

## Encephalopathy in pediatric patients after allogeneic hematopoietic stem cell transplantation is associated with a poor prognosis

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### Summary:

**Encephalopathy is a poorly characterized complication of hematopoietic stem cell transplantation (HSCT). No comprehensive report of encephalopathy exists for children, and the literature contains only a few for adults. We analyzed a large cohort of 405 pediatric patients who underwent allogeneic HSCT during a 10-year period and identified 26 patients (6.4%) who experienced encephalopathy. Identifiable causes of encephalopathy included infection ( $n=5$ ), single or multiorgan failure ( $n=4$ ), medication-related complications ( $n=3$ ), nonconvulsive seizures ( $n=4$ ), acute disseminated encephalomyelitis ( $n=2$ ), thrombotic thrombocytopenic purpura ( $n=2$ ), and stroke ( $n=1$ ). We were unable to identify the etiology of encephalopathy in five (19%) patients. The prognosis for pediatric patients with encephalopathy was poor: only four (15%) experienced complete neurologic recovery, and 10 (38%) patients experienced partial recovery with residual neurologic deficits. Nine (35%) patients with complete or partial recovery survive long term. A total of 17 patients died; one died of progressive encephalopathy, and 16 died of either relapse of primary disease or toxicity. MRI, CSF analysis including molecular testing for infectious pathogens, and brain biopsy were helpful in obtaining a diagnosis in most of our patients. However, a standardized approach to accurate and timely diagnosis and treatment is needed to improve outcome in these patients.**

*Bone Marrow Transplantation* (2004) 33, 1151–1157.  
doi:10.1038/sj.bmt.1704480

Published online 12 April 2004

**Keywords:** encephalopathy; leukoencephalopathy; pediatrics

Encephalopathy after hematopoietic stem cell transplantation (HSCT) is a poorly described complication. Case reports have identified infectious causes of encephalopathy: JC virus,<sup>1,2</sup> central nervous system (CNS) toxoplasmosis,<sup>3–6</sup> human herpes virus-6 (HHV-6),<sup>7–9</sup> and a variety of fungal agents.<sup>4,5</sup> Noninfectious causes of encephalopathy included hypertension,<sup>10</sup> reversible posterior leukoencephalopathy syndrome,<sup>11</sup> and parkinsonism.<sup>12</sup> Encephalopathy can also be caused by cyclosporine, tacrolimus, ganciclovir, dimethyl sulfoxide, and amphotericin,<sup>11</sup> among other medications.

There are few comprehensive reports of encephalopathy in the literature. In one series, 25% of 115 adults with leukemia who underwent HSCT experienced major neurologic complications, including metabolic encephalopathy, seizures, psychiatric symptoms, or a combination of these conditions.<sup>13</sup> The incidence of neurologic complications may be higher after receiving bone marrow from a matched unrelated donor rather than from a matched sibling donor. In another series of 141 adult patients, the most frequently described complication was metabolic encephalopathy, which occurred in 18% of the patients.<sup>14</sup> In another review of neurologic complications of autologous and allogeneic HSCT, 11% of adult patients developed CNS or peripheral nervous system complications due to metabolic encephalopathy, electrolyte disturbances, or hypoxia.<sup>15</sup>

Little is known about encephalopathy after allogeneic HSCT in pediatric patients.

### Patients and methods

All patients were treated in the Hematopoietic Stem Cell Transplant Program at St Jude Children's Research Hospital on treatment protocols approved by the Institutional Review Board between November 1991 and January 2000, inclusive.

### HSCT and supportive treatment

Following HSCT, neutrophil engraftment was defined as the first occurrence of three consecutive days in which the patient's absolute neutrophil count was  $\geq 500/\text{mm}^3$ . Platelet engraftment was defined as the first day the patient's platelet count was  $\geq 20\,000/\text{mm}^3$  without transfusion.

