Journal of Pediatric Intensive Care 3 (2014) 169–181
DOI 10.3233/PIC-14100
IOS Press

Acute central nervous system complications in pediatric hematopoietic stem cell patients

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Received 2 August 2014
Revised 20 September 2014
Accepted 2 November 2014

Abstract. Acute neurologic complications in pediatric hematopoietic stem cell transplant (HSCT) patients cause significant morbidity and mortality. To conduct a comprehensive review of the existing literature reporting acute neurologic complications of the central nervous system among children undergoing HSCT. Comprehensive literature review from 2000 to 2014 using Medline. A total of 566 pediatric articles were reviewed and data from 66 studies selected. A brief overview of morbidity and mortality in pediatric HSCT patients is provided followed by a summary of findings related to acute neurologic complications. Acute central nervous system complications in pediatric HSCT patients are varied and are the result of multiple causes including infection, drug-related toxicity, immune suppression, vascular injury and neoplasms.

Keywords: Hematopoietic stem cell transplantation, central nervous system, graft-versus-host disease, pediatrics

1. Introduction

Hematopoietic stem cell transplant (HSCT) is used in the treatment of pediatric patients with hematologic malignancies, solid tumors, bone marrow aplasia, and a variety of dyshematopoietic and metabolic diseases. Patients usually receive conditioning with high doses of chemotherapy, frequently including total-body irradiation, to destroy the native hematopoietic system and to suppress the immune system, especially T cells, to prevent graft-versus-host disease (GVHD).

Acute central nervous system (CNS) complications represent an important cause of morbidity and contribute significantly to mortality after HSCT. The reported incidence varies from 5% to 14% [1–11]. Neurological complications after HSCT may arise from the toxicity of the conditioning and radiotherapy regimens, immunosuppressive agents, infections, GVHD and veno-occlusive disease [4]. Other significant risk factors include mismatched related or unrelated donor allogeneic transplantation [10]. Neurological complications after HSCT commonly occur at three different time periods including during the period of HSCT depletion, after HSCT engraftment and long-term (Table 1). We conducted a review of the literature reporting acute CNS complications among children undergoing HSCT.

2. Materials and methods

Studies were identified by searching electronic databases using search strategies developed and executed by a Seattle children's hospital medical librarian, Susan Klawansky. Searches were performed in January

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Table 1
Time periods for acute neurological complications post hematopoietic stem cell transplant

Time periods	Acute neurological complications post hematopoietic stem cell transplant
0–1 mo	Multi-organ dysfunction syndrome
	Drug toxicities
	Infections
	Coagulopathies
	Posterior reversible leukoencephalopathy syndrome
2–6 mo	Chronic immunosuppression
	Graft-versus-host disease
	Viral infections
	Opportunistic infections
>6 mo	Relapse
	Secondary neoplasms

2014 on the Ovid platform: Medline. Retrieval was limited to the years 2000 to current, ages 0–18 and English language. Appropriate index terminology (medical subject headings, psychological thesaurus of index terms, and entree headings were used respectively, along with text words. (Fig. 1 preferred reporting items for systematic meta-analyses flow diagram).

3. Results

We reviewed 66 publications that identified 339 pediatric HSCT patients with acute CNS complications of whom, 335 received allogeneic and only four autologous transplants. Mortality was 40% (136/339). The most frequent neurologic complications included infections, drug related toxicities and posterior reversible encephalopathy syndrome (PRES). (Fig. 2) The spectrum of clinical symptoms was broad and often non-specific, including seizures, encephalopathy, visual disturbances, headaches, hemiparesis, abnormal movements, drowsiness and agitation (Fig. 3).

4. Infectious diseases (Table 2)

4.1. Viral

Infections are the leading cause (35%) of acute neurologic complications. Pretransplant viral status, defined as a higher number of positive herpes group (varicella zoster virus [VZV], herpes simplex virus, Epstein-Barr virus [EBV], cytomegalovirus [CMV]) serologies in recipients before transplantation correlated with neurologic complications [4].

