

REVIEW ARTICLE



Symptom-guided approach to central nervous system complications in allogeneic hematopoietic cell transplant recipients: Best practice recommendations from the EBMT Practice Harmonisation and Guidelines committee

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Central nervous system complications (CNSC) after allogeneic hematopoietic cell transplantation (allo-HCT) are relatively common and may have a major impact on patients' outcomes. Neurological symptoms may occur at any point during the post-transplant course, although they are more common early after HCT, with a wide range of possible presentations. As many of CNSC symptoms are non-specific, the initial assessment is often difficult, and early decisions regarding the diagnostic work-up can influence the identification of the underlying cause. Blood tests, neuroimaging and cerebrospinal fluid (CSF) analyses are particularly important, as they frequently provide the first clues that help narrow the very wide differential diagnoses. In view of these challenges, an international EBMT working group composed of haematologists, infectious disease specialists, neurologists, a neuroradiologist, and a microbiologist developed symptom-based recommendations for the early evaluation of CNSC after allo-HCT. The work summarizes key aspects of the clinical presentation and outlines practical steps for the initial diagnostic approach. These recommendations are intended to support haematologists, who are usually the first to assess these patients, in promptly recognizing CNSC so to start timely appropriate management.

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QUESTIONS ASKED/ISSUES TO BE ADDRESSED

In these recommendations, the following challenging questions are addressed:

- What is the prevalence and timing of central nervous system complications (CNSC) after allogeneic hematopoietic cell transplantation (allo-HCT), and how do they typically present?
- What are the main challenges in diagnosing CNSC early after allo-HCT?
- Which diagnostic tools and procedures are most useful for the initial assessment of CNSC?
- What symptom-based recommendations can guide haematologists in the early recognition and management of CNSC?

CURRENT STATE OF THE ART

Central Nervous System neurological complications (CNSC) after allogeneic hematopoietic cell transplantation (allo-HCT) encompass

a heterogeneous group of disorders with multifactorial causes, including infectious, neoplastic, vascular, metabolic, immune-mediated, toxic/drug-related and psychological mechanisms which interfere with the normal functioning of the nervous system (Fig. 1). Their diagnosis and management are complex, as clinical manifestations may be subtle, nonspecific, or subjective, commonly requiring inpatient neurology consultation [1]. However, the initial evaluation is usually performed by the haematologist, who plays a key role in early recognition of neurological symptoms and initiating the diagnostic work-up [2, 3]. Establishing a differential diagnosis, based on the presenting symptoms, is key guiding the choice of neuroimaging, cerebrospinal fluid (CSF) studies, and/or other testing.

The frequency of CNSC depends on individual risk factors and on the patient population. In an EBMT prospective study, the overall CNSC frequency was 2.9%, higher after allogeneic (4.6%) than autologous HCT (0.3%) and in children (4.3%) compared with adults (2.5%) [4]. A retrospective allo-HCT study reported a 17% incidence over a 20-year period, with a median follow-up of 6.8

