● INVITED REVIEW

Neurological complications of hematopoietic cell transplantation in children and adults

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Abstract

Hematopoietic cell transplantation (HCT) is widely performed for neoplastic and non-neoplastic diseases. HCT involves intravenous infusion of hematopoietic progenitor cells from human leukocyte antigen (HLA)-matched donor (allogeneic) or from the patient (autologous). Before HCT, the patient is prepared with high dose chemotherapy and/or radiotherapy to destroy residual malignant cells and to reduce immunologic resistance. After HCT, chemotherapy is used to prevent graft rejection and graft *versus* host disease (GvHD). Neurological complications are related to the type of HCT, underlying disease, toxicity of the conditioning regimens, immunosuppression caused by conditioning regimens, vascular complications generated by thrombocytopenia and/or coagulopathy, GvHD and inappropriate immune response. In this review, neurological complications are presented according to time of onset after HCT: (1) early complications (in the first month) - related to harvesting of stem cells, during conditioning (drug toxicity, posterior reversible encephalopathy syndrome), related to pancytopenia, (2) intermediate phase complications (second to sixth month) - central nervous system infections caused by prolonged neutropenia and progressive multifocal leukoencephalopathy due to JC virus, (3) late phase complications (after sixth month) - neurological complications of GvHD, second neoplasms and relapses of the original disease.

Key Words: neurological complications; hematopoietic cell transplantation; posterior reversible encephalopathy syndrome; central nervous system infections; progressive multifocal leukoencephalopathy; graft versus host disease; second neoplasm; immune reconstitution inflammatory syndrome; post-transplant acute limbic encephalitis; drug reaction with eosinophilia and systemic symptoms

Introduction

Hematopoietic cell transplantation (HCT) is an effective therapy for an expanding range of neoplastic conditions, aplastic anemia, metabolic and autoimmune diseases. The median age of patients is 10 years older than it was two decades ago and indications for transplantation may be conditions associated with significant pre-transplantation neurological deficits (Copelan, 2006; Hart and Peggs, 2007; Center for International Blood and Marrow Transplant Research, 2008; Quant and Wen, 2008; Strober et al., 2009; Passweg et al., 2014).

The long-term survival rates in children and adolescents have increased over the past 10 years and now approach 50%. Central nervous system (CNS) complications are considered an important cause of morbidity and significantly contribute to mortality after HCT (Bleggi-Torres et al., 2000; An et al., 2016; Lee et al., 2017; Maffini et al., 2017). Previous clinical studies reported neurological abnormalities in 11–59% of patients after HCT (Azik et al., 2014; Cordelli et al., 2017; Lee et al., 2017; Maffini et al., 2017). However, in autopsy studies neuropathological abnormalities were found in more than 90% of patients who died after HCT. The most common autopsy findings have been reported as subarachnoid and intraparenchymal hemorrhage with a 58.7% incidence of cerebrovascular complications, fungal infection, Wernicke encephalopathy, microglial nodular encephalopathy and toxoplasmosis (Bleggi-Torres et al., 2000). In particular, cerebrovascular bleeding, fungal infection and toxoplasmosis were found as causes of death in these studies (Bleggi-Torres et al., 2000). Mismatched related or unrelated donor allogeneic transplantation and the occurrence of graft *versus* host disease (GvHD) were the most significant risk factors for development of neurological complications, most probably related to pronounced immunosuppression in such patients (An et al., 2016; Lee et al., 2017; Maffini et al., 2017).

Transplantation Procedure

HCT consists of intravenous infusion of hematopoietic progenitor cells from HLA-matched donor (allogeneic) or from the patient itself (autologous) to restore the bone marrow function eradicated by high doses of chemotherapy and/or radiotherapy. The procedure generated complications related to: (1) the pre-transplantation conditioning regimen, either full intensity (myeloablative) or reduced intensity (nonmyeloblative), (2) donor type, either from a relative or unrelated human leukocyte antigen (HLA)-compatible donor (allogeneic transplantation) or from the patient prior to marrow ablation (autologous transplantation), and (3) source of stem cells (bone marrow, peripheral, or umbilical cord blood). With recognition that graft *versus* tumor effects are important therapeutic adjuncts, reduced intensity protocols have emerged for many hematologic disorders, and this less toxic procedure is commonly used in patients over age 50. Minimal intensity conditioning using antibody-based cell depletion is an investigational strategy currently under

study for primary immunodeficiency disease (Straathof et al., 2009).

A 2012 survey collecting data from 661 centers in 48 countries reported 37,818 HCT in 33,678 patients (42% allogeneic and 58% autologous) and included 4097 pediatric patients < 18 years of age receiving HCT (71% allogeneic and 29% autologous). The proportion of allogeneic transplantation is higher in children in comparison to adults, the main indication for allogeneic transplantation in children being acute lymphoblastic leukemia (ALL) and primary immune deficiencies, while autologous transplantation has been mainly used for treating solid tumors, neuroblastoma and lymphoma (Passweg et al., 2014). In children, the vast majority of papers reported neurological complications to allogeneic HCT (Schmidt-Hieber et al., 2016).

Neurological Complications (NCs)

NCs after HCT can be classified according to: time of onset, clinical manifestations and etiology. NCs are related to the type of HCT, underlying disease, toxicity of the conditioning regimens, immunosuppression caused by conditioning regimens, vascular complications generated by thrombocytopenia and/or coagulopathy, GvHD and inappropriate immune response.