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Received 28 October 2003; accepted 19 December 2003  
Published online 12 April 2004

Patients who received unmanipulated bone marrow grafts from a matched sibling donor also received graft-vs-host disease (GVHD) prophylaxis with cyclosporine and short-course methotrexate. Grafts from unrelated donors or partially matched family members were partially T-cell depleted using anti-CD6/CD8 antibodies and complement; patients who received these types of transplants also received GVHD prophylaxis with cyclosporine.

#### *Retrospective review of patient medical records*

The clinical database of the Stem Cell Transplant Service and International Classification of Disease-Ninth Revision (ICD9) codes were reviewed to identify patients with neurologic complications, encephalopathy, or both after HSCT. Encephalopathy was defined as altered mental status or sensorium persisting 24 h or longer that was not caused by narcotic or sedative medications. Patient medical records were reviewed in detail to assess comorbid conditions, prior neurologic status, pretransplantation conditioning, and donor source. Additionally, relevant diagnostic imaging, laboratory studies, and neurologic examinations were carefully reviewed. All diagnostic testing was performed using standardized laboratory methods. All CNS diagnostic images were reviewed by a single neuro-radiologist (KH).

Computed tomography (CT) and magnetic resonance imaging (MRI) of the brains of patients with encephalopathy were reviewed and compared. In most cases, MRIs included T1- and T2-weighted images, diffusion-weighted and fluid-attenuated inversion recovery (FLAIR) images. Electroencephalograms (EEGs) were reviewed by one of two neurologists (RBK or ST). Brain biopsy was performed in some patients when imaging revealed focal or biopsy-accessible lesions, when cerebral spinal fluid (CSF) tests were inconclusive, when the patient's status did not improve or worsened, or a combination of these events. Encephalopathy was attributed to Amphotericin B or Cyclosporine when a compatible MRI picture was seen, other diagnostic possibilities were excluded, and/or resolution of symptoms was seen after withdrawal of the medication. Patients were considered to have viral encephalopathy despite negative cultures if brain biopsy material, other site cultures, EEG, or MRI findings were most consistent with viral encephalitis and other causes were excluded.

#### *Statistical analyses*

The Fisher's exact test, Chi-square test, or both were used to determine statistically significant differences between patients with encephalopathy and those without in terms of sex, race, primary diagnosis, donor type, degree of HLA match, and presence of GVHD. The Student's *t*-test was used to determine whether there was a statistically significant difference in age at the time of HSCT between the two groups.

## **Results**

### *Patient characteristics*

Encephalopathy developed in 26 of 405 (6.4%) pediatric patients who had received allogeneic HSCT (Table 1). The onset of encephalopathy occurred at a median of 64.5 days after transplantation (range, 0–203 days). The median age at the time of HSCT was 11 years (range, 1–21 years). Four donors were matched siblings, 16 were matched unrelated donors, and six were partially matched family donors. In general, the patients had complex medical problems, with a number of comorbid conditions noted at the onset of encephalopathy (Table 1). There was a trend toward older age at the time HSCT being associated with encephalopathy; the median age at HSCT of those who experienced subsequent encephalopathy was 11.2 years, and that of patients who did not was 8.8 years ( $P=0.078$ ). There was no significant difference in sex, race, primary diagnosis, donor type, degree of HLA match, or presence or absence of GVHD between patients with or without encephalopathy.

### *MRI findings*

MRI was performed in 22 of the 26 (85%) patients (Table 2); MRI assessment in only one (4.5%) patient was normal. The most frequently seen abnormality was leukoencephalopathy (LE), which occurred in 12 (54.5%) patients (Figure 1). Other abnormalities included the presence of both cerebral atrophy and a subdural hemorrhage (SDH) ( $n=1$ , 4.5%), infarctions ( $n=2$ , 9%), and focal lesions ( $n=3$ , 14%) (Figure 2). Images from three patients showed an unusual pattern of hyperintensity of the pituitary on T1-weighted, T2-weighted, or both MRIs (Figure 3). This pattern has not been previously described. Diagnoses in these patients included parkinsonism caused by Amphotericin B treatment, thrombotic thrombocytopenic purpura (TTP), and uremia.