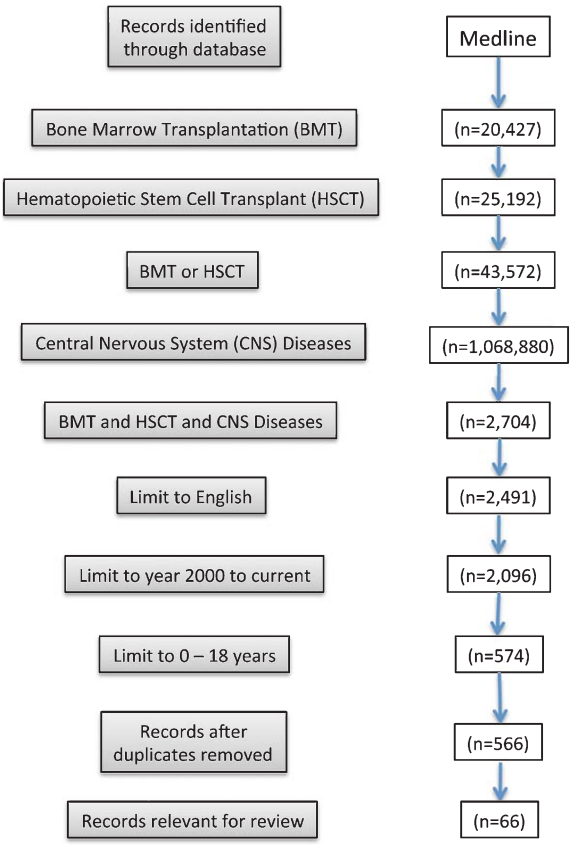

Fig. 1. Preferred reporting items for systematic meta-analyses flow chart.

Following primary infection, human herpes virus (HHV) −6 and HHV-7 are marked by primary infection followed by latency in lymphocytes and monocytes/macrophages [12–14]. Approximately 40% of HSCT patients experience early reactivation of HHV-6 especially in patients with allogeneic transplants or GVHD [15, 16]. HHV-6 can cause limbic encephalitis, interstitial pneumonitis, fulminant hepatitis, bone marrow suppression, delayed engraftment or graft failure and skin rash predominantly located on the cheeks, and resembling acute skin GVHD [12, 14, 17]. HHV-6 limbic encephalitis is characterized by short-term memory loss, sleep disturbances, and confusion [17]. Magnetic resonance imaging (MRI) reveals hyperdensity within one or both hippocampi on T2-weighted images and follow-up MRI suggests hippocampal injury may result in sclerosis [17]. Treatment with ganciclovir and/or foscarnet decreases cerebrospinal fluid (CSF) polymerase chain reaction (PCR) counts and produces cure in some cases. Mortality remains high [12, 15].

Table 2
Infectious causes of acute central nervous system complications

Infection types	Microorganism	Serum	Cerebrospinal fluid	Imaging	Treatment	References
Viral	Human herpes virus-6 and human herpes virus-7	PCR herpes DNA	PCR herpes DNA	MRI (hyperdensity within one or both hippocampi)		12–19
	Cytomegalovirus	Serologies PCR	PCR	MRI	Ganciglovir, foscarnet	20–23
	Enterovirus	Reverse transcriptase PCR	Reverse transcriptase PCR	MRI	IVIg, intravenous β-interferon	25
	Varicella zoster virus	PCR	PCR	MRI	IVIg, acyclovir	26
Fungal	Aspergillosis	Cerebrospinal fluid fungal culture, PCR, ELISA, latex agglutination test, galactomannan antigen	Cerebrospinal fluid fungal culture, PCR, ELISA, latex agglutination test, galactomannan antigen	MRI (acute hemorrhagic infarcts, ring or nodular enhancing abscesses)	Amphotericin B, liposomal amphotericin B, variconazole	27–29
Opportunistic parasites	Toxoplasmosis	PCR, hyponatremia	PCR	MRI (ring enhancing lesions)	Trimethoprim/ sulfamethoxazole, pyrimethamine/ sulfadoxine, folinic acid	30–33
	Nocardia			MRI (abscess)		35
	Amoebae		PCR, microscopic examination			36

PCR = Polymerase chain reaction; ELISA = Enzyme-linked immunosorbent assay; MRI = Magnetic resonance imaging; IVIg = Intravenous immunoglobulin.

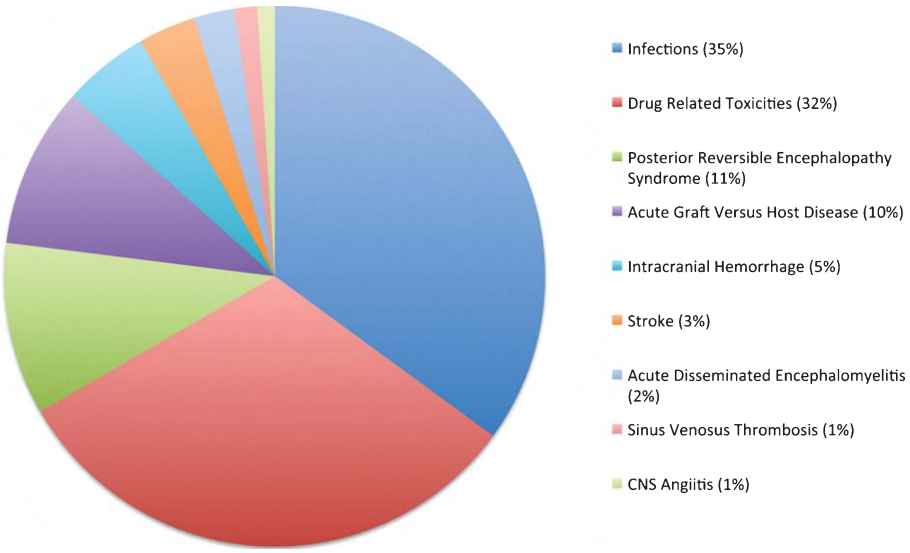

Fig. 2. Acute central nervous system complications.