From the point of view of the onset time we can identify: (1) the early complications (the first month including HCT, conditioning transplantation procedures for HCT and the period before HCT engraftment); (2) the intermediate period complications (occurring from the second through the sixth months after transplantation); and (3) the late complications (occurring beyond six months after transplantation) (**Additional Table 1**). During the pre-engraftment period (< 30 days) the immune system of the patient is completely suppressed and the hematopoietic system is destroyed. Pancytopenia occurs especially associated with severe neutropenia (less than 100/mm^3) causing a high risk of infections. The high dose of chemotherapy and irradiation can cause damage in mucosa, liver and other tissues. In the intermediate phase (second to sixth month) immune recovery status starts although immune depletion continues. Acute GvHD may develop, caused by alloreactive donor-derived T-cells attacking antigens in different tissues (skin, liver and intestinal tract) causing erythematous maculopapular rash, persistent anorexia, vomiting and/or diarrhea and liver dysfunction. The prophylaxis of GvHD mainly consists of post-transplant administration of immunosuppressive drugs (cyclosporine, tacrolimus, methotrexate, steroids, anti T-cell antibodies, *etc.*) and may impair the post-transplant immunologic reconstitution. After sixth months, immune recovery occurs progressively towards complete recovery but GvHD may develop. In chronic GvHD, patients with only liver and skin involvement have a better prognosis. Patients with extensive involvement of multiple organ systems may experience prolonged cellular and humoral immunosuppression associated with the immunosuppressive regimens necessary to control GvHD and the prognosis may be poor. Graft failure or relapse of the underlying disease may occur

during this phase (Schmidt-Hieber et al., 2016).

Early neurologic complications (in the first month)
Complications related to harvesting of stem cells
Prior to cell harvesting, during administration of hematopoietic growth factors, patients with preexisting autoimmune diseases such as multiple sclerosis may experience exacerbations of their underlying disease (Openshaw et al., 2000; Burt et al., 2001). In children as well as in adults, the use of cytotoxic chemotherapy (cyclophosphamide) in addition to growth factors in the cell mobilization regimen reduces this risk of disease relapse although can be associated with increased risk of infection (Burt et al., 2001; Uy et al., 2015).

During the harvesting of stem cells, complications are very rare, such as an accidental entry into the subarachnoid space leading to a syndrome of intracranial hypotension.

Complications during conditioning
Although allogeneic hematopoietic cell transplants have been generally thought to have higher risk of adverse effects, a large retrospective study of 425 adult patients demonstrated a similar incidence of neurologic problems in autologous and allogeneic HCT recipients (Rosenfeld and Pruitt, 2006). On the contrary, in children allogeneic HCT was associated more frequently than autologous HCT with neurologic complications and increased morbidity and mortality due to the immunosuppression toxicity used to prevent GvHD and mismatched transplantation, primary disease being acute myeloid leukemia (AML), older age and the presence of grade II or higher GvHD (Maher et al., 2017).

Most complications during conditioning have been attributed to high-dose chemotherapy, prophylactic drugs against GvHD, total body irradiation and antibiotics used for prophylaxis or treatment of infections. Drug-to-drug interactions and the combination of different neurotoxicities of those drugs that are administered simultaneously play a pivotal role in the appearance of neurologic complications.

The most common of the NCs produced by the preparative regimens are: seizures (busulfan - the estimated incidence of seizures is 10% and with use of antiepileptic drug prophylaxis only 1.3%, cytarabine, melphalan, ifosfamide), severe encephalopathy and posterior reversible encephalopathy syndrome (PRES) (carboplatin, carmustine, cyclophosphamide, etoposide, fludarabine, ifosfamide, melphalan), peripheral neuropathy (carboplatin, etoposide) and ototoxicity (carboplatin), pancerebellar syndrome (cytarabine), lymphocytic meningitis (cytarabine, thiotepa), progressive multifocal leukoencephalopathy (PML) (monoclonal antibodies such as alemtuzumab or rituximab, fludarabine), necrotizing microangiopathy, additive toxicity with cranial irradiation, transient stroke-like episodes with diffusion weighted imaging-magnetic resonance imaging (DWI-MRI) abnormalities, transverse myelitis (methotrexate), Listeria myelitis, cytomegalovirus (CMV) encephalitis, immune reconstitution inflammatory syndrome (IRIS), Guillain-Barré syndrome (alemtuzumab) (Pruitt et al., 2013).

Antibiotics used in infection prophylaxis or treatment of infectious complications may also produce NCs: seizures (acyclovir, cefepime, imipenem), parkinsonism and confusion (amphotericin B), encephalopathy (acyclovir, cefepime), myoclonus (cefepime), ischemic optic neuropathy, PRES, serotonin syndrome, neuropathy (linezolid, posaconazole enhances vincristine neuropathy), reversible cerebellar disease, sensorimotor peripheral neuropathy, optic neuropathy and autonomic dysfunction (metronidazole) (Hobson-Webb et al., 2006; Patel et al., 2008), visual hallucinations (voriconazole). There are several reports on neurotoxic effects of carbapenemics particularly imipenem/cilastatin (Norrby, 2000). Quinolone neurotoxicity may manifest with seizures, encephalopathy, myoclonus and toxic psychosis (Isaacson et al., 1993).

