Neurological Complications

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53.1 Definitions and Epidemiology

Neurological complications after HSCT are frequent and can be highly challenging to manage. The reported incidence ranges from 8% to 65%, depending on types of manifestation included, transplant setting, and patient population (Maffini et al. 2017). The severity varies widely, ranging from mild transient disorders to life-threatening illness. Main factors and causative agents include neurotoxic drugs, infectious pathogens, cerebrovascular illness, metabolic encephalopathy, and immune-mediated diseases. CNS relapse of the underlying disease, thrombotic microangiopathy (TAM), and post transplant lymphoproliferative disorder (PTLD) should also be ruled out (Table 53.1).

Neurological complications can be classified by their time of onset after HSCT. Early events are mainly due to drugs used in the conditioning regimen and IS therapy, whereas later complications are usually associated with immunodeficiency. Because clinical manifestations are often misleading and nonspecific, finding the right etiology may be long and difficult. Yet, early diagnosis and treatment are of paramount importance to reduce the risk for irreversible complications, impairment of quality of life, and transplantation-related death.

Table 53.1 Main causes of neurological complications after HSCT

	Causative agents
Drug-related	Calcineurin inhibitors (PRES) Methotrexate/cytotoxic agents (busulfan, fludarabine) Anti-infective agents Opioids, benzodiazepines
Infectious pathogens	Fungi and parasites (*Toxoplasma gondii, Aspergillus* spp., *Candida* spp., mucorales, *Cryptococcus neoformans, Histoplasma capsulatum)* Viruses (HHV6, CMV, VZV, HSV, JC virus, West Nile virus, adenovirus) Bacteria (Gram-negative rods, gram-positive *cocci*, *Mycobacterium tuberculosis, nocardia*)
Metabolic	Uremic encephalopathy Hepatic encephalopathy
Cerebrovascular	Hemorrhage Ischemic stroke
Immune-mediated	Demyelinating diseases Myositis Myasthenia gravis CNS chronic GVHD CRS
Thrombotic microangiopathy	Calcineurin inhibitors Infectious pathogens
Malignancies	PTLD Hematological disease relapse

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53.2 Causative Agents and Types of Neurological Complications

53.2.1 Neurotoxic Drugs

Calcineurin inhibitors (CNIs), antibiotics, antiviral drugs, and cytotoxic agents used in conditioning regimen are the most frequent causes of drug toxicity (Table 53.2). In addition, drug-drug interactions are a common cause of neurotoxicity and must be carefully checked.

53.2.1.1 Calcineurin Inhibitors

CSA and TAC are associated with neurological complications in 25% to 59% of HSCT patients (Reece et al. 1991). The clinical picture of CNI-induced neurotoxicity ranges from transient isolated symptoms to severe manifestations such as TAM (see Chap. 42) or posterior reversible encephalopathy syndrome (PRES) (Table 53.2).

Table 53.2 Neurotoxicity of the main drugs used in HSCT

Drug	Most common symptoms
Cyclosporine A	PRES, confusion, tremor, ataxia, seizures, cortical blindness
Methotrexate	Leukoencephalopathy, headache, lethargy, dysarthria
Busulfan	Seizures
Fludarabine	Acute toxic leukoencephalopathy
Thiotepa	Headache, encephalopathy, seizures, paresthesia
Rituximab	PML
Blinatumomab	Encephalopathy, headache, aphasia, ataxia, tremor, seizures
Sorafenib	PRES
Imipenem	Seizures, tremor, vertigo, paresthesia, somnolence, encephalopathy
Cefepime	Headache, paresthesia, encephalopathy
Voriconazole	Headache, seizures, vision changes, hallucinations, numbness encephalopathy
Amphotericin B	Headache, encephalopathy, numbness, vision changes
Aciclovir	Headache, tremor, dysarthria, hallucinations, encephalopathy
Foscarnet	Headache, vertigo, paresthesia, seizures, tremor, encephalopathy
Ganciclovir	Headache, numbness, tremor, seizures

PRES refers to a disorder of reversible subcortical vasogenic brain edema and is caused by endothelial injury related to abrupt blood pressure changes or direct effects of cytokines on the endothelium. It may occur in 1.6–7.2% of HSCT recipients and, if diagnosed early, is reversible after CNI withdrawal. Headache, visual disturbance, seizure, encephalopathy or focal neurologic deficit in the setting of renal failure, or blood pressure fluctuations are highly suggestive of PRES (Schmidt et al. 2016).