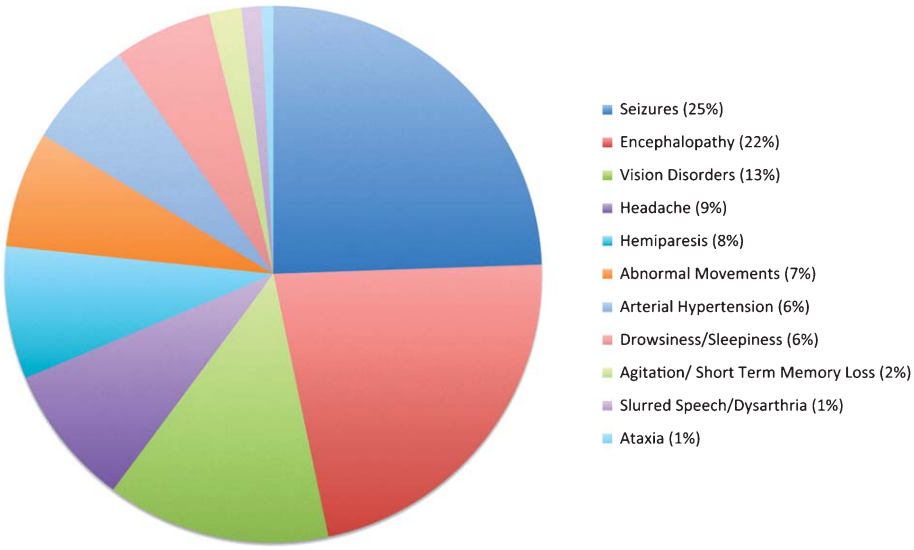

Fig. 3. Reported clinical symptoms.

Although rare, HHV-7 can cause fatal encephalitis in immunocompromised patients [18, 19].

CMV infection is an important cause of complications in HSCT patients [20]. In seropositive recipients, CMV remains latent in peripheral leukocytes and reactivates as secondary infection [20]. CMV causes primary infection in seronegative recipients who receive seropositive transplants or from other exogenous sources. Risk factors for CMV include allogeneic transplant, T-cell depletion, GVHD, and failed engraftment [4, 20]. CMV disease can develop despite prophylaxis because of the emergence of drug-resistant CMV strains [21], after prolonged exposure to antiviral agents. Although rare, CMV encephalitis has a poor prognosis. Ganciclovir and foscarnet have poor CSF penetration [4, 21–23].

Screening and preemptive antiviral treatment has reduced the negative impact of CMV [4]. Early and

rapid tapering of immunosuppressants when GVHD is well controlled has been found to limit CMV disease as donor immunity plays a key role in viral clearance [22].

Progressive multifocal leukoencephalopathy, a fatal demyelinating disease caused by the John Cunningham virus has been reported in a transplanted child who received aggressive conditioning chemotherapy [24].

Meningoencephalitis is increasingly recognized as a complication of enterovirus infection in the post-transplant period [25]. Diagnosis is made with MRI and reverse transcriptase-PCR (RT-PCR). Reported treatments include high dose intravenous immunoglobulin (IVIg) alone, or with intrathecal immunoglobulin, or intrathecal immunoglobulin and intravenous β-interferon.

VZV meningitis rarely complicates HSCT because of antiviral prophylaxis. Risk factors for VZV infections include age greater than 10 yr at transplantation, hematologic malignancy, total body irradiation, and allogeneic transplant. Recurrent VZV meningitis was reported in two allogeneic HSCT recipients with no skin lesions [26] 9 days and 9 mo after transplantation despite valaciclovir prophylaxis. Both patients were treated with intravenous acyclovir and IVIg.