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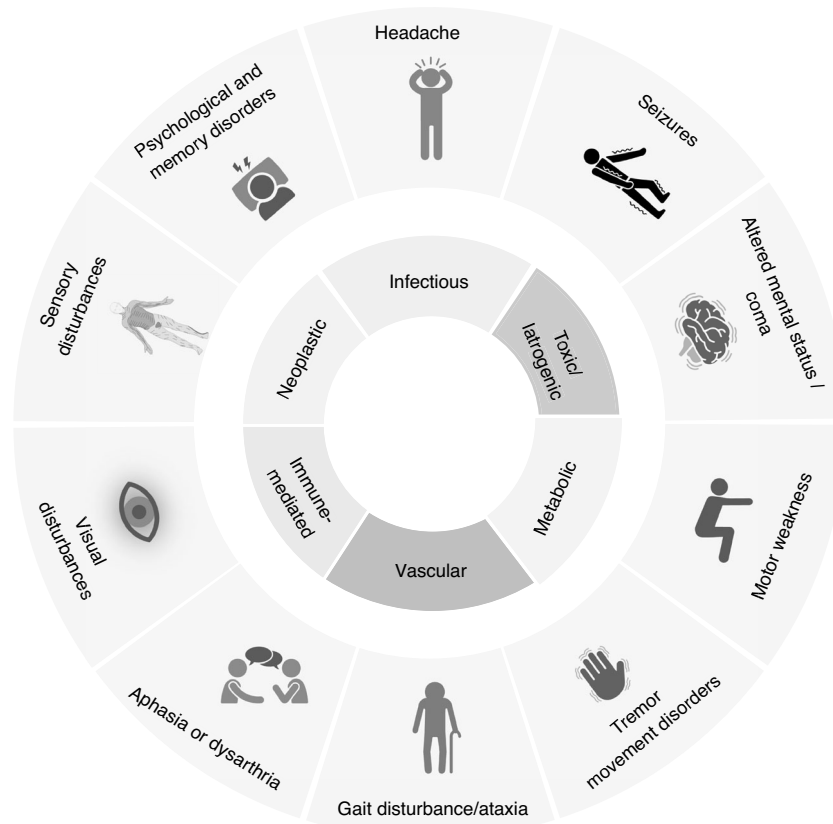


Fig. 1 Graphical representation of the main neurological symptoms affecting the CNS and their key potential underlying aetiologies. The outer ring represents symptoms/signs, and the inner ring represents the main neurologic etiologic categories.

years, and a decline in recent years [5]. Described frequencies of CNSC after allo-HCT largely vary and may exceed 50% [6–9].

CNSC can be divided into infectious and non-infectious [4, 6, 7]. In a recent retrospective study over a 20-year period, calcineurin inhibitors (CNI)-associated CNSC were most common (42%), followed by infections (30%) and vascular complications (13%) [5]. Non-infectious CNSC include drug toxicities, metabolic disorders, immunological (including graft versus host disease (GVHD) and Guillain Barré-Syndrome), disease relapse, and vascular complications such as posterior reversible encephalopathy syndrome (PRES), cerebral haemorrhage, and stroke, as well as psychological causes [4, 5, 10, 11].

CNS infections can be classified based on their anatomical involvement, in encephalitis, meningitis, myelitis, or brain parenchymal disease [12–15]. Infectious CNSC are predominantly viral, with Human herpesvirus 6 (HHV-6) as the leading cause [4, 7]. Invasive fungal infections of the brain, historically associated with *Aspergillus* spp., and Mucorales, remain one of the most common causes of brain space occupying lesions [4, 7, 16–18].

CNSC may occur at any time after allo-HCT, depending on the underlying cause, conditioning, GVHD prophylaxis, presence of GVHD, immune reconstitution, among other factors [13, 19–21]. In the above mentioned EBMT study, the median onset was 31 (IQR 15–57) days [4]. Another prospective study reported median time at onset of 101 days for infectious and 50 days for non-infectious CNSC [7].

Risk factors for CNSC include the type of allo-HCT, post-HCT phase, neutropenia, corticosteroid use, specific drug exposures, prior neurosurgery, intracerebral devices, and prior CNS involvement [14, 15, 22, 23]. Some proposed risk factors may reflect confounders or shared predisposing conditions [24].

CNSC are associated with worse outcomes after allo-HCT. In a recent prospective EBMT study, the 24-month overall survival (OS)

was lower in patients with a CNSC (53%) as compared to controls (82%) [4]. In another study, the development of a CNSC was also associated with increased mortality (HR = 4.62) and treatment related mortality (HR = 5.37) [5]. In paediatric cohorts, older age, alemtuzumab use, and neurological sequelae were the strongest predictors of mortality [9].

The prognosis regarding mortality rates and neurological sequelae might be generally better for non-infectious than infectious CNSC. However, it might differ significantly between specific CNSC subtypes (e.g. major CNS bleeding vs. CNI neurotoxicity). Patients with vascular CNSC have a poorer prognosis (mortality