Although vasogenic edema can be visualized on CT in some patients, brain MRI is much more sensitive. MRI shows bilateral multifocal areas of hyperintensivity in T2-weighted sequences, especially in the white matter of parieto-occipital regions. Other variations may exist, such as superior frontal sulcus pattern of holohemispheric watershed pattern. Persistent neurological sequelae have been reported, especially if PRES is not rapidly diagnosed and treated.

53.2.1.2 MTX and Cytotoxic Agents

GVHD prophylaxis with short course of MTX may cause minor neurological disorders (lethargy, dysarthria, headache) and, very rarely, diffuse necrotizing leukoencephalopathy (Paudyal et al. 2010). BU is associated with seizure and requires preventive prophylaxis with benzodiazepines (Eberly et al. 2008). For FLU, the main neurological complication is acute toxic leukoencephalopathy. The clinical syndrome is characterized by visual disturbance, sensitive defects, and cognitive impairment.

Brain MRI shows bilateral areas of hyperintensivity in T2-weighted sequences in the white matter, which differ significantly from the MRI findings seen in PRES. Classical PRES arises from subcortical white matter, whereas acute toxic leukoencephalopathy arises from periventricular white matter.

Risk factors include poor renal function, older age, fludarabine dose, previously treated CNS disease, or previous FLU-based conditioning regimen.

Outcomes are very poor with irreversible neurological sequelae and median OS of 2 months (Beitinjaneh et al. 2011).

53.2.1.3 Immunotherapy and Tyrosine Kinase Inhibitors (TKI)

Rituximab, TKI, and bispecific T-cell engaging antibodies such as blinatumomab are increasingly used after HSCT. Their neurological side effects are described in Table 53.2.

53.2.1.4 Anti-Infective Drugs

Anti-infective drugs are among the main causes of neurological complications. Dose adaptation is warranted in case of drug-drug interaction or impaired renal function. Their neurological side effects are described in Table 53.2.

53.2.2 Infectious Pathogens

Among the long list of pathogens responsible of CNS infections after HSCT, the most frequent are *Toxoplasma gondii, Aspergillus* spp., and HHV6 (Denier et al. 2006; Ogata et al. 2015). The clinical symptoms and the time of onset after HSCT may be helpful to decipher the correct diagnosis.

53.2.3 Metabolic Complications

Pharmacologic sedation with major opioids, systemic inflammatory response, and hemophagocytic lymphohistiocytosis are among the first causes to exclude in the differential diagnosis of metabolic causes of neurological dysfunction. Other causes include uremic encephalopathy—associated with CNI nephrotoxicity or TAM—and hepatic encephalopathy, associated with SOS/VOD or severe hepatic GVHD.

53.2.4 Cerebrovascular Disease

Cerebrovascular hemorrhagic or thrombotic events represent potentially lethal complications.

One of the most frequent events is subdural hematoma, which may occur in 2.6% of the patients (Colosimo et al. 2000). Risk factors for CNS hemorrhagic complications include falls, prolonged severe thrombocytopenia or refractoriness to platelet transfusions, grade III–IV GHVD, and arterial hypertension (Zhang et al. 2016). CT scans usually confirm the diagnosis but can be negative in 20–25% of the patients. Risk factors for CNS thrombotic complications include active infections, atrial fibrillation, hypercoagulative state, chronic GVHD, and corticosteroid treatment (Coplin et al. 2001).

53.2.5 Immune-Mediated Diseases

The most frequent immune-mediated neurological diseases include Guillain-Barré-like demyelinating polyneuropathy, myositis, myasthenia gravis, cytokine release syndrome (CRS), and CNS manifestations of chronic GVHD. Assigning the right diagnosis can be highly challenging and may require a neurologic consultation.