4.2. Fungal infections

Invasive CNS aspergillosis remains a leading cause of death from infection in HSCT patients despite newer antifungal agents [27, 28]. Aspergillosis, occurs primarily in the lungs, brain, sinus/nose and skin [27, 28]. Aspergillus may invade blood vessels, causing CNS infarction (hemorrhagic); abscesses form later. Findings include headache, altered mental status, seizures, and focal neurological signs. Brain MRI demonstrates acute infarcts or ring or nodular enhancing lesions. Diagnosis remains difficult and is frequently delayed [29]. Examination of the CSF does not usually provide definitive evidence of CNS infection. *Aspergillus galactomannan* antigen detection may be positive, but definitive diagnosis requires positive CSF fungal culture, a positive PCR or enzyme-linked immunosorbent assay or latex agglutination test.

4.3. Opportunistic parasitic infections

Toxoplasmosis is a life-threatening complication of immune suppression occurring in 0.1% and 6% of HSCT patients [30–32]. Toxoplasmosis should be considered in all HSCT patients with neurological dysfunction. *Toxoplasma gondii* is acquired by ingestion of raw or undercooked meats containing the cysts or by exposure to soil contaminated with cat feces [33]. Risk factors for reactivation include allogeneic transplant, GVHD, immunosuppression, receipt of T-cell-depleted grafts, cord blood transplantation, and conditioning regimens that include anti-thymocyte globulin [4, 33, 34]. The highest risk for reactivation of disease occurs at approximately 2 to 6 mo after transplant [4].

Toxoplasma reactivation may produce encephalitis, pneumonitis or myocarditis. Clinical features of toxoplasma encephalitis are nonspecific: fever, seizures, headaches, lethargy, confusion, tremor, hemiparesis, personality changes and cognitive disturbances [32, 33]. Hyponatremia occurs and may be due to inappropriate antidiuretic hormone secretion or cerebral salt wasting [32]. MRI abnormalities do not always demonstrate the 'typical' ring enhancement [33]. Diagnosis is made with blood and CSF PCR testing for toxoplasma [33]. Brain biopsy reveals trophozoites [32]. The prognosis for HSCT patients with toxoplasmosis is poor with a mortality ranging from 60% to 90% [4, 33].

Treatment for toxoplasmosis among HSCT recipients remains combined therapy with trimethoprim/sulfamethoxazole or pyrimethamine/sulfadoxine, and folinic acid to reduce toxic side effects. Prophylaxis does not always prevent protozoal reactivation. The treatment of choice in reactivation is a combination of pyrimethamine with folinic acid plus sulfadiazine or clindamycin [4, 32, 33]. A course of at least 4–6 wk after resolution of all findings is recommended.

Nocardia asteroides rarely causes CNS infections especially in pediatric HSCT patients, but should be considered in patients presenting with brain abscess [35]. The incidence of nocardial infection among HSCT patients varies from 0.3% to 0.7% [35]. Risk factors include exposure to soil, neutropenia, GVHD and lack of trimethoprim/ sulfamethoxazole prophylaxis.

Recipients of HSCT are also at increased risk of serious amoebic infections [36]. Amoebae are environmental eukaryotes found in soil, air, and both fresh and salt water. The CSF demonstrates eukaryotic amoebic cells. PCR amplification helps to identify the species of amoebae. Amoebic encephalitis is sometimes identified on biopsy of brain lesions or during post-mortem examination.

5. Drug and radiation induced neurotoxicity

5.1. PRES

PRES is a clinical-neuroradiologic illness characterized by headaches, seizures, altered mental status and visual disturbances associated with a typical imaging pattern demonstrating transient subcortical vasogenic edema most commonly affecting the posterior regions of the brain [5, 37, 38]. Several explanations for its occurrence have been offered. One hypothesis suggests that a sudden rise in blood pressure exceeds the auto-regulatory capacity of the brain [39]. The hypertension causes cerebral arteriolar vasodilatation, opening endothelial tight-junctions, leading to plasma and red blood cell leakage into the extracellular space. Another theory involves the direct cytotoxic effects of chemotherapeutic agents on endothelial cells [39]. The resulting endothelial dysfunction produces blood-brain barrier disruption. PRES is believed to occur in the posterior cerebral area presumably because adrenergic sympathetic innervation is less robust in the vertebrobasilar system than in the carotid system. In addition to the typical involvement of the parieto-occipital lobe, PRES can affect the basal ganglia, thalamus, frontal lobe, brainstem, and deep cerebral white matter [39].

PRES most often develops after HSCT for acute leukemia [39]. If not promptly recognized, PRES may lead to permanent neurologic sequel or death. The incidence of PRES in allogeneic HSCT recipients is 1.6–20%. One-year survival of patients with PRES was significantly inferior to those without PRES (27% versus 67%) [5, 40]. Induction regimens for acute lymphoblastic leukemia present the greatest risk factor for PRES due to their deleterious effects on the CNS endothelium [40]. Tumor lysis, high blood pressure, systemic inflammatory response syndrome, sepsis and renal failure contribute to the development of PRES [40]. Additional risk factors include long-term use of tacrolimus or cyclosporine A (CSA), methylprednisolone, total body irradiation, grade III GVHD, thrombotic microangiopathy, and unrelated and/or human leukocyte antigen mismatched donor [39, 40].