Chemotherapy used for post-transplant GvHD prophylaxis have been reported to produce the following NCs: tremor (cyclosporine), PRES (cyclosporine, tacrolimus, sirolimus), progressive multifocal leukoencephalopathy (PML) (mycophenolate), chronic inflammatory demyelinating polyneuropathy (CIDP) (cyclosporine, tacrolimus), mutism, pseudotumor cerebri (cyclosporine), brachial plexopathy, optic neuropathy, hearing loss (tacrolimus), seizures (cyclosporine, tacrolimus) (Kang et al., 2015). Seizures and encephalopathy are most common immediately after the actual hematopoietic cell infusion; seizures are typically generalized and do not recur, even without antiepileptic drugs. This is probably related to toxicity from dimethyl sulfoxide used as a cryopreservative and may be associated with diffuse white matter changes on magnetic resonance imaging (MRI) that resolve over days to weeks (Higman et al., 2000; Bauwens et al., 2005). Many patients experience delirium without focal neurologic deficits within 30 days of HCT (Fann et al., 2002; Fann et al., 2007). Risk factors for development of delirium include elevated pre-transplant levels of alkaline phosphatase and blood urea nitrogen, as well as post-transplant use of opiates (Fann et al., 2011).

Among the most important and reversible conditions that may occur is PRES (**Figure 1**). Also known as reversible posterior leukoencephalopathy syndrome, PRES is most common during this early post-transplant period but risk continues throughout the patient's course. Calcineurin inhibitors such as cyclosporine and tacrolimus are the major offenders, but PRES has been described with sirolimus and everolimus as well as with dexamethasone (Nguyen et al., 2009; Shkalim-Zemer et al., 2017; Zama et al., 2018). PRES is manifested by: acute mental status changes, cortical blindness, hypertension and seizures and MRI may show petechial, lobar or subarachnoid hemorrhage. The syndrome results from dysregulation of cerebral vasculature, leading to vasogenic edema preferentially but not exclusively, affecting the parieto-occipital regions. Brainstem, basal ganglia, and spinal cord involvement all have been reported as well as status epilepticus (McKinney et al., 2007; Briganti et al., 2009; Tambasco et al., 2016). Two theories have been formulated to explain the development of cerebral vasogenic edema: the first theory incriminates hypertension suggesting

that rapidly increasing blood pressure produce cerebral hyperperfusion and damage of the capillary bed with leakage of the fluid in the interstitium, and the second theory point to the endothelial cell activation with subsequent cerebral vasoconstriction and hypoperfusion (Cordelli et al., 2017). The development of PRES with the use of one immunosuppressive drug does not preclude safe use of another related agent. A clinical dilemma is related to the appropriate choice and duration of antiepileptic drug therapy. The use of non-enzyme-inducing antiepileptic therapy has been proposed during and for one month following the acute episode of PRES if accompanied by clinical seizures.

Complications of pancytopenia

Thrombocytopenia and coagulation disturbances generate vascular complications. Subdural hematoma is the most common vascular complication, but intraparenchymal hemorrhage (IPH), subarachnoid hemorrhage, cerebral venous thrombosis and infarction may occur (**Figure 2**). In adults, autopsy series suggest an incidence of subdural hematoma up to 11.9% (Mohrmann et al., 1990) while retrospective clinical reviews have documented this complication in 2% to 5.7% of patients (Najima et al., 2009; Zhang et al., 2016).

A retrospective review of 622 allogeneic HCT recipients (Najima et al., 2009), over a period of 20 years identified a total of 21 cases (3.4%) including 15 cases of intraparenchymal hemorrhage (IPH), two cases of subarachnoid hemorrhage (SAH), and four cases of subdural hematoma (SDH). The median time from transplantation to the onset of ICH was 63 days (range 6-3488 days). The clinical features of post-transplant intracerebral hemorrhage patients were similar and included hypertension, diabetes mellitus, chronic GvHD, systemic infection, and veno-occlusive disease (VOD), recently referred to as sinusoidal obstruction syndrome, in addition to severe thrombocytopenia. Mortality rate was especially high (89%) after IPH with a median survival of 2 days (range 0–148 days). In contrast, all patients with SAH or SDH following HCT survived. The cause of post-transplant ICH appears to be multifactorial, including thrombocytopenia, hypertension, acute GvHD, VOD, and radiation therapy. In children, intracranial hemorrhage has been reported as life-threatening complication after HCT in a small number of patients (Uckan et al., 2005) and thrombotic disease is reported in association with endocarditis, indwelling catheter and characteristically with treatment with L-asparaginase in acute lymphoblastic leukemia (ALL) (Caruso et al., 2006).

Coagulation deficits generates hepatic veno-occlusive disease also called sinusoidal obstruction syndrome, that may present with encephalopathy, fluid retention and rising bilirubin (Caruso et al., 2006).

