only one of the 10 cases reported (13). Increasing HLA disparity in allogeneic BMT is associated with an increased prevalence of GVHD, which is a risk factor for microangiopathy (20). Microangiopathy and endothelial injury have been proposed as etiologic factors in CyA toxicity (4, 13, 16, 21–24). CyA neurotoxicity may therefore be expected to occur with increased frequency in those prone to the development of microangiopathy. We discuss the frequency of CyA-associated neurotoxicity in patients undergoing allogeneic BMT for malignant hematologic disease, examine its relationship to HLA matching, and describe its serial imaging appearance.

Methods

Records of 87 patients undergoing allogeneic BMT for malignant hematologic processes between January 1994 and April 1996 were reviewed. All patients received high-dose chemotherapy with or without radiation prior to receiving donor marrow. On the day before marrow reinfusion (day −1), CyA (3 mg/kg per day) was started in all patients as GVHD prophylaxis. Dosage estimates were based on CyA levels. Marrow matching was performed for a best possible match of six HLA loci. If no appropriate donors were available, a matched unrelated donor was identified through the national bone marrow program. Donor marrow from an HLA-matched related or matched unrelated donor was reinfused on day 0. Further immunosuppression with steroids was given to all patients starting on day 7.

Fifty patients received marrow from a 5/6 or 6/6 HLA-identical sibling, 33 from a matched unrelated donor, and four from a related donor with a 3/6 or 4/6 match (haplotypic donor). Eight patients who presented with neurologic symptoms and had MR imaging within 24 hours of symptom onset were identified. Four patients also had a CT study at presentation. The time of presentation ranged from day 12 to day 304 after transplantation. MR imaging was performed with both T1-weighted (450–600/10–19/1 [repetition time/echo time/excitation]), fast spin-echo proton density–weighted (2500–2800/15–17/2), and T2-weighted (4200/102/2) sequences. Patients who were imaged before July 1995 had T1-weighted and fast spin-echo T2-weighted studies only. T1-weighted studies were also obtained after intravenous infusion of gadodiamide at standard dosages (0.1 mmol/kg). All MR imaging was done on a 1.5-T unit. Images were examined for the presence of cortical and subcortical signal abnormality, gyral swelling, and edema. The presence, location, and extent of contrast enhancement was noted. Images were reviewed by two neuroradiologists, and interpretations were obtained by consensus. Clinical information was available at the time of imaging review. Follow-up studies were obtained as clinically indicated, ranging from 1 day to 16 weeks after presentation. Six patients had follow-up MR examinations and two had follow-up CT studies.

CyA levels were noted at the time of presentation, along with levels of magnesium, blood urea nitrogen, creatinine, and blood pressure. Evidence of GVHD was noted, of which typical manifestations include skin rash, diarrhea, and liver function abnormalities. The presence of microangiopathic hemolytic anemia was sought by examination of peripheral blood smears and comparison with laboratory examinations, such as decreased platelet count and increased lactate dehydrogenase and bilirubin.

Results

Of the 87 patients who underwent allogeneic BMT, eight (9%) incurred severe neurologic symptoms and underwent MR imaging. Fifty patients had received marrow from a matched, 5/6 or 6/6, HLA-identical sibling; 33 from a matched unrelated donor; and four from a related mismatched, 3/6 or 4/6 (haplotypic), donor. Six of the eight patients with neurologic changes had received marrow from a matched unrelated (n = 4) or haplotypic (n = 2) donor. They presented a median of 28 days (range, 12 to 48 days) after transplantation. The two patients who had a 5/6 or 6/6 matched donor presented much later after transplantation (days 197 and 304, respectively). The frequency of CyA neurotoxicity was 4% for patients with a 5/6 or 6/6 HLA match, 13% for those with matched unrelated donor transplants, and 50% for those with haplotypic 3/6 or 4/6 transplants.