PRES may be indistinguishable from other neurologic lesions, especially infarction. Seizures are a common manifestation of PRES, particularly occipital lobe seizures. Reversible status amauroticus because of occipital lobe status epilepticus may be the presenting symptom of PRES. Early electroencephalography (EEG) is important, as status amauroticus responds well to anti-epileptic medications [38]. In one study, 40% of the patients with PRES presented with focal nonconvulsive status epilepticus, an under-recognized event that can exacerbate CNS injury [5]. The onset of status epilepticus is characterized by subtle and stereotypical clinical signs such as gaze deviation, oculoclonic movements, and mental status changes. EEG monitoring is fundamental to diagnosing non-convulsive status epilepticus. Intractable seizures developed only in patients with residual abnormalities on MRI [30]. Irreversible or recurrent cases have been described [39].

PRES should be considered in HSCT patients with acute neurological illness [41]. The differential diagnosis for PRES includes asparaginase-induced toxicity (bleeding or thrombotic events) and methotrexate-induced encephalopathy (cerebral white matter) [39]. Methotrexate-induced encephalopathy tends to occur within a few weeks after intrathecal methotrexate infusion. Early control of blood pressure or withdrawal of causative drugs can reverse PRES [41]. Long-term anticonvulsant therapy is frequently required. Structural sequels are usually visible on MRI imaging. Long-term follow-up is recommended [39]. Prevention remains elusive [40].

5.2. CSA

CSA, a calcineurin inhibitor, effectively prevents and treats GVHD [23]. Side effects include hypertension, renal and hepatic toxicity. Neurological complications of CSA include paresthesia, headache, seizures, confusion, visual hallucinations, cortical blindness, ocular flutter, cerebellar-like syndromes, leukoencephalopathy, encephalopathy and intractable epilepsy associated with mesial temporal sclerosis [9, 42]. Patients with CSA encephalopathy characteristically demonstrate hypertension. Factors that may exacerbate its CNS toxicity include hypomagnesaemia, hypertension, acute kidney injury, hypocholesterolemia, and corticosteroids [42]. Neurotoxicity cannot always be predicted by monitoring blood CSA levels. Yanagimachi et al. [43] found influential gene polymorphisms in patients with calcineurin inhibitor-related neurotoxicity after HSCT. In one study of children treated with cyclosporine after HSCT, 8% had acute seizures [8]. Risk factors associated with seizures included lower age at transplantation

(3–5 yr) and longer duration of CSA treatment [8].

Irreversible leukoencephalopathy with severe neurologic deterioration has been described following allogeneic transplantation [44]. All reported patients received CSA, but none had elevated drug levels. Symptoms at onset included confusion, altered mental status, sluggish pupillary responses, abnormal movements, and seizures. Two patients died while four developed persistent encephalopathy. MRI revealed periventricular or subcortical white matter involvement in all, and basal ganglia involvement in half. Patients with CSA neurotoxicity may develop T2-weighted sequence abnormalities on MRI with multifocal areas of hyperintensity, often in the occipital lobe with associated cortical blindness [2, 45, 46]. Commonly drug discontinuation is followed by remission of symptoms. EEG and neuroimaging demonstrate abnormalities predominantly in the occipital regions.

5.3. Tacrolimus

Tacrolimus is used to prevent GVHD post-transplantation. Tacrolimus encephalopathy may result from vascular endothelial damage in the brain [47]. Factors that enhance the risk of endothelial injury include irradiation, intrathecal methotrexate, busulfan, fludarabine, steroids, infection, and GVHD. Acute hypertension may exceed the auto-regulatory capacity of brain capillaries, causing blood-brain barrier breakdown. Symptoms usually improve with the treatment of the hypertension. Tacrolimus encephalopathy can result in seizures, headache, nausea, altered mental status, confusion, verbal disorder, cortical blindness, and hemiplegia. More rarely, it causes cerebral hemorrhage and infarction. One report described tacrolimus encephalopathy in 20% of HSCT patients [47]. CSA and tacrolimus should be reduced or discontinued when patients develop hypertension even without signs of neurotoxicity.

5.4. Dimethyl sulfoxide (DMSO)

DMSO, used for the cryopreservation of stem cells in autologous transplantation is believed to cause acute vasoconstriction [48]. One report described a child with Hodgkin lymphoma who developed transient blindness after stem cell infusion [48]. Acute ischemia from vasoconstriction of occipital lobe vessels may be the reason for vision loss. Common side effects of DMSO include nausea, vomiting, abdominal cramps, hyper/hypotension, arrhythmias, respiratory arrest, and elevated lactate dehydrogenase levels. Neurological toxicity such as reversible leukoencephalopathy, seizures, stroke, and transient amnesia has also been reported. Decreasing the amount of DMSO used for stem cell cryopreservation without detriment in cell viability or engraftment time appears to have reduced side effects.