Neutropenia may cause infections due to viruses, bacteria, fungi and parasites. Clinical infectious manifestations may be absent due to host's immunosuppression, but CNS infection should be suspected upon occurrence of new neurological signs, fever or systemic, particularly pulmonary, infection (**Figures 3**–**5**). Nosocomial infections may be caused by
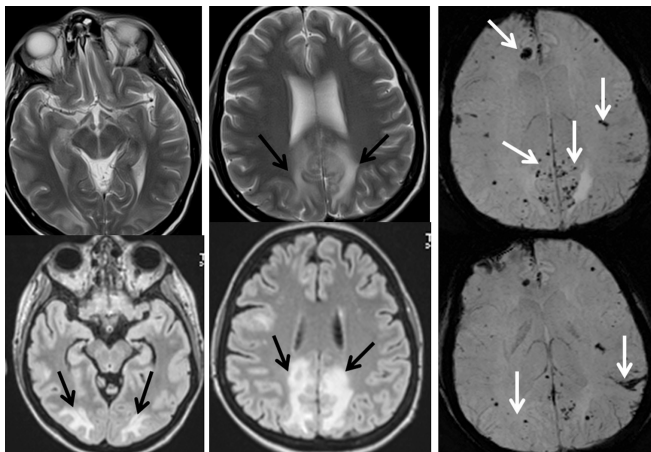
Figure 1 Brain MRI of a 32-year-old female with Hodgkin lymphoma treated with allogeneic hematopoietic cell transplantation on March 23, 2018.
Posterior reversible encephalopathy syndrome (PRES) typical magnetic resonance imaging (MRI) aspect (black arrows)- symmetrical areas of T2 and Flair hyperintensity in both parieto-occipital lobes. Multiple supratentorial hemosiderotic spots (white arrow).
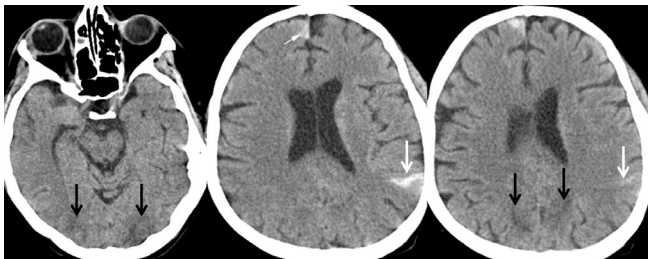

Figure 2 Brain CT-scan of a 32-year-old female with Hodgkin lymphoma treated with allogeneic hematopoietic cell transplantation on March 23, 2018.
Parieto-occipital bilateral hypodensities (black arrows). Small hemorrhagic left parietal and right frontal SAH accumulations (white arrow).
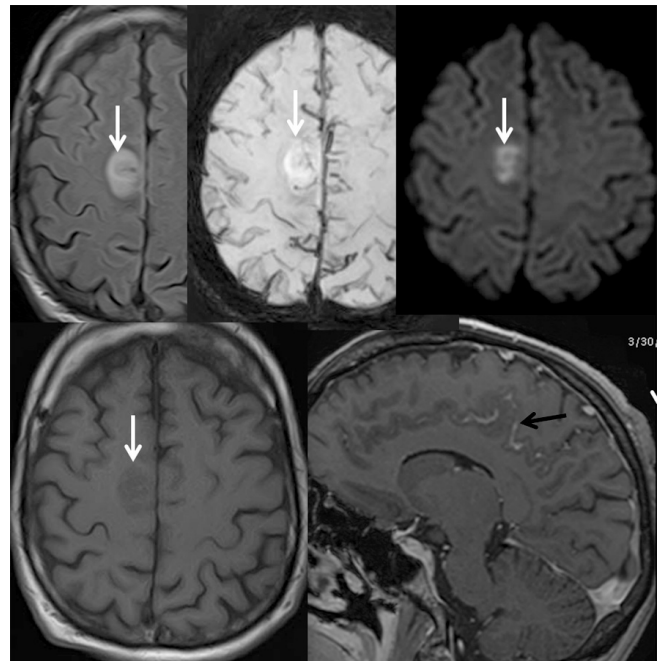

Figure 3 Brain MRI of a 30-year-old male with acute myeloid leukemia who received allogeneic hematopoietic cell transplantation on December 19, 2017.
Right frontal cortical parasagital lesion with "acute" pattern (restriction of water on diffusion weighted imaging (DWI))- (white arrow) and leptomeningeal enhancement (black arrows).

methicillin-resistant Staphylococcus aureus, multiresistant enterococci, and gram-negative organisms, while intravenous lines may be a potential source of infection with Candida (Cesaro et al., 2018). CNS candidiasis involves vasculitis, hemorrhage and, less commonly, thrombotic infarction and it comprises multiple ring-enhancing micro-abscesses at the cortico/medullary junction, cerebellum, and basal ganglia (Lai et al., 1997).

In children, the predominant fungal pathogen is Aspergillus spp., with Aspergilus fumigatus prevailing over other species with an annual incidence of 0.4% of hospitalized immunocompromised children (Zaoutis et al., 2006; McDonald, 2010; Groll et al., 2014; Cordelli et al., 2017). Although culture from a sterile site remain the gold standard for diagnosis and provide antifungal susceptibilities information, invasive procedures are needed, and the diagnostic yield is low. Since Aspergillus is rarely recovered from blood cultures (Qualter et al., 2014; Cordelli et al., 2017), in many patients the diagnosis relies on indirect findings including

fungal markers (galactomannan antigen and 1,3-β-d-glucan) and neuroimaging findings. Typical neuroimaging features include ring-enhancing lesions, with a central T2 hypointensity area, associated with hemorrhagic foci and peculiar intracavitary projection at the diffusion study, representing fungal hypae (Luthra et al., 2007; Cordelli et al., 2017) mainly located to thalami, basal ganglia, and corpus callosum and subcortical regions, as Aspergillus has a peculiar "philia" for perforating arteries. Due to its angioinvasive nature, arterial infarction (lacunar and territorial), vasculitis, and mycotic aneurysm can be encountered (Yamada et al., 2002; Cordelli et al., 2017). Treatment includes amphotericin B lipid formulations and azoles (Kleinschmidt-DeMasters, 2002; Schwartz et al., 2005; Dotis et al., 2007; Cordelli et al., 2017). Prognosis correlates primarily with immune status, with allo-HCT patients having sixfold greater odds of death (Burgos et al., 2008; Cordelli et al., 2017).