The typical imaging findings are described in the Table and illustrated in Figures 1 and 2. The most common finding was involvement of the posterior portions of the cerebral hemispheres and was seen in seven of the eight patients. The occipital lobe was involved in seven patients, and the parietal lobe in six. Findings were usually symmetric. All occipital and parietal lobe abnormalities were identifiable as regions of T1 hypointense and T2 hyperintense signal affecting the cortex as well as the subcortical white matter, with associated gyral swelling and sulcal effacement. In three patients who had coincident CT studies, scans showed hypodensity of the cortex and the subcortical white matter in the affected areas. One patient had normal CT findings at presentation.

Three patients had associated posterior temporal cortical and subcortical abnormalities at presentation. In addition, frontal lobe abnormalities were identified on both T1- and T2-weighted images in three patients. The remainder of the parenchymal abnormalities were not associated with significant mass effect and were most apparent on T2-weighted images. One patient had T2 bright signal abnormality within the pons without the occipital or parietal findings seen in the other seven patients. Abnormality in the pons was seen in one other patient. Other findings included T2 bright signal abnormalities in the thalami (n = 1), midbrain (n = 1), and caudate nuclei (n = 1). One patient had evidence of a small cortically based occipital hemorrhage at presentation (Fig 1).

In four patients, cortical enhancement was seen on the initial MR examination. All three of the patients who presented with seizures had frontal and parietal abnormalities on imaging, and each had patchy cortical enhancement. This subtle cortical enhancement involved the pericentral gyri in two patients and the parietal and postcentral regions in one patient; another patient who presented with visual disturbance had extensive posterior temporal and occipital en-

Clinical characteristics and imaging findings in eight patients with cyclosporine neurotoxicity after allogeneic bone marrow transplantation

Case	Age, y/Sex	Hematologic Disease	Donor Characteristics	No. of Days after BMT that Toxicity Developed	Clinical Presentation	Area/Type of Abnormal MR Findings	Survival after Toxicity, d
1	12/M	AML	3/6 Sibling	32	Seizures	Bioccipital, biparietal, postcontrast enhancement	176
2	28/F	Aplastic anemia	6/6 Sibling	304	Visual disturbance	Bioccipital, biparietal	112
3	28/F	NHL	Matched unrelated donor	12	Cortical blindness	Bioccipital, hemorrhage	21
4	22/M	AML	4 /6 Sibling	48	Seizures	Bioccipital, biparietal, bifrontal, post-contrast enhancement	15
5	22/M	CML	Matched unrelated donor	37	Seizures, visual disturbance	Bioccipital, biparietal, postcontrast enhancement	152
6	44/F	CML	Matched unrelated donor	22	cortical blindness	Bioccipital, biparietal, bifrontal	166
7	45/M	NHL	6/6 Sibling	197	Visual disturbance	Pons	153
8	20/F	ALL	Matched unrelated donor	16	Cortical blindness	Bioccipital, postcontrast enhancement	16

Note.—ALL indicates acute lymphocytic leukemia; AML, acute myelogenous leukemia; CML, chronic myelogenous leukemia; MUD, matched unrelated donor; and NHL, non-Hodgkin lymphoma.

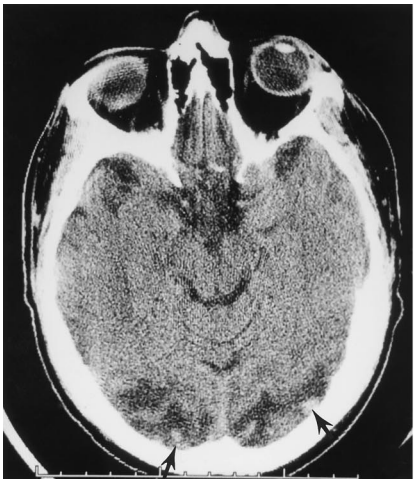


FIG 1. Patient 3: 12 days after transplantation. Axial noncontrast CT scan shows characteristic bioccipital hypodensity. Also seen is minimal cortical hemorrhage (*arrows*).