5.5. Other neurotoxic drugs

Potentially life-threatening neurologic adverse drug reaction can result from cyclophosphamide infusion. In one report, a patient developed generalized seizures within 30 min of the cyclophosphamide infusion [43]. Other medication-related neurotoxic findings include high dose cytarabine associated cerebellar toxicity, methotrexate-induced leukoencephalopathy, and amphotericin-associated parkinsonism. Acyclovir at doses of 1500-3000 mg/m^2/day can also cause tremulousness, agitation or lethargy, occasionally with epileptiform changes on EEG [49].

6. Post-irradiation somnolence syndrome

Post-irradiation somnolence syndrome, first described in 1973, [50] has been observed in children who received 1800–2400 cGy cranial irradiation [49]. The incidence of somnolence syndrome following HSCT remains unknown. Somnolence does not occur in patients receiving total body irradiation for HSCT. Patients develop somnolence, low-grade fever, anorexia, nausea, vomiting, cerebellar ataxia, dysphagia, and headache usually between 3 and 12 wk following completion of radiation. Somnolence lasts 3–14 days before resolving but its mechanism remains unknown. EEG usually reveals moderate to severe diffuse general slowing.

7. Cerebrovascular diseases

7.1. Cerebral hemorrhage

Cerebrovascular diseases include cerebral hemorrhage and thrombotic, thrombocytopenic, purpura-associated ischemic strokes. Vascular damage induced by immunosuppressive drugs and exacerbated by GVHD contributes to cerebral hemorrhage [51]. Arte-

rial hypertension may lead to the development of cerebral hemorrhagic infarction and hemorrhage via reperfusion of blood flow to damaged vessels. Cerebral hemorrhage associated with CSA/tacrolimus-related encephalopathy was reported in a 16-year-old female after allogeneic HSCT [51].

7.2. Mycotic aneurysm

Mycotic aneurysm is a rare, but often fatal complication of HSCT. In one report, a child who had received an allogeneic HSCT developed an Aspergillus middle ear infection complicated by mycotic aneurysm of the internal carotid artery and cerebral hemorrhagic infarction [28]. Successful treatment included coil embolization of the internal carotid artery and long-term antifungal agents. *Aspergillus* sp. show tropism for the vascular wall and invasion of vessels resulting in thrombosis; vessel wall destruction is common. The intraluminal vascular extension of fungal hyphae can cause in situ thrombosis and infarction of the affected vascular distribution.

7.3. Cerebral venous sinus thrombosis

Cerebral venous sinus thrombosis can complicate HSCT [46]. Risk factors for cerebral venous sinus thrombosis include infections (sinusitis, mastoiditis, sepsis, and meningitis), meningeal neoplastic infiltration, prothrombotic states (factor-V Leiden, protein S and C deficiency), subclavian central lines insertion, use of L-asparaginase in patients with acute lymphocytic leukemia and CSA-induced thrombosis. MRI with magnetic resonance venography is the imaging modality of choice. Therapy of cerebral sinus venous thrombosis includes anticoagulation and/or local thrombolysis.

7.4. GVHD-associated CNS angiitis

GVHD-associated CNS angiitis has been reported rarely after HSCT, but may be under-diagnosed. Symptoms vary greatly so diagnosis is made by brain biopsy or angiogram [52]. Biopsy usually reveals generalized vasculitis involving small to medium-small vessels of the parenchyma and meninges. CNS angiitis should be considered after exclusion of infectious etiologies and leukoencephalopathies. MRI, which may have poor sensitivity early in the disease, demonstrates multifocal or confluent white matter signal changes. High dose steroids may be of benefit and should be considered early in the disease [52].

7.5. VZV-associated CNS vasculitis

VZV can cause vasculitis, which may result in mild to severe neurologic injury [53]. Treatment usually includes high dose steroids. One report documented successful treatment of severe, progressive VZV-associated CNS vasculitis with pulses of cyclophosphamide in an immunocompromised child [53]. Anticoagulation in the initial phase of VZV-associated arterial ischemic stroke may be helpful in preventing extension or embolization. The recurrence rate of stroke has been reported at 45% and residual neurologic deficits at 68% [54].

