**Neuroimaging findings and risk factors for neurologic toxicity after hematopoietic stem cell transplant in children**

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Abbreviations Table:

| **Abbreviation** | **Full Term** |
|---|---|
| HSCT | hematopoietic stem cell transplant |
| MRI | magnetic resonance imaging |
| CNS | central nervous system |
| GVHD | graft-versus-host disease |

**Abstract**: Neurologic complications after hematopoietic stem cell transplant (HSCT) in children are poorly described, but may contribute to morbidity and mortality. We retrospectively reviewed 261 patients who underwent allogeneic or autologous HSCT, of whom 57 had brain magnetic resonance imaging (MRI) post-transplant, and subsequently identified indications for imaging and determined correlation of findings with neurologic symptoms. Approximately half of imaging studies were done to investigate new neurologic symptoms; of those, 1/3 had acute findings on MRI that correlated with symptoms. Imaging done in patients at risk for neurologic processes but without active neurologic symptoms did not demonstrate acute or actionable findings.

**Introduction:**

Pediatric hematopoietic stem cell transplantation (HSCT) is increasingly performed to treat hematologic and non-hematologic disease. While multiple studies have explored cognitive and behavioral sequelae of HSCT in children, few have specifically addressed neurologic complications in this population, for which MR imaging is used to facilitate early and accurate diagnosis.[1] As neurologic toxicity can contribute to overall morbidity and mortality, better characterization of the short- and long-term neurologic sequelae is important for monitoring and management of these patients, and earlier detection and treatment of central nervous system (CNS) toxicities may lessen morbidity for HSCT recipients.[2,3] In this study, we analyzed neuroimaging studies performed during and after HSCT in children to identify risk factors for neurologic morbidity.

**Methods:**

We performed an IRB-approved retrospective review of patients who underwent HSCT at Boston Children's Hospital from 2013 to 2016. Patients with primary brain tumors, metabolic and CNS inflammatory disorders were excluded. We reviewed the subset of patients with available MR brain imaging up to three years post-transplant. Extracted data included demographic and clinical/treatment details, MR findings and associated neurologic symptoms.

**Results:**

A total of 261 patients underwent HSCT during the study period (158 boys; mean age at transplant 8.5 ± 6.5 years, range 0-24). Of those, 57 patients (22%; 41 boys; mean age at

transplant 8.7 ± 6.9 years, range 0-23) underwent 93 MRIs (range 1-7 scans/patient). Demographics, diagnoses, and treatments are detailed in Table 1.

Some MRI findings were clinically correlated with acute symptoms, while others were considered asymptomatic/incidental (Table 2). Nearly half (42/93, 45%) of MRIs were performed after development of acute neurologic symptoms. Screening MRI was performed in the remaining 51 (55%). Of the MRIs performed for acute symptoms, 14/42 scans (33%, N=10 individual patients) demonstrated acute findings which changed clinical management.

The majority of imaging studies revealed incidental findings not associated with acute clinical symptoms (69/93, 74%). These included non-specific white matter T2 hyperintensities, volume loss/ex-vacuo dilatation, sinus disease, stable or improved known intracranial lesions, and chronic microhemorrhage. Only 10 (11%) MRIs were normal.

**Discussion:**

One-fifth of patients in this pediatric HSCT cohort not transplanted for known CNS disease underwent at least one brain MRI during or after transplant, of which nearly half were performed to investigate new neurologic symptoms. One-third of neuroimaging studies performed for acute symptoms had correlative imaging findings that were actionable. The majority of imaging studies had subacute/incidental findings considered clinically asymptomatic. Despite multiple screening MRIs in patients considered at risk for neurologic toxicity without active symptoms, none demonstrated acute findings.

There is a wide variability in the reported incidence of neurologic complications in adults after HSCT, ranging from 5 to 65%,[4,5,6] with slightly lower incidence after reduced-intensity transplant.[7,8] Case series and reports of neurologic complications include metabolic

encephalopathy, headache, tremor, seizures, posterior reversible encephalopathy syndrome, cognitive/psychiatric changes, intracranial hemorrhage, stroke, thrombotic microangiopathy and other cerebrovascular complications, acute disseminated encephalomyelitis, secondary CNS cancers, CNS infection, peripheral neuropathy and myopathy.[9,10,11,12,13,14] In a study of 383 pediatric HSCT recipients, 18% experienced neurologic complications, the majority within the first 100 days post-transplant.[15] Calcineurin inhibitor-related neurotoxicity was most common. Risk factors for mortality included time to engraftment, chronic graft-versus-host disease (GVHD) and persistent neurologic symptoms. Other suggested risk factors for neurologic toxicity in children include medication-related effects, acute and chronic GVHD and lengthy immunosuppression.[16] The true incidence of neurotoxicity may ultimately be significantly higher, as suggested by an autopsy study of 180 adult patients with neuropathologic changes in 90% after bone marrow transplant, including intracranial hemorrhage, fungal infection, Wernicke's encephalopathy, microglial nodular encephalopathy, and neurotoxoplasmosis; central nervous system pathology was identified as the main cause of death in 17%.[17]

It will be important to further characterize brain MR findings in symptomatic and asymptomatic pediatric patients before and after HSCT, with correlative neurologic exams and neuropsychological testing, in order to better understand and prevent morbidity and mortality related to neurologic toxicity in this population.

**Conflict of Interest Statements:**

Elizabeth Duke, MD has nothing relevant to disclose.

Nicole Ullrich, MD, PhD has nothing relevant to disclose.

Leslie Lehmann, MD has nothing relevant to disclose.

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