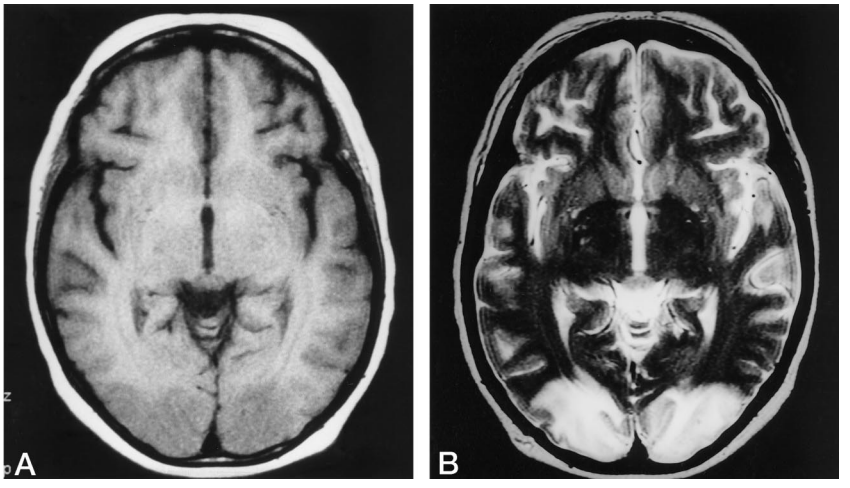


FIG 2. Patient 2: 304 days after transplantation.
Axial T1-weighted (450/19/1) (*A*) and T2-weighted (3800/102/2) (*B*) images show characteristic bioccipital signal abnormality involving the cortex and subcortical white matter, with associated gyral swelling and sulcal effacement.

hancement (Figs 3–5). Contrast enhancement was noted in matched unrelated donor and haplotypic transplants only. In one patient, T2 bright signal abnormality and enhancement within the cingulate gyrus developed 2 weeks after presentation.

The most common neurologic symptom was visual disturbance (n = 6), including cortical blindness in three patients. Two patients had generalized seizures but no visual changes, and one patient had both visual disturbances and seizures at presentation. Symptoms were not correlated with CyA levels, and no patient had elevated CyA levels at the time of presentation with neurologic symptoms. Magnesium and creatinine levels were normal in all patients, as was the mean blood pressure. Blood urea nitrogen was minimally elevated in two patients. CyA was discontinued in seven patients; one patient was judged to be at high risk for the development of GVHD and therefore CyA was maintained at a reduced dose. All neurologic sequelae improved after the discontinuation or reduction of CyA.

Follow-up studies showed improvement in all patients after reduction or discontinuation of CyA. The earliest sign of improvement was resolving edema, with decreases in cortical swelling and sulcal effacement. However, all patients had residual abnormalities on follow-up images. This was best seen as gyriform hyperintensity on proton density–weighted fast spin-echo MR images (Figs 5 and 6). One patient also had gyriform T1 hyperintense signal in the right frontal cortex (Fig 6). Brain stem abnormalities became less apparent on follow-up T2-weighted images. Residual signal abnormality was seen on MR studies up to 10 weeks after presentation, which was the latest follow-up MR study obtained (Fig 6). The two patients who had follow-up CT had residual bioccipital