Disseminated Rhiszopus microspores infection, Rhizomucor pussilus infection zycomycosis, mucormycosis and Lichteimia ramose infection have been also reported in children after HCT particularly for aplastic anemia (Rawlinson et al., 2011; Ye et al., 2013; Pana et al., 2016).

In adult recipients of HCT, another cause of CNS infection is Listeria monocytogenes that produces brain abscess, with a decreasing trend because of the use of trimethoprim–sulfamethoxazole and Nocardia asteroids (Safdar et al., 2002). In children, Listeria monocytogenes brain abcesses are rarely reported (Viscoli et al., 1991).
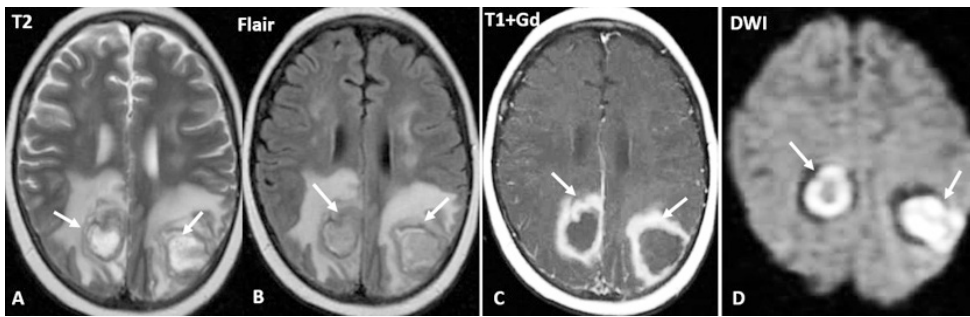
Cryptococcal meningitis is typical for HIV-infected pa-

Figure 4 Brain MRI of a 12-year-old male with acute lymphoblastic leukemia treated with allogeneic hematopoietic cell transplantation.
Cerebral abscesses located into parieto-occipital regions: typical magnetic resonance imaging (MRI) aspects-ring-enhancing lesions, with high signal intensity on T2-weighted images and low signal intensity on T1-weighted images.
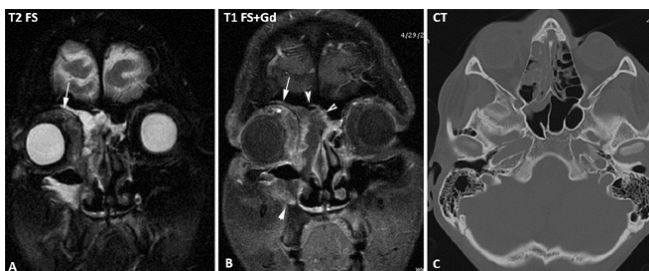

Figure 5 Brain MRI of a male treated with allogeneic hematopoietic cell transplantation in 2010.
Right orbital cellulitis: magnetic resonance imaging (MRI) and CT aspects: oedema and inflammation of the periorbital and orbital contents (white arrow); right invasive maxillo-ethmoido-frontal sinusitis (head arrows)

tients and it is very rarely reported in HCT recipients. Toxoplasma gondii allograft transmission is most strongly associated with cardiac transplantation but among HCT recipients the rates vary from 0.3% to 13% and are higher in countries where toxoplasmosis is more prevalent (Martino et al., 2000; Fricker-Hidalgo et al., 2009). Neurotoxoplasmosis presents with multiple abscesses in the white and gray matter of cerebral hemispheres associated with ring enhancement on CT and MRI. Detection of toxoplasma-DNA by polymerase chain reaction (PCR) in cerebro-spinal fluid (CSF) and stereotactic biopsy with histologic confirmation establish the diagnosis. Trimetroprim-sulphametoxazole (TMP-SFX) associated with clyndamicin or pyrimethamine is the current therapy of choice and prevention therapy with antiprotozoal molecules have been recommended.

Frequent viral infections are caused by herpesviridae (herpes simplex, Epstein-Barr virus, varicella zoster virus, cytomegalovirus (CMV) and HHV-6) and polyomaviridae (JC polyomavirus – JCV). Extensive chronic GvHD is reported to be associated with an increased rate of viral infections (Verdeguer et al., 2010). Appropriate prophylaxis has delayed the onset of such infections but reactivation of CMV has been associated with an increased risk of Listeria meningitis that might present as diffuse cerebritis or rhombencephalitis (Safdar et al., 2002).

CMV affects both peripheral and central nervous system, chorioretinitis and myelitis-radiculitis followed by encephalitis and ventriculitis being the most common forms of neurologic involvement. Ganciclovir and foscarnet are the most effective first line agents for CMV infection after HCT. HHV-6 primary infection may be asymptomatic or may cause a febrile exanthema (roseola infantum). The virus is latent in the salivary gland, white blood cells and the brain and may express as encephalitis characterized by temporal lobe seizures, fever and mental status changes including insomnia. Diagnosis is made by PCR analysis for HHV-6 in CSF and confirmation of HHV-6B protein by immunohistochemistry. Brain MRI usually shows confluent hyperintense lesion on T2 sequences and no enhancement on T1 sequences involving the mesial temporal lobes and limbic system. However acute necrotizing encephalopathy with symmetric involvement of the basal ganglia, thalamus and brainstem may occur (Ohsaka et al., 2006). Also, reactivation of pre-existing neurocysticercosis has been described (Teive et al., 2008). Donor derived infections like hepatitis B, C, CMV to neurologically specific viral contaminations such as adenovirus or Coxsackie virus B4 that produce encephalitis may be fatal (Cree et al., 2003; Gigliotti et al., 2003; Zekri et al., 2004). At 2 to 4 weeks after engraftment may appear fever, rash and headache, as the absolute neutrophil count exceeds 500.