8. Relapses and post-HSCT carcinogenesis

8.1. Secondary malignancies

Secondary malignant and benign CNS tumors including astrocytoma, meningioma and glioblastoma have been described in long-term survivors of conventional myeloablative allogeneic HSCT [55]. Radiation and chemotherapy insults to the brain are major contributing factors. In one study, children younger than 10 yr of age were 36 times more likely to develop secondary malignancies, and over half of the solid tumors, involved the brain and thyroid gland [56]. Most affected patients had received cranial irradiation.

8.2. CNS relapse

The incidence of isolated CNS relapse in pediatric acute myeloid leukemia (AML) ranges from 2% to 8.8% [57]. Risk factors for CNS relapse in AML include tumor histology, young age, high white blood count or CNS disease at diagnosis and abnormalities of chromosome 11 [58]. Infants are more susceptible than adolescents and adults to develop CNS leukemia because of a higher proportion of vasculature in the leptomeninges.

8.3. CNS post transplant lymphoproliferative disease (PTLD)

Isolated CNS involvement of EBV-associated PTLD is rare. Two children who developed isolated CNS PTLD had high EBV burdens pre-transplant [59].

Their asymptomatic EBV reactivation was readily managed with intravenous rituximab administration. Peripheral blood EBV PCR did not reflect accurately the CNS load. Intrathecal administration of rituximab was required to achieve sustained clinical response of CNS PTLD as many chemotherapy agents and rituximab have poor CNS penetration. In these patients, the EBV PCR load decreased with intrathecal treatment, which correlated with improvement in clinical and MRI findings. The prognosis of CNS PTLD in children is usually poor. Cellular therapy with allogeneic EBV-specific cytotoxic T-lymphocytes has been found to be effective in systemic PTLD [59].

9. Immune-mediated inflammatory disorder of the CNS

9.1. Acute disseminated encephalomyelitis (ADEM)

ADEM is a rare autoimmune, inflammatory disorder of the CNS, commonly preceded by viral infection or vaccination. ADEM affects the white matter of the brain and spinal cord and occurs uncommonly after allogeneic HSCT [6]. T-lymphocytes directed against viral epitopes may also respond to amino acid sequences in CNS myelin antigens [6]. Symptoms include dysarthria, facial nerve palsy, gait disturbance, altered mental status, confusion and paraplegia. Treatment includes high dose steroids, and IVIg or plasmapheresis for steroid refractory cases. Some patients require mechanical ventilation. MRI abnormalities occur on T2-weighted and fluid-attenuated inversion recovery sequences and involve the subcortical white matter of the cerebral hemispheres, the cerebellum, the brainstem, and the spinal cord. CSF findings (60–80%) are non-specific and may include pleocytosis, elevated protein levels and oligoclonal bands [6]. ADEM should be considered for post-transplant multifocal neurologic symptoms as early diagnosis may improve outcomes.

9.2. Idiopathic inflammatory demyelinating diseases of the CNS

Other uncommon inflammatory demyelinating CNS complications following allogeneic HSCT include multiple sclerosis, neuromyelitis optica, and progressive multifocal leukoencephalopathy [6]. Diagnosis is made by MRI or brain biopsy.

10. Metabolic encephalopathy

10.1. Electrolyte disturbances, nutritional deficiencies, and hepatic or uremic encephalopathy

Electrolyte disturbances commonly precipitate acute neurologic complications in HSCT patients [4]. Rapid changes in electrolyte balance contribute to increased vulnerability to seizures and altered mental status [4]. Rapidly evolving hyponatremia, a medical emergency, may produce seizures, coma, permanent brain damage, respiratory arrest, brainstem herniation and death [60]. Hyponatremia and syndrome of inappropriate antiduretic hormone secretion commonly complicate HSCT, especially in children below 4 yr of age. HHV-6 has been described as a cause for seizures and hyponatremia [61, 62].

Nutritional deficiencies may also cause and contribute to neurologic abnormalities in the pediatric HSCT patient. Wernicke encephalopathy from thiamine deficiency may occur in HSCT patients receiving prolonged parental nutrition without adequate vitamin supplementation [63]. It classically presents with ophthalmopathy, nystagmus, vertigo, ataxia, headaches and altered mental status, but this classic presentation occurs only in approximately 16% of patients [63]. Wernicke encephalopathy is difficult to distinguish from other encephalopathies; however, timely diagnosis is critical because early treatment improves outcomes. Without thiamine treatment, mortality reaches 17–20% mortality while progression to Korsakoff syndrome with memory impairment occurs in 80% of cases [63]. On MRI, lesions in the thalamus and mammillary body are most common, but the tectal plate and cranial nerve nuclei can also be involved.

Hepatic or uremic encephalopathy may also be observed in the setting of HSCT. They are most often associated with gram-negative sepsis or the use of sedative-hypnotic drugs.