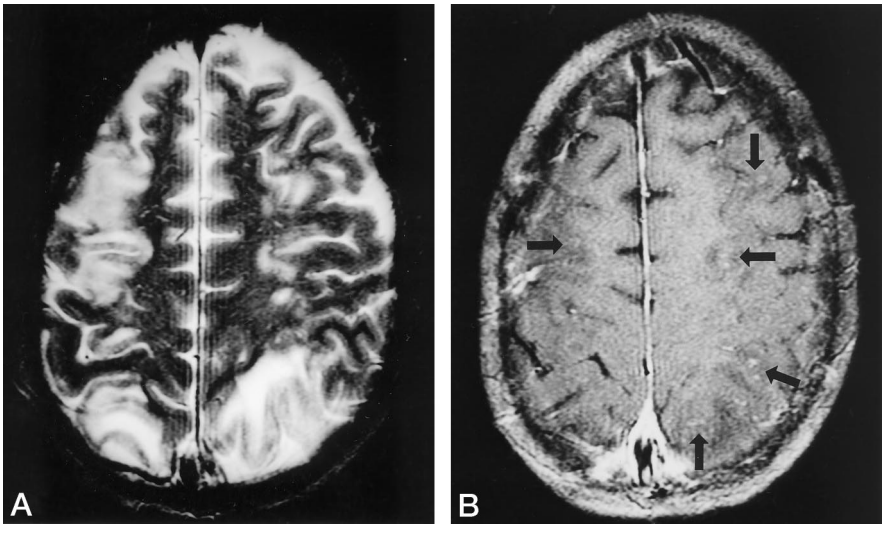


FIG 3. Patient 4: 48 days after transplantation.
A, Axial T2-weighted (4300/102/2) image shows bifrontal/biparietal cortical and subcortical abnormalities.
B, Axial contrast-enhanced T1-weighted (500/19/1) image shows cortical swelling and subtle, patchy cortical enhancement (*arrows*).

hypodensity, seen at 16 weeks in patient 2 and at 2 weeks in patient 8. Survival time is indicated in the Table; all deaths were attributed to complications related to the patient's primary disease and to immunosuppression.

Discussion

A number of previous reports (3–16) have described the syndrome of CyA neurotoxicity and its imaging appearance on CT and MR studies. The initial clinical manifestations may be subtle, and the diagnosis may be missed without imaging examinations. Early diagnosis is important as it may lead to alterations in immunosuppressive therapy, although discontinuation of CyA may be unnecessary (12, 13). The transient and potentially reversible nature of this syndrome has been emphasized previously; however, we found residual cortical signal abnormality on follow-up MR images in patients with CyA neurotoxicity after allogeneic BMT, a finding that may indicate more extensive cellular injury in this population.

The pathogenesis of this syndrome is not clear. Increased CyA levels, hypocholesterolemia, hypomagnesemia, and aluminum overload have all been discussed as possible contributing causes (25–29). Low serum cholesterol may lead to increased brain uptake by increasing the concentration of CyA in lipoprotein particles (25). Hypomagnesemia and aluminum overload may increase the potential for seizures in these patients (27, 29). However, we found no evidence that these were contributing factors in our group of patients.

More recently, the similarity between CyA neurotoxicity, hypertensive encephalopathy, eclampsia, and chemotherapeutic neurotoxicity has been noted (15, 17, 19, 30–33). It has been postulated that the characteristic posterior cerebral location of both CyA and hypertensive encephalopathy is due to the posterior circulation's decreased ability to respond (owing to decreased sympathetic innervation) to increases in systemic blood pressure via autoregulatory vasoconstriction. Because the mechanism of CyA-associated hypertension is thought to be caused by activation of the sympathetic nervous system, even subtle increases in blood pressure in a state of chronic sympathetic activation could theoretically lead to edema within the posterior circulation (15, 34, 35). It has been suggested that this high-pressure autoregulatory failure may lead to cerebral hyperperfusion, resulting in disruption of the blood-brain barrier, extravasation of fluid, and cerebral edema. With early diagnosis and treatment, these changes may be reversible. Without treatment, permanent cortical injury may result (33). In our series, all eight patients had normal blood pressure readings before neurologic symptoms developed, although subtle increases or transient elevations could easily have been missed.

In our series, the development of severe CyA-related neurotoxicity was noted in eight (9%) of 87 patients undergoing allogeneic marrow transplantation. Neurotoxicity was noted with increased frequency in HLA-disparate patients: 4% of patients with an HLA-identical (5/6 or 6/6) match were affected, 13% of patients with matched unrelated donor transplants were affected, and 50% of the patients with haplotypic HLA (3/6 or 4/6) transplants were affected (n = 4). Clinical presentation also appears to differ for the matched unrelated donor transplants and the haplotypic transplants. These patients presented earlier after transplantation (median, day 28) and had a very poor prognosis, with a median survival of only 98 days after the syndrome developed. The two patients with HLA-identical sibling donors presented later in the course of their disease (median, day 250) and lived a median of 130 days after neurotoxicity developed. In general, more extensive changes were noted in patients who presented soon after transplantation (Figs 3, 4, and 6).