53.2.5.1 Demyelinating Polyneuropathies

Immune-mediated demyelinating polyneuropathies, which include Guillain-Barré-like syndrome, may occur in 1% of the patients, especially within the first 3 months after HSCT (Rodriguez et al. 2002). Progressive symmetrical ascending motor deficiency, numbness, hyporeflexia, and respiratory insufficiency are suggestive of Guillain-Barré-like syndromes. Lumbar puncture, MRI, and nerve conduction studies should be performed rapidly. Symptoms may resolve with polyclonal gamma globulin therapy. Rituximab may be used in unresponsive patients.

53.2.5.2 Myositis

Myositis is characterized by proximal muscle weakness, is often associated with chronic GVHD, and may occur in 2–3% of HSCT recipients (Stephenson et al. 2001). Levels of creatine phosphokinase are elevated, electromyography shows myopathic pattern, and MRI is useful to establish the diagnosis and monitor the response to treatment. Diagnosis can be proven by muscle biopsy. Patients may respond to corticosteroid therapy after 1–6 weeks of treatment.

53.2.5.3 Myasthenia Gravis

Myasthenia gravis usually occurs after the onset of GVHD in less than 1% of HSCT recipients (Lefvert and Björkholm 1987). The main symptoms include ptosis, facial weakness, diplopia, dysarthria, and dysphagia. The diagnosis is confirmed with electromyography showing a progressive decrease in the muscle action potential. Cholinesterase inhibitors and corticosteroid therapy are the treatments of choice.

53.2.5.4 Cytokine Release Syndrome

CRS can be observed after haploidentical HSCT with PT-CY and infusion of chimeric antigen receptor T (CAR T) cells or blinatumomab. CRS may cause life-threatening complications, including CNS involvement (encephalopathy, hemiparesis, ataxia, aphasia). Patients can be effectively treated with cytokine blockade using the antibodies siltuximab or tocilizumab, respectively, targeting IL-6 or the IL-6 receptor (Frey 2017).

53.2.5.5 Central Nervous System GVHD

The incidence of CNS manifestations of chronic GVHD is probably underestimated. Three main clinical manifestations have been described (Grauer et al. 2010; Saad et al. 2009). Demyelinating diseases have been reported in the cerebral white matter, optic nerve, or spinal cord. Symptoms follow a relapsing-remitting course, as observed in multiple sclerosis. The treatment consists in corticosteroid pulses. Sphingosine-1-phosphate receptor agonists, such as fingolimod, could be efficient in refractory/relapsing patients (Gauthier et al. 2018).

Vasculitis may involve small- to large-sized arterial vessels of cerebral parenchyma and meninges. Ischemic lesions, minute hemorrhages, and multifocal signal changes in the white matter can be observed on MRI. Diagnosis can be confirmed by brain biopsy, and treatment relies on corticosteroids in combination with cyclophosphamide.

Finally, patients may develop immune-mediated encephalitis. Definite diagnosis requires repeated analysis of CSF to rule out infectious encephalitis.

53.3 Diagnostic Algorithm

When faced with neurological complications following HSCT, the following ten steps can be helpful to promptly assign the correct diagnosis and start the right treatment:

1. Carefully review the medication history and search for (or exclude) metabolic disorders.
2. Are the clinical signs and/or symptoms generalized (e.g., altered consciousness, seizure) or focal (e.g., stroke, mass lesion)?
3. What is the time of onset of neurological signs and/or symptoms after HSCT?
4. Perform CT scan or MRI for ruling out PRES, encephalitis, infectious or immune parenchymal infiltrate, cerebrovascular events, or hematological disease relapse.
5. Analyze CSF for diagnosing infectious complications, Guillain-Barré-like syndrome, or underlying disease relapse.
6. Perform electroencephalography in patients with altered consciousness, hallucinations, or seizure.
7. Perform electromyography in patients with polyneuropathy or peripheral neuromuscular weakness.
8. Repeat each of the previous steps: Tests may be negative when performed early, and symptoms may evolve or fluctuate after the onset of the disease.
9. Brain or neuromuscular biopsy may be required to confirm/exclude opportunistic infections, PML, vasculitis, PTLD, or other malignancies.
10. The opinion of a neurologist at each step is highly recommended, especially for complicated clinical cases.

53.4 Conclusions

Neurological complications after HSCT, and especially allo-HSCT, are frequent and may lead to lethal complications. The main causative factors include drug-related toxicities, metabolic disorders, infections, cerebrovascular evens, immune-mediated disorders, and disease recurrence. Although their clinical diagnosis and

management can be highly challenging, early treatment is extremely important to reduce mortality and improve quality of life.