11. Less frequent neurologic complications

11.1. Epilesia partialis continua (EPC)

EPC after allogeneic HSCT presents as a focal encephalopathy mainly affecting the motor region [63, 64]. In children, EPC is most commonly caused by Rasmussen encephalitis, a condition of unclear

etiology that has been associated with antibodies against glutamic acid receptors and viral infections. Patients with Rasmussen encephalitis can present with intractable focal motor seizures, progressive hemiparesis, neuropsychological deterioration, homonymous hemianopsia and loss of language-skills. EEG findings vary but may include poor background activity and delta waves over the affected hemisphere and the continuous spike discharges can originate from one portion of the cortex. Initially brain MRI usually appears normal. But when the disease progresses MRI may show focal cortical atrophy, white matter or cortical hyperintensity, and atrophy of the head of the caudate nucleus. Hemispherectomy is the standard of treatment and other measures such as IVIgs, steroid and plasmapheresis, have not shown to be effective [65].

11.2. Transmissible spongiform encephalopathy

Transmissible spongiform encephalopathy has also been reported in the setting of pediatric HSCT [66]. In one report, a rapidly progressive encephalopathy occurred in a 6-year-old boy 5 mo after matched unrelated cord blood transplant [66]. Autopsy revealed spongiform changes in his brain consistent with transmissible spongiform encephalopathy. Transmissible spongiform encephalopathy can be classified into the sporadic, iatrogenic, familial, and variant forms of Creutzfeldt-Jacob disease.

11.3. Cerebral GVHD

Cerebral GVHD has also been reported among the pediatric HSCT population. Kyllerman et al. [67] described the case of a girl with Hurler disease (mucopolysaccharidosis type I) who underwent allogeneic HSCT. One year post transplantation she was noted to have developed cerebral GVHD. The process was reversed with prednisolone and CSA.

11.4. Pseudotumor cerebri

Pseudotumor cerebri is a syndrome of increased intracranial pressure with normal CSF content and normal neuroimaging. A child who underwent HSCT developed pseudotumor cerebri secondary to maxillary sinusitis [68]. Lumbar puncture and treatment of the underlying cause sufficed to reverse the process.

12. Discussion

Severe neurologic complications occur commonly after HSCT. The reported incidence ranges from 5% to 14% with an average mortality of 40% [1–11]. The incidence of neurological complications appears highest in unrelated allogeneic transplantations (39%), followed by related allogeneic (21%) and autologous transplantations (11%) [10]. Neurologic complications in children receiving HSCT have been found to cause 8.5% of post-transplant deaths [42].

The causes of CNS complications following HSCT are variegated. In our review, the majority of the neurologic complications were caused by infections, drug-related toxicities, PRES, neoplasm, vascular, and metabolic disturbances. However, multiple rare etiologies also exist and must be considered in the work-up of HSCT patients with neurologic changes. Direct toxicity of the conditioning regimen (busulfan), radiotherapy, immunosuppressive agents, GVHD and sinusoidal obstruction syndrome produce severe suppression of cell-mediated immunity predisposing patients to infections and neurological complications after HSCT. Additional risk factors of severe neurological complications include severe GVHD (>grade II), mismatched HSCT, diagnosis of AML, older age and other transplant complications [3].

Clinical findings are broad and non-specific, and include seizures, encephalopathy, vision disorders, headaches, focal deficits, abnormal movements, drowsiness, increased intracranial pressure and agitation. There appears to be no close correlation between pre-transplant disease or symptoms and etiology of CNS complications. One-year survival declined significantly in patients who experienced seizures (57% versus 75%) [69]. Risk factors for seizures included young age, allogeneic transplant, acute GVHD and hyponatremia.

Neurodiagnostic imaging, laboratory examinations and clinical examination are most helpful with establishing a diagnosis. CSF cell counts may not be a reliable means of assessing infection in immunocompromised HSCT patients. PCR-based testing of the CSF for infectious pathogens and/or brain biopsy should be considered in these patients. Brain anomalies are detected on MRI in the vast majority of patients evaluated for encephalopathy [2]. Brain biopsies can also be a useful diagnostic tool that is safe and well tolerated. It should be considered in the evaluation of undiagnosed encephalopathy, infections or tumors.

EEG assessment is also vital in the evaluation of encephalopathic patients. Positron-emission tomography and single-photon emission computed tomography have been found to be more sensitive than computerized tomography or MRI, but their roles require further elucidation [2].

In conclusion, an early and aggressive diagnostic workup, in combination with the appropriate medical therapy and intensive rehabilitation, may improve the prognosis in pediatric patients who experience a devastating neurologic complication of allogeneic HSCT. A standardized approach to accurate and timely diagnosis and treatment is needed to improve outcomes in these patients.

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