CyA has profound effects on the vascular endothelium, causing endothelial cells to release endothelin, a potent vasoconstrictor, as well as prostacyclin and thromboxane A2, which have been

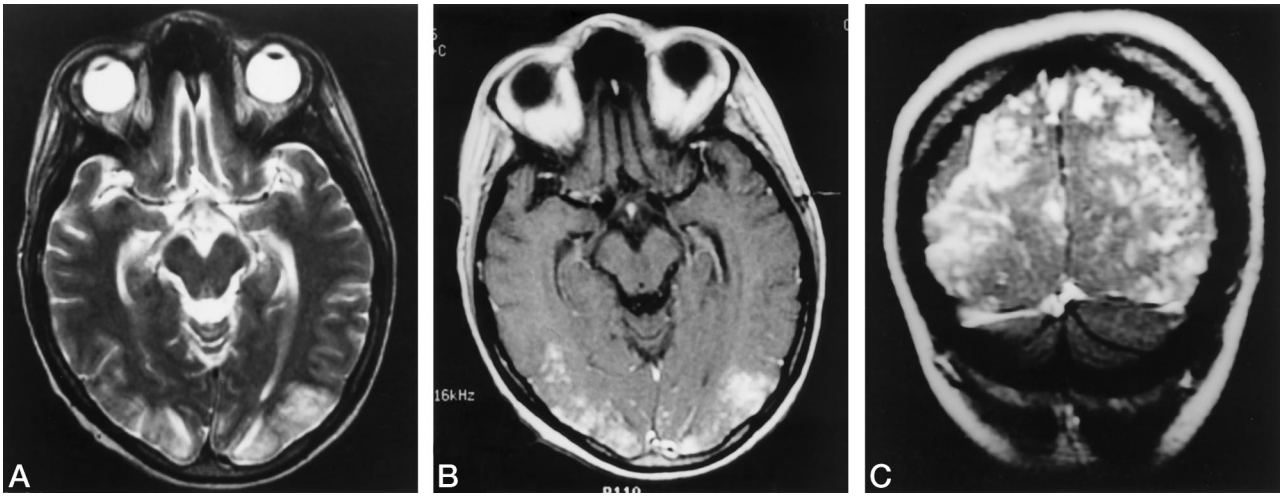
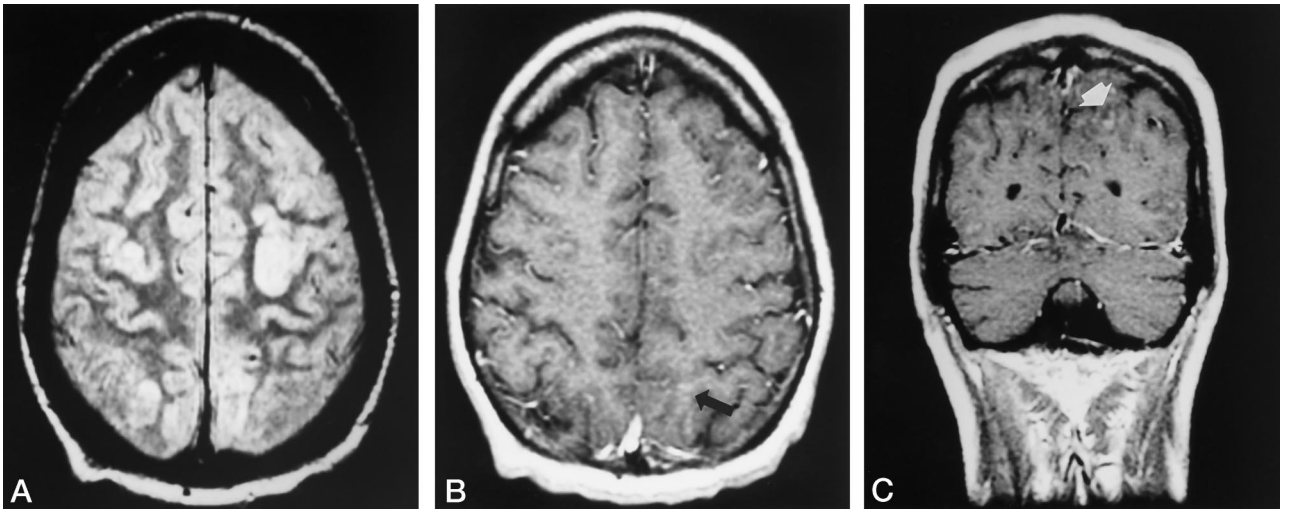


FIG 4. Patient 8: 16 days after transplantation.