Key Points

- Neurological complications after HSCT require prompt diagnosis and timely treatment to reduce post transplant mortality and improve the quality of life of the patients.
- Their etiology is often multifactorial and includes neurotoxic drugs, infectious pathogens, cerebrovascular illness, metabolic encephalopathy, and immune-mediated diseases.
- TAM, PTLD with CNS involvement, and CNS relapse of the underlying hematological disease should be included in the differential diagnosis.
- CNS manifestations of GVHD are rare and often highly challenging to manage.

References

Beitinjaneh A, McKinney AM, Cao Q, Weisdorf DJ. Toxic leukoencephalopathy following fludarabine-associated hematopoietic cell transplantation. Biol Blood Marrow Transplant. 2011;17:300–8.

Colosimo M, McCarthy N, Jayasinghe R, et al. Diagnosis and management of subdural haematoma complicating bone marrow transplantation. Bone Marrow Transplant. 2000;25:549–52.

Coplin WM, Cochran MS, Levine SR, Crawford SW. Stroke after bone marrow transplantation: frequency, aetiology and outcome. Brain. 2001;124:1043–51.

Denier C, Bourhis J-H, Lacroix C, et al. Spectrum and prognosis of neurologic complications after hematopoietic transplantation. Neurology. 2006;67:1990–7.

Eberly AL, Anderson GD, Bubalo JS, McCune JS. Optimal prevention of seizures induced by high-dose busulfan. Pharmacotherapy. 2008;28:1502–10.

Frey N. Cytokine release syndrome: who is at risk and how to treat. Best Pract Res Clin Haematol. 2017;30:336–40.

Gauthier J, Vermersch P, Chauvet P, et al. Successful treatment with fingolimod of graft-versus-host disease of the central nervous system. Blood Adv. 2018;2:10–3.

Grauer O, Wolff D, Bertz H, et al. Neurological manifestations of chronic graft-versus-host disease after allogeneic haematopoietic stem cell transplantation: report from the Consensus Conference on Clinical Practice in chronic graft-versus-host disease. Brain. 2010;133:2852–65.

Lefvert AK, Björkholm M. Antibodies against the acetylcholine receptor in hematologic disorders: implications for the development of myasthenia gravis after bone marrow grafting. N Engl J Med. 1987;317:170.

Maffini E, Festuccia M, Brunello L, et al. Neurologic complications after allogeneic hematopoietic stem cell transplantation. Biol Blood Marrow Transplant. 2017;23:388–97.

Ogata M, Fukuda T, Teshima T. Human herpesvirus-6 encephalitis after allogeneic hematopoietic cell transplantation: what we do and do not know. Bone Marrow Transplant. 2015;50:1030–6.

Paudyal B, Viets R, Skliut M. A case of low-dose oral methotrexate–induced reversible neurotoxicity. Am J Neuroradiol. 2010;31:E77.

Reece DE, Frei-Lahr DA, Shepherd JD, et al. Neurologic complications in allogeneic bone marrow transplant patients receiving cyclosporin. Bone Marrow Transplant. 1991;8:393–401.

Rodriguez V, Kuehnle I, Heslop HE, et al. Guillain-Barré syndrome after allogeneic hematopoietic stem cell transplantation. Bone Marrow Transplant. 2002;29:515–7.

Saad AG, Alyea EP, Wen PY, et al. Graft-versus-host disease of the CNS after allogeneic bone marrow transplantation. J Clin Oncol. 2009;27:e147–9.

Schmidt V, Prell T, Treschl A, et al. Clinical management of posterior reversible encephalopathy syndrome after allogeneic hematopoietic stem cell transplantation: a case series and review of the literature. Acta Haematol. 2016;135:1–10.

Stephenson AL, Mackenzie IR, Levy RD, Road J. Myositis associated graft-versus-host-disease presenting as respiratory muscle weakness. Thorax. 2001;56:82–4.

Zhang X-H, Wang Q-M, Chen H, et al. Clinical characteristics and risk factors of intracranial hemorrhage in patients following allogeneic hematopoietic stem cell transplantation. Ann Hematol. 2016;95:1637–43.