Another neurologic complication is post-transplant acute limbic encephalitis (PALE) characterized by anterograde amnesia, the syndrome of inappropriate antidiuretic hormone secretion, mild CSF pleocytosis and EEG abnormalities with or without clinical seizures (Seeley et al., 2007). The most common cause of this syndrome is HHV-6, usually due to a reactivation of host infection. The disease is frequently associated to severe GvHD due to unrelated donors or conditioning regimens containing antithymocyte globulin, sirolimus, interleukin 12 antibodies and especially in patients receiving alemtuzumab. PALE treatment is represented by antiepileptic therapy, ganciclovir and foscarnet.

A syndrome that resembles PALE is drug reaction (or rash) with eosinophilia and systemic symptoms (DRESS). DRESS is characterized by skin eruption, fever, lymphadenopathy, syndrome of inappropriate antidiuretic hormone secretion with hyponatremia and multiorgan involvement and can be triggered by sulfonamides and antiepileptic drugs. DRESS is associated with reactivation of CMV, EBV and HHV-1, 6, 7 and may resemble GvHD. Skin biopsy helps to differentiate the two conditions (Seishima et al., 2006).

Immune reconstitution inflammatory syndrome (IRIS) may occur during engraftment, but has also been reported later after HCT and even several months after discontinua-

tion of immunosuppression. IRIS is caused by an immune rebound leading to Th1 immune response against infectious antigens and in some cases unknown antigens. Alemtuzumab, an anti-CD52 monoclonal antibody, has been reported to increase the risk of IRIS with both systemic (Graves disease) and neurological involvement after initial cryptococcal meningitis treatment.

IRIS should be considered when a patient has had an infection and there are (1) new or worsening clinical or radiologic manifestations consistent with an inflammatory process; (2) symptoms during receipt of appropriate antibiotic therapy that cannot be explained by newly acquired infection; and (3) negative results of cultures or stable or reduced biomarkers for the initial pathogen during the diagnostic workup for the inflammatory process (Ingram et al., 2007; Airas et al., 2010).

Intermediate phase neurologic complications (second to sixth month)

The most common complications of the intermediate phase are: central nervous system infections caused by prolonged neutropenia and progressive multifocal leukoencephalopathy (PML) due to JC virus. Rare cases were reported with neurologic complications such as: acute and chronic demyelinating polyneuropathy and immune mediated demyelinating disease.

Invasive opportunistic fungal diseases are important causes of morbidity and mortality in pediatric patients who have had an allogeneic HCT (Groll et al., 2014). Aspergillosis is one of the most common infections in allogeneic HCT group (Ingram et al., 2007; Airas et al., 2010), the risk reaching 10%, especially for patients receiving conditioning regimens with fludarabine and alemtuzumab. The usual route of infection is respiratory with pulmonary and paranasal sinus disease. Hematogenous spread leads to mycotic aneurysm, vasculitis and subarachnoid hemorrhage. Multiple septic infarcts may occur, involving the lenticulostriate and thalamoperforating arteries associated with hemorrhage and abscess formation. The areas commonly involved are basal ganglia, thalamus, corpus callosum and brainstem. There may be little or no pleocytosis in the CSF and daily serum galactomannan testing has been used to establish when to use preemptive therapy (Maertens et al., 2005). CNS aspergillosis may be treated with amphotericin B, voriconazole or caspofungin but mortality rates remain high.

Toxoplasma gondii allograft transmission may be present in HCT patients, with a rate of 2.94%, especially in countries where toxoplasmosis is more prevalent. Mortality rate is very high in cerebral toxoplasmosis and the occurrence is reduced by use of trimethoprim-sulfamethoxazole prophylaxis (Hakko et al., 2013).

Viral infections are other important causes of mortality and morbidity in children receiving HCT. Activation of latent herpes virus type 6 and 7 (HHV-6 and HHV-7) were reported to be common in pediatric HCT. Most infections were self-limited and were associated with adenovirus infection and severe GvHD (Fule Robles et al., 2014). Encephalitis due to primary HHV-6B infection in young children

is commonly reported in Japan, but very rarely elsewhere, suggesting a genetic predisposition. Limbic encephalitis due to reactivation of HHV-6B was reported in HCT pediatric patients, particularly after receipt of cord blood. It has a poor outcome, preventive strategies being ineffective. In children receiving HCT, cytomegalovirus reactivation was associated with increased relapse rate; accelerated overall immune recovery rather than CMV-driven immunity had a favorable outcome impact on relapse rate (Jeljeli et al., 2014). In a study which included 2628 patients after allogeneic HCT, viral encephalitis was reported as being caused by HHV-6 (28%), Epstein-Barr virus (19%), herpes simplex virus (13%), JC virus (9%), varicella zoster virus (6%) and adenovirus (3%). In 16% of patients more than one virus was identified. The use of OKT-3 and alemtuzumab was associated with increased risk of viral encephalitis after allogeneic HCT (Schmidt-Hieber et al., 2011; Yuan et al., 2018). Progressive multifocal leukoencephalopathy, a subacute demyelinating disorder caused by JC virus has been associated with fludarabine and rituximab therapy in transplanted population. Symptoms typically develop more than one month after HCT and have been reported as late as several years post-transplantation at a time of apparent minimal immunosuppression (Gheuens et al., 2010). Long-term immunosuppression in patients who underwent transplantation from alternative donors, such as mismatched unrelated donors or umbilical cord blood, represents a cause of very high risk of infection (Servais et al., 2014).