Axial T2-weighted (4300/102/2) image (*A*) and axial (*B*) and coronal (*C*) contrast-enhanced T1-weighted (600/23/1) images show bioccipital T2 hyperintense signal and extensive enhancement.



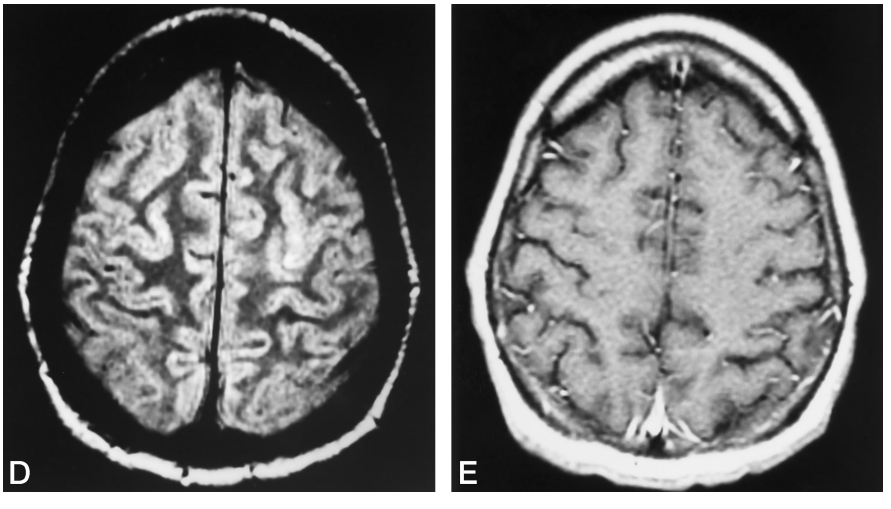


FIG 5. Patient 5.

At 37 days after transplantation, proton density–weighted (2700/17/2) image shows bifrontal/biparietal hyperintense signal abnormalities, and contrast-enhanced axial (*B*) and coronal (*C*) T1-weighted (500/19/1) images show sulcal effacement and subtle parietal enhancement (*arrow*), best seen on the coronal image.

At 54 days after transplantation, proton density–weighted image (*D*) shows residual gyriform abnormality, and axial T1-weighted image (*E*) shows decrease in sulcal effacement and resolution of cortical enhancement.