### *EEG findings*

A total of 17 (65%) patients had an EEG performed; only one (5.9%) study revealed no abnormalities. EEG revealed diffuse slowing in 11 (65%) patients, bilateral frontal slowing in one patient, and combinations of frontal and diffuse slowing and epileptiform discharges in four (24%) patients.

### *CSF findings*

Lumbar punctures were performed on 17 (65%) patients (Table 2). Seven (41%) patients had normal cell counts and levels of glucose and protein. Other CSF studies revealed elevated protein only in four (24%) patients, elevated WBC count only in two (12%) patients, and elevations in both WBC count and protein in three (18%) patients. No patient had a positive CSF culture for bacteria, viruses, or fungi. PCR analysis of the CSF was performed in only five (23%) patients; the studies were negative for Epstein-Barr virus (EBV) ( $n=4$ ), herpes simplex virus (HSV) ( $n=4$ ), cytomegalovirus (CMV) ( $n=3$ ), HHV-6 ( $n=3$ ), enteroviruses

**Table 1** Patient demographics

Patient no.	Age <sup>a</sup> (years)	Sex	Primary diagnosis	Comorbidity	HSCT donor	Time to onset <sup>b</sup> (days)
1	21	F	SAA	Colitis, renal insufficiency	MUD	0
2	21	M	Biphenotypic leukemia	None	MSD	70
3	16	M	CML	Infection, hemorrhagic cystitis, renal failure	MUD	47
4	10	F	ALL	Renal insufficiency	MUD	73
5	9	F	AML	None	MSD	67
6	11	F	ALL	None	MUD	62
7	10	F	ALL	Hemorrhagic cystitis, hyperammonemia	MUD	93
8	7	M	MDS	Hypertension	MUD	76
9	5	M	ALL	Hypertension	MFM	13
10	5	M	ALL	Infection	MUD	98
11	15	M	ALL	MSOF	MFM	19
12	5	M	AML	None	MUD	76
13	17	F	AML	Renal failure GVHD	MUD	25
14	11	F	CML	ARDS, GVHD	MSD	69
15	19	M	ALL	Guillain-Barre syndrome	MFM	56
16	1	M	OI	None	MFM	13
17	6	M	ALL	Colitis, hemorrhagic cystitis, hypertension, infection	MUD	203
18	14	M	MDS	None	MSD	82
19	2	M	AML	GVHD	MUD	88
20	18	M	AML	Infection, VOD	MUD	12
21	18	M	2ALL	Hyperbilirubinemia, renal insufficiency	MFM	17
22	9	F	ALL	GVHD	MUD	27
23	10	M	CML	Infection	MUD	56
24	12	M	SAA	GHVD, renal failure, TTP	MFM	45
25	13	F	CML	Graft failure, hemorrhagic cystitis, renal insufficiency	MUD	69
26	17	F	AML	Hemorrhagic cystitis, pericardial effusion, renal failure	MUD	92

<sup>a</sup>Age at the time of HSCT.

<sup>b</sup>Time to onset indicates the number of days between HSCT and the diagnosis of encephalopathy. HSCT = hematopoietic stem cell transplantation; F = female; M = male; SAA = severe aplastic anemia; CML = chronic myelogenous leukemia; AML = acute myeloid leukemia; ALL = acute lymphoblastic leukemia; 2ALL = secondary ALL; MDS = myelodysplastic syndrome; OI = osteogenesis imperfecta; GVHD = graft-vs-host disease; TTP = thrombotic thrombocytopenic pupura; MSD = matched sibling donor; MUD = matched unrelated donor; MMFM = mismatched family member; VOD = veno-occlusive disease; MSOF = multisystem organ failure; ARDS = adult respiratory distress syndrome.

(*n* = 2), varicella-zoster virus (VZV) (*n* = 1), adenovirus (*n* = 1), and BK virus (*n* = 1).

### Brain biopsy findings

Brain biopsies were performed on six (23%) patients. In one patient who had TTP, the brain biopsy was non-diagnostic. In two patients, both histology and culture were positive for *Aspergillus* species. In two patients, morphologic findings were consistent with acute disseminated encephalomyelitis (ADEM). In one patient, perivascular inflammation and cuffing were detected, which suggested a viral etiology. One biopsy was nondiagnostic.

### Summary of diagnoses

A definitive diagnosis was made in 21 (81%) patients. Diagnoses included TTP (*n* = 2), parkinsonism with or without akinetic-mutism caused by Amphotericin B (*n* = 2), seizures or nonconvulsive status epilepticus (*n* = 4), viral encephalitis (*n* = 3), ADEM (*n* = 2), hyperammonemia/hepatic failure (*n* = 2), uremia (*n* = 1), CNS aspergillosis (*n* = 2), stroke (*n* = 1), cyclosporine neurotoxicity (*n* = 1), and multisystem organ dysfunction (*n* = 1). These diagnoses were made by characteristic pathologic findings on blood smear, brain biopsy, EEG, or MRI. Viral encephalitis was diagnosed by brain histology in conjunction with

isolation of adenovirus in blood and stool cultures, by EEG and MRI findings, and by presence of BK viuria in conjunction with a progressive multifocal leukoencephalopathy-like picture on MRI.

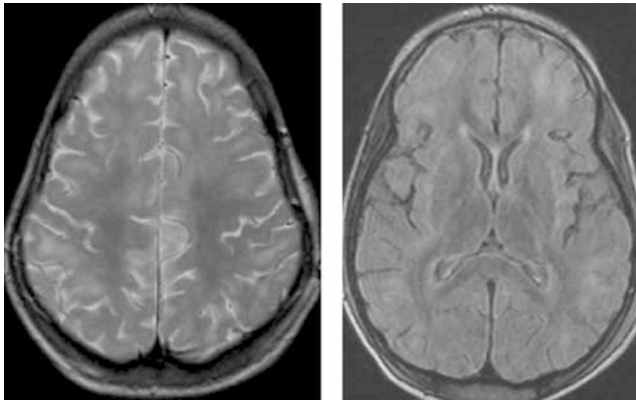
### Outcome of encephalopathy

Four of 26 (15%) patients experienced a full neurologic recovery (Table 2). Diagnoses associated with complete recovery included ADEM (*n* = 1), seizures (*n* = 1), stroke (*n* = 1), and viral encephalitis (*n* = 1). Three of these patients are alive and well; one subsequently died of relapse. In total, 10 (38%) patients experienced partial recovery but had residual neurologic sequelae. Diagnoses associated with partial recovery included ADEM (*n* = 1), CSA toxicity (*n* = 1), idiopathic causes (*n* = 2), parkinsonism with TTP (*n* = 1), CNS Aspergillosis (*n* = 1), nonconvulsive seizures (*n* = 3), and uremia (*n* = 1). Six of these patients survive and three died of other causes. Patients with seizures were treated with anticonvulsants, and patients with idiopathic causes were treated empirically with antivirals, anticonvulsants, and intravenous immunoglobulin. Residual neurologic sequelae included seizures, cognitive impairment, behavior problems, language disorder, and residual confusion. In all, 17 (65%) patients died, 12 (46%) of whom died with no resolution of encephalopathy. The etiology of encephalopathy in

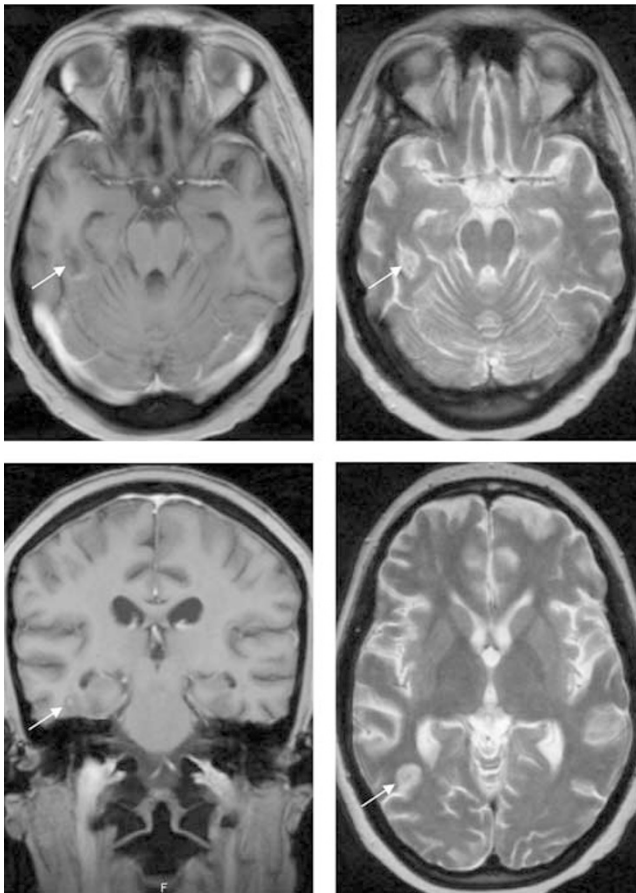
**Table 2** Diagnostic findings and outcome in patients with encephalopathy

Patient	Onset (day post-BMT)	EEG	MRI	Brain biopsy	CSF	Diagnosis	Outcome	Alive/dead (cause of death)
1	0	DS	Hyperintense pituitary (T1W)	ND	ND	TTP	NR	Dead (aspergillosis, MSOF)
2	70	DS	ND (CT normal)	ND	ND	Idiopathic	NR	Dead (GVHD)
3	47	DS	Multiple focal T2W hyperintensities	ND	ND	Seizures	CR	Alive
4	73	ND	Infarct	ND	Negative	Stroke	CR	Alive
5	67	DS	LE	ND	Negative	Seizures	PR	Alive
6	62	DS, epileptiform activity	LE	C/w viral process: perivascular cuffing	Negative	Viral	NR	Dead (progressive leukoencephalopathy)
7	93	DS	ND (CT atrophy and LE)	ND	ND	Hyperammonemia	NR	Dead (liver failure)
8	76	DS	LE with small lacunes	ND	5 WBC/mm <sup>3</sup> , 82% lymphs, TP 62 mg/dl	Idiopathic	PR	Alive
9	13	DS, epileptiform activity	LE	ND	Negative	Cyclosporine	PR	Dead (relapse)
10	98	FS, epileptiform activity	Right parietal/occipital ischemia	Aspergillus	Negative	CNS Aspergillosis	NR	Dead (CNS Aspergillosis)
11	19	ND	ND (CT normal)	ND	819 RBC/mm <sup>3</sup> , TP 96 mg/dl	MSOF	NR	Dead (MSOF)
12	76	DS	LE	ND	Negative	Seizures	PR	Alive
13	25	ND	Normal	ND	ND	Liver failure	NR	Dead (Liver failure)
14	69	DS	Focal T2W hyperintensity right medial temporal lobe	Inclusion bodies; EM: myelin debris	11 WBC/mm <sup>3</sup> , 87% lymphs, TP 67 mg/dl	ADEM	PR	Dead (MSOF)
15	56	ND	LE	ND	ND	Idiopathic	NR	Dead (MSOF)
16	13	ND	Atrophy, right SDH	ND	ND	Seizures	PR	Alive
17	203	Normal	LE	ND	26 WBC/mm <sup>3</sup> , 87% neutrophils, TP 251 mg/dl	Idiopathic	PR	Alive
18	82	FS, epileptiform activity	Multiple focal T2W hyperintensities	ND	ND	Viral	CR	Alive
19	88	ND	LE	Perivascular inflammation, edema; demyelination	68 RBC/mm <sup>3</sup> , TP 74 mg/dl	ADEM	CR	Dead (relapse)
20	12	ND	ND (CT normal)	ND	12 WBC/mm <sup>3</sup> , 89% lymphs	Idiopathic	NR	Dead (infection)
21	17	ND	Hyperintense pituitary (T1W)	ND	ND	Uremia	PR	Dead (relapse)
22	27	ND	LE	Aspergillus	356 RBC/mm <sup>3</sup>	CNS Aspergillosis	PR	Dead (MSOF)
23	56	DS	LE	ND	TP 91 mg/dl	Viral	NR	Dead (MSOF)
24	45	DS	LE	Nondiagnostic	Negative	TTP	NR	Dead (MSOF)
25	69	FS	LE	ND	26 WBC/mm <sup>3</sup> , 97% L	Parkinsonism/TTP	PR	Alive
26	92	DS	Hyperintense pituitary (T1W)	ND	63 RBC/mm <sup>3</sup> , TP 84 mg/dl	Parkinsonism	NR	Dead (infection)

DS = diffuse slowing; ND = not done; FS = focal slowing; T1W = T1-weighted; T2W = T2-weighted; CT = computed tomography; LE = leukoencephalopathy; SDH = subdural hemorrhage; EM = electron microscopy; WBC = white blood cells; TP = total protein; RBC = red blood cells; MSOF = multisystem organ failure; GVHD = graft-vs-host disease; CNS = central nervous system; NR = no resolution; PR = partial resolution; CR = complete resolution.

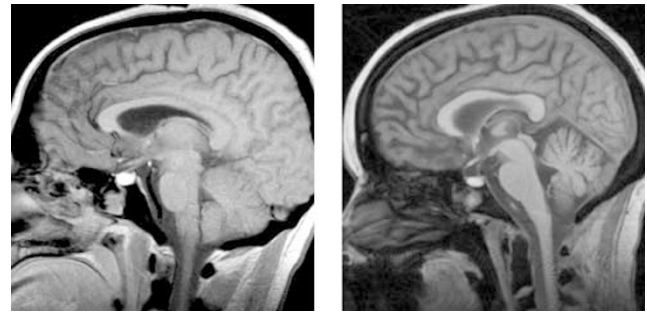


**Figure 1** (a) Axial T2-weighted, and (b) axial FLAIR images. Mild diffuse hyperintensities involving the bilateral deep white matter, consistent with leukoencephalopathy.



**Figure 2** (a) Axial T1-weighted postcontrast, (b) axial T2-weighted, (c) coronal T1-weighted postcontrast, and (d) axial T2-weighted images. There are hyperintense, minimally enhancing right temporal lobe lesions.

these patients was organ failure (hepatic,  $n=2$ ; multi-system,  $n=1$ ), infection (CNS aspergillosis,  $n=2$ ; viral encephalitis,  $n=2$ ), TTP ( $n=2$ ), parkinsonism ( $n=1$ ), or idiopathic causes ( $n=3$ ). In all cases but one of viral etiology, death was due to other causes.



**Figure 3** (a, b) Sagittal T1-weighted noncontrasted midline images, from two different patients. Abnormally high signal of the pituitary glands, suspicious for hemorrhage.

## Discussion

Encephalopathy after allogeneic HSCT is associated with a grim prognosis. In our experience, only four of 26 pediatric patients experienced a complete recovery, and only three of those are long-term survivors. A total of 10 patients experienced partial recovery, and six of those remain long-term survivors with residual neurologic sequelae such as learning disabilities or seizures.

Nonconvulsive seizures were the most frequently identified cause of encephalopathy in our patients. Four patients in our cohort had ongoing nonconvulsive seizures at the time of EEG; anticonvulsant therapy was either initiated or augmented as a result. EEG assessment is a necessary part of the evaluation of patients with encephalopathy after HSCT as such seizures may not be clinically apparent.

Five patients had encephalopathy related to CNS infection; none were caused by a bacterial pathogen. Two additional patients had encephalopathy related to ADEM, which may be associated with prior viral infection. In patients with CNS Aspergillosis, MRIs showed an area of infarction in one patient and leukoencephalopathy in another. The CSF was normal in one patient and revealed an increased number of red blood cells in the other patient. Both patients required brain biopsy for diagnosis. In three patients with presumed viral causes, two had leukoencephalopathy on MRI and one had multiple focal T2W hyperintensities. CSF was tested in two; one was normal and one showed increased total protein only. Brain biopsy was carried out in one patient and revealed perivascular cuffing, a finding most consistent with a viral process. In the two patients with ADEM, MRI showed leukoencephalopathy in one patient and focal hyperintensity of the temporal lobe in another patient. The CSF revealed elevated WBC with a lymphocytic predominance and elevated total protein in one patient and elevated RBC and total protein in another patient. Both had brain biopsy performed, which revealed perivascular inflammation in one and inclusion bodies consisting of myelin debris in another. These findings suggest that CSF differentials may not be a reliable means of assessing infection in immunocompromised HSCT patients. Further diagnostic considerations in such patients include PCR-based testing of the CSF for infectious pathogens and/or brain biopsy. Indeed,

molecular testing for a number of viral pathogens is a relatively recent development; therefore, this crucial data is missing for most patients treated during the study period. Some of the patients with idiopathic encephalopathy may have suffered from undiagnosed viral disease. In patients with encephalopathy, CSF samples are now assayed for these pathogens as well as HSV, VZV, BK virus, and JC virus. The list of candidate pathogens for testing will continue to increase as PCR becomes available for additional agents. Six patients had brain biopsies performed with no complications, yielding a diagnosis in five. This methodology was safe and well tolerated and should be considered in the evaluation of encephalopathy after HSCT.

Medication-related encephalopathy occurred in three patients. Cyclosporine-induced encephalopathy and Amphotericin-related Parkinsonism are associated with characteristic MRI findings. MRI should be a routine part of the evaluation of encephalopathy after HSCT.

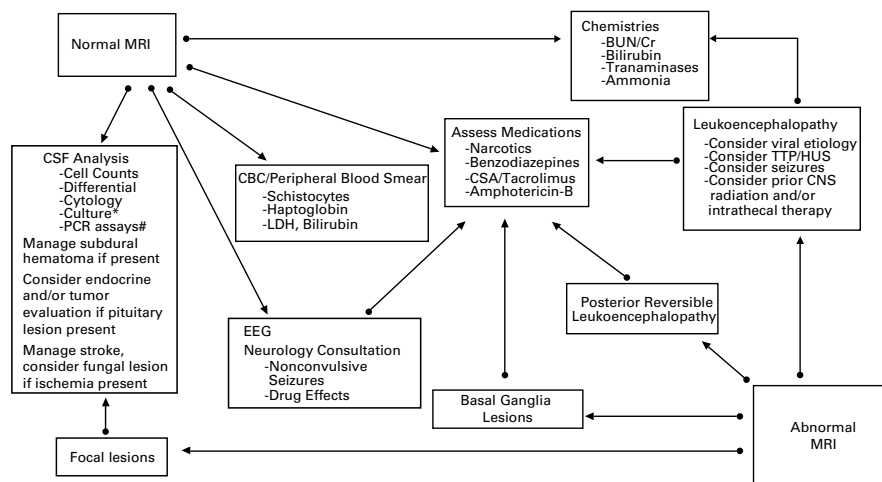
TTP-related encephalopathy occurred in two patients. This entity is well characterized after HSCT and can generally be detected by review of the peripheral blood smear and review of lactate dehydrogenase, haptoglobin, and reticulocyte count. These tests should be part of the evaluation of encephalopathy after HSCT.

Less frequent causes of encephalopathy included stroke, liver failure, uremia, and multisystem organ failure, all of which were readily apparent at the time encephalopathy developed.

Brain abnormalities were detected in 95% of the patients who had an MRI assessment. The most common abnormality was LE, which is a relatively common finding in children receiving treatment for ALL.<sup>16</sup> In our study, five of 12 patients who had LE also had ALL. The remaining seven patients had AML ( $n=3$ ), CML ( $n=2$ ), MDS ( $n=1$ ), or SAA ( $n=1$ ). Therefore, in our small cohort, encephalopathy did not appear to be more common in patients with ALL. At this time, a prospective study at our

institution is assessing the incidence of LE and other abnormalities among pediatric patients with ALL; this study should shed more light on this phenomenon.

We detected an unusual pattern of pituitary enhancement on the MRIs of three patients. These patients had TTP, drug-related Parkinsonism, and uremia. The association between encephalopathy and pituitary changes, endocrine abnormalities, or malignant changes remains unclear, because all three patients died before more extensive endocrine or histologic evaluation could be undertaken. This is an interesting finding as this is the point in development (postadolescence) at which pituitary size is maximal. The clinical symptoms in patients are consistent with pituitary apoplexy with headache and mental status changes. Interestingly, these are common presenting symptoms for pituitary apoplexy.<sup>17,18</sup> Our three patients did not report visual field deficits but were all encephalopathic at the time these symptoms may have developed. All patients were severely thrombocytopenic (platelet range 5000–23 000/mm<sup>3</sup>) around the time a CNS event could have occurred. It is intriguing that one patient likely developed this in association with severe sepsis with hypotension and uremia. This clinical scenario is similar to that seen with Sheehan's syndrome with an abrupt decrease in perfusion. One patient carried a diagnosis of TTP. One patient has been reported with pituitary apoplexy and immune thrombocytopenic purpura (ITP).<sup>19</sup> Although the mechanism of thrombocytopenia is different with TTP and ITP, the result is severe thrombocytopenia which may predispose a patient to pituitary hemorrhage. A third patient had this MRI finding in association with drug-related Parkinsonism. In the future, the presence of this feature on the MRI of a patient who has received HSCT will indicate the need for additional diagnostic considerations, including endocrinologic evaluation. We recommend that MRIs be performed on all patients showing signs of encephalopathy. Focal lesions on MR images may lead the clinician to the appropriate diagnostic test or change in medication in



**Figure 4** Algorithm for standardized diagnosis of encephalopathy in pediatric patients who have undergone allogeneic HSCT. The CSF should be cultured for bacterial, fungal, and viral pathogens. PCR testing should include those available viruses such as CMV, EBV, VAV, HHV-6, and adenovirus. If the above-described measures are inconclusive, then brain biopsy for histologic analysis, pathogen culture, and PCR testing should be considered.

many cases. Indeed, focal MRI findings led to a brain biopsy in six patients included in this study.

Positron-emission tomography (PET) or single-photon emission computed tomography (SPECT) scans were not available in this group of patients. PET or SPECT imaging may have provided additional diagnostic information. SPECT imaging has been shown to be more sensitive than CT or MRI in defining anatomic abnormalities in cases of epilepsy<sup>20,21</sup> and viral encephalitis.<sup>22–24</sup>

Encephalopathy after allogeneic HSCT occurs in approximately 6% of pediatric patients. A uniform approach to diagnosis of encephalopathy is needed. We have attempted to design a diagnostic algorithm based on our experience (Figure 4). Although, not complete, this algorithm represents a framework for approaching the treatment of such patients. Standardized testing including MRI, EEG, and molecular studies for infectious pathogens are mandatory. The role of PET/SPECT scans requires evaluation. Brain biopsy may be required if the above measures are inconclusive or if focal lesions are seen on the MRI. Refinements will be made as data become available from prospective studies that include a full array of modern diagnostic tests. It is worth noting that nearly all of the causes of encephalopathy that we identified are treatable if diagnosed early. Therefore, early and aggressive diagnostic measures, in combination with appropriate medical therapy and intensive rehabilitation may improve the prognosis in pediatric patients who experience this devastating complication of allogeneic HSCT.

### Acknowledgements

This work was supported in part by Cancer Center Support (CORE) Grant P30 CA 21765 from the National Cancer Institute and by the American Lebanese Syrian Associated Charities (ALSAC). We express our appreciation to the nurses, nurse practitioners, and physician assistants involved in the care of these patients and to the Department of Scientific Editing for review of this manuscript.

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