Peripheral nervous system involvement has been reported in the intermediate phase after HCT. Guillain-Barre syndrome (acute polyradiculoneuritis) was reported in three children who received allogeneic HCT and conditioning regimen containing high dose cytosine arabinoside therapy (Rodriguez et al., 2002). In contrast with the report of human CMV encephalitis in adult, in children it was reported a CMV radiculopathy with good outcome (Colombo et al., 2012).

Immune mediated demyelinating disease (IMDD) have been reported mostly in adults after allogeneic HCT. In a study including 1484 transplanted patients 7 patients (0.5%) suffered from IMDD, the median time from transplant to neurologic symptoms being 120 days (range 60–390 days). Three patients had acute demyelinating encephalomyelitis (ADEM), three acute inflammatory demyelinating polyradiculopathy (AIDP) and one autonomic neuropathy. Patients were treated with IV immunoglobulin, high-dose steroids and/or rituximab and five patients had a significant recovery (Delios et al., 2012).

Late phase neurologic complications (after sixth months)
In the late phase after HCT the possible neurologic complications are: CNS relapses of the original disease, neurologic complications of GvHD and second neoplasms.

GvHD occurs after allogeneic HCT in two major forms: acute (< 100 days post-transplant) and chronic (> 100 days). It most frequently involves skin, liver, gastrointestinal tract, eyes and peripheral nerves (Jagasia et al., 2015).

Neurological manifestation of chronic GvHD are rare and

can affect both peripheral and central nervous system. They usually occur several months to years after HCT after administration of multiple potentially neurotoxic drugs, when often infectious and metabolic complications have occurred.

Manifestations of peripheral nervous system, neuromuscular junction and muscle involvement in GvHD include polymyositis, myasthenia gravis (MG) and chronic inflammatory demyelinating polyneuropathy (CIDP) often developing late after HCT at a time of reduction in immunosuppressive therapy (Kamble et al., 2007; Grauer et al., 2010).

Chronic GvHD-related myositis appears to be similar to idiopathic polymyositis in its clinicopathological presentation (Sharaf and Prayson, 2014), especially in juvenile polymyositis where maternal microchimerism has been demonstrated (Tse et al., 1999).

Myasthenia gravis is rarely reported post-HCT in children and have a severe clinical presentation (Tse et al., 1999). There is one report of myasthenia gravis in a 2 years and 10 months old female with Griscelli syndrome who developed severe MG at 22 months post-HCT. She was unresponsive to cyclosporine A, methylprednisolone, intravenous immunoglobulin, and mycophenolate mofetil and the symptoms could only be controlled after plasma exchange and subsequent use of rituximab, in addition to cyclosporine A and mycophenolate mofetil maintenance (Unal et al., 2014).

CNS involvement in GvHD is quite rare and occurs almost exclusively in adults during chronic GvHD, requiring differentiation from B-cell lymphoproliferative processes. Neurologic presentation is highly variable and may include: vasculitis with angiographic manifestations of dilated and narrowed arteries and aneurysms leading to parenchymal hemorrhage (Ma et al., 2002), focal lymphocytic encephalitis sometimes with aspect of mass lesion (inflammatory pseudotumor) (Tsutsumi et al., 2005), acute demyelinating encephalomyelitis (Tomonari et al., 2003) or relapsing-remitting multiple sclerosis (Armstrong et al., 2010) and T-cell meningitis with high protein in CSF and non-specific abnormalities on MRI (Kyllerman et al., 2008).

Recent studies analyzing cohorts with a high number of pediatric recipients of HCT showed increased risk of second neoplasms (SNs) among all primary childhood cancer cases (Meadows et al., 2009; Danner-Koptik et al., 2012). When compared to the general population, the overall standardized incidence ratio of developing SNs was 6.4 with an estimated 30-year cumulative incidence of 9.3%. The use of high dose chemotherapy to eradicate disease in these aggressive pediatric malignancies, specifically alkylating agents, anthracyclines, and epipodophyllotoxins increased the risk of SNs. Radiation has also been shown to increase the risk of SNs. It has been shown that there is a close relationship between the risk of SNs and radiation dose in childhood cancer survivors (Hijiya et al., 2007). Central nervous system (CNS) SNs, specifically subsequent gliomas and meningiomas, have been associated with prior radiation therapy (Walter et al., 1998; Majhail et al., 2011). Allogeneic hematopoietic stem cell transplantation also increases the risk for SNs in children (Wong et al., 2009). Even for children who received autolo-

gous HCT, the risk of developing SNs is 24 times higher than in the general population and the types of tumors reported were: neuroblastoma (39%), lymphoma (26%), sarcoma (18%), CNS tumors (14%) and Wilms tumor (2%) after a median follow-up of 8 years.

There is also an important concern about cognitive impairment due to total body irradiation,

GvHD treatments, and cytotoxic agents. A recent prospective study examined cognitive changes in 284 adult patients 2 years after HCT. Allogeneic HCT recipients demonstrated worse scores in processing speed, executive function and verbal fluency compared with autologous recipients. Only two-thirds of all patients were working part time or full time one year after diagnosis, although employment status clearly depended on the underlying disease. However, the issue of cognitive impairment after HCT was not studied in pediatric patients.

Conclusion

Neurological complications are an important cause of morbidity and mortality in children and adults who underwent allogeneic as well as autologous HCT. They are mainly related to CNS toxicity of immunosuppressive drugs used for preconditioning regimens, to pancytopenia following chemotherapy as well as CNS infections that represent a major challenge being associated to high mortality. The peripheral nervous system involvement, manifested as acute polyradiculoneuritis, radiculopathies and polyneuropathies, was also reported. Neuromuscular junction and muscle pathology were present in some cases of GVHD. Several studies analyzing cohorts showed that the incidence of developing secondary neoplasms is increased in pediatric patients who received HCT when compared with general population. Although domain-specific neurocognitive deficits were reported in adult patients receiving HCT, cognitive impairment was not studied in pediatric patients. All these complications preferentially occur at specific intervals after HCT and neurologist must recognize them in order to promptly diagnose and apply appropriate treatment.

Additional file:
Additional Table 1: Neurological complications of hematopoietic cell transplantation.

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Additional Table 1 Neurological complications of hematopoietic cell transplantation

Early NCs (< 1 month)						Intermediate phase NCs (2-6 months)	Late phase NCs (> 6 months)
During harvesting	During conditioning			Pancytopenia		Aspergillosis (fludarabine and alemtuzumab)	GvHD
Exacerbation of a preexisting autoimmune disease	Preparative regimens	Busulfan Cytarabine Melphalan ifosfamide	seizures	Thrombocytopenia	subdural hematoma, intraparenchymal hemorrhage, subarachnoid hemorrhage, cerebral venous thrombosis and infarction)	Toxoplasma gondii neuroinfection	CIDP MG polymiositis
		Carboplatin Carmustine cyclophosphamide etoposide fludarabine ifosfamide melphalan	PRES	Coagulation deficits	hepatic veno-occlusive disease also called sinusoidal obstruction syndrome)	Viral infections (HHV6, HHV7, CMV, EBV, HSV, JCV, VZV, adenovirus	CNS Vasculitis Focal lymphocitic encephalitis Acute demyelinating encephalomyelitis RRMS T-cell meningitis
		Carboplatin etoposide	Peripheral neuropathy and ototoxicity	Neutropenia infections	Viral infections herpesviridae (herpes simplex, Epstein-Barr virus, varicella zoster virus, CMV and HHV-6) and polyomaviridae (JCV)	GBS	Second neoplasms (mostly in children): Neuroblastoma Glioma Lymphoma
		cytarabine	pancerebellar syndrome		Bacteria Nosocomial - methicillin-resistant Staphylococcus aureus, multiresistant enterococci, and gram-negative organisms Listeria monocytogenes Nocardia asteroides	IMDD ADEM AIDP	Sarcoma Wilms tumor
		cytarabine, thiotepa	lymphocytic meningitis		Fungi (Candida, Aspergillus, Rhiszopus		Cognitive changes in adults
		alemtuzumab rituximab fludarabine	PML		Parazytes (toxoplasma gondii)		
		methotrexate	Necrotizing micronagiopathy	PALE	HHV-6, GvHD		
		alemtuzumab	Transient stroke-like episodes with DWI-MRI abnormalities	DRESS	CMV, EBV and HHV-1,6,7 and may resemble GvHD		
			Transverse myelitis CMV encephalitis IRIS GBS	IRIS	alemtuzumab		
	Antibiotics	acyclovir, cefepime, imipenem	seizures				
		amphotericin B acyclovir, cefepime	Parkinsonism and confusion encephalopathy				
		cefepime	myoclonus				
		linezolid, posaconazole	ischemic optic neuropathy, PRES, serotonin syndrome, neuropathy				
		metronidazole	reversible cerebellar disease, sensorimotor peripheral neuropathy, optic neuropathy and autonomic dysfunction				
		voriconazole	visual hallucinations				
	Chemotherapy used for post-transplant GvHD prophylaxis	cyclosporine	tremor				
		cyclosporine, tacrolimus, sirolimus	PRES				
		mycophenolate	PML				
		cyclosporine, tacrolimus	CIDP				
		cyclosporine	Mutism, pseudotumor cerebri				
		tacrolimus	brachial plexopathy, optic neuropathy, hearing loss				
		Cyclosporine, tacrolimus	seizures				

NCs: Neurological complications; PRES: posterior reversible encephalopathy syndrome; PML: progressive multifocal leukoencephalopathy; IRIS: immune reconstitution inflammatory syndrome; CIDP: chronic immune demyelinating polyneuropahy; PALE: post-transplant acute limbic encephalitis; DRESS: drug reaction with eosinophilia and systemic symptoms; GvHD: graft *versus* host disease; GBS: Guillaine-Barre syndrome; IMDD: Immune mediated demyelinating disease; ADEM: acute demyelinating encephalomyelitis; AIDP: acute inflammatory demyelinating polyradiculopathy; MG: myasthenia gravis; HHV: human herpesvirus; CMV: cytomegalovirus; EBV: Epstein-Barr virus; HSV: herpes simplex virus; JCV: JC polyomavirus; VZV: varicella-zoster virus; CNS: central nervous system; DWI-MRI: diffusion weighted imaging-magnetic resonance imaging.