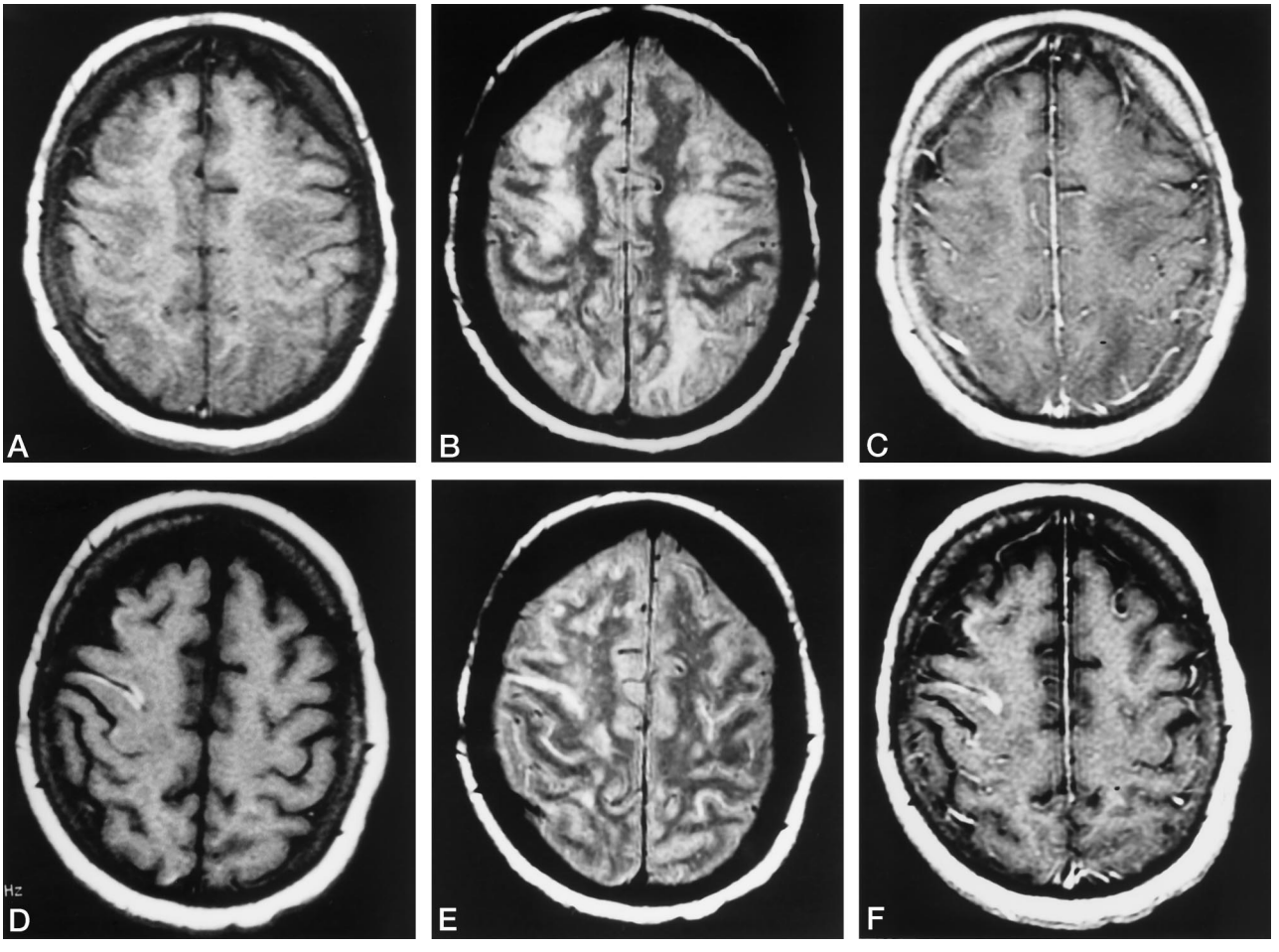


FIG 6. Patient 6.

At 26 days after transplantation, axial T1-weighted (400/10/1) image (*A*) and proton density–weighted (2800/17/2) image (*B*) show extensive bilateral T1 hypointense and proton-density hyperintense frontoparietal signal abnormalities involving the cortex and subcortical white matter. Axial contrast-enhanced T1-weighted (400/10/1) image (*C*) does not show cortical enhancement.

At 92 days after transplantation, axial T1-weighted (*D*) and proton density–weighted (*E*) images show the interval development of gyriform T1 and proton-density hyperintense signal involving the right frontal cortex. There has been an interval decrease in gyral swelling and edema. Note gyriform hyperintensity involving the left frontal and parietal cortex on proton density–weighted image; no corresponding signal abnormality is seen on the T1-weighted image. Again, axial contrast-enhanced image (*F*) does not show enhancement.

associated with thrombotic microangiopathy in BMT patients (17, 22–24). A recent review suggests that CyA toxicity may be related to transplantation-associated thrombotic thrombocytopenic purpura (TTP), and that distinguishing between the two entities may be difficult (36). CyA-induced endothelial damage has been proposed as the cause of post-BMT TTP (37–42). Since the majority of patients who receive CyA do not contract TTP or neurotoxicity, other factors must be involved. Earlier investigators have suggested GVHD is the most significant risk factor for the development of microangiopathy. (20) A cytokine release cascade initiated by endothelial damage could explain both the clinical and radiologic picture of CyA-induced neurotoxicity. Since increasing HLA disparity is associated with an increased risk of GVHD, the accompanying cytokine release could explain the increasing frequency of CyA neurotoxicity as HLA disparity increases. It is noteworthy that none of our patients had evidence of hemolysis, which is the hallmark of TTP.

One group of investigators has stated that cortical abnormalities seen best on proton density–weighted MR images are an early sign of CyA toxicity. However, in their series, patients were imaged late (mean, 18 days) after onset of neurologic symptoms (16). We believe that subcortical/white matter edema is an earlier imaging finding than the previously described cortical hyperintensity seen on proton density–weighted images. In our series, all patients were imaged within 24 hours of presentation, and cortical swelling and associated white matter edema were seen in seven of the eight patients. Follow-up imaging studies showed resolution of the subcortical abnormalities, although we did find residual cortical abnormalities similar to those described in the earlier study (16) (Figs 5 and 6). We believe that this residual cortical hyperintensity on proton density–weighted images is actually a late finding. We do agree, though, that this cortical signal abnormality most likely reflects severe cellular injury.

In contrast to that prior report (16), we noted that

the location of the cortical abnormalities on MR images corresponded to clinical symptomatology. All patients with occipital abnormalities at imaging reported some degree of visual disturbance (Figs 1, 2, and 4). The three patients who presented with generalized seizures had frontoparietal abnormalities on MR studies as well as pericentral enhancement on postcontrast images (Figs 3 and 5). Residual right cortical hyperintensity at 10 weeks also corresponded to residual weakness of the left arm in one patient (Fig 6). In patient 6, the T1 hyperintensity had a striking similarity to cortical laminar necrosis, with T1 hyperintensity most likely representing fat-laden macrophages or subacute hemorrhage (43, 44) (Fig 6). These findings bolster the theory that cortical signal abnormality is indicative of severe cellular injury and support a hypoxic or vasculitic pathogenesis as a factor in the development of CyA neurotoxicity. Complete resolution of the cortical signal abnormality on follow-up imaging would not necessarily be expected.

We agree that this syndrome should not be referred to as a posterior leukoencephalopathy (19), because, in our experience with CyA neurotoxicity, the cortex is invariably involved. In no instance were the imaging abnormalities completely reversible, in contrast to descriptions in previous reports (4, 6, 7, 17). This lack of reversibility may be due to the fact that our follow-up was relatively short, the longest being 16 weeks for CT and 10 weeks for MR imaging. However, the length of follow up was limited by patient survival. It is more likely that this syndrome represents a spectrum of disease processes, with varying degrees of severity. In mild cases, reversible white matter edema may be the only imaging abnormality evident. With more severe involvement, cell death and permanent cortical injury may occur. In cases of extensive involvement, such as that seen in our patients with matched unrelated donor and haplotypic donor transplants, severe injury may lead to early disruption of the blood-brain barrier and cortical enhancement on the initial study (Figs 3–5). This theory is supported by our finding that cortical enhancement was seen only in patients with transplants from HLA-disparate donors.

Conclusion

Although our patient population was small, our findings suggest that the frequency of CyA neurotoxicity increases with increasing HLA disparity. While hypertension most likely plays an important role in the development of CyA neurotoxicity, we believe that immune factors, which may result in an aggravated cytokine response, may also play an important etiologic role. These cytokines may contribute to vascular injury, leading to disruption of the blood-brain barrier and, ultimately, to cortical injury. If edema is the earliest radiologic sign of CyA neurotoxicity, it is reasonable to assume that MR imaging is more sensitive than CT in the early detection of this syndrome, since the former is more sensitive to subtle changes in tissue water content. MR imaging has been shown to be more sensitive in the detection of hypertensive encephalopathy (45), although CT may be preferable for excluding associated hemorrhage (15) (Fig 1). Our data support the utility of MR imaging for the diagnosis of CyA neurotoxicity. By indicating early disruption of the blood-brain barrier, the addition of MR contrast agents may help to identify patients who are at greatest risk for severe or permanent cortical injury. It is hoped that increased awareness of this syndrome, as well as the development of new treatment regimens for the acutely ill transplant patient, will make longer term follow up possible, which, in turn, may shed further light on its etiologic factors and natural history. Since the neurologic symptoms may initially be subtle and missed without imaging, close clinical follow-up with early radiologic studies, such as MR imaging, is appropriate in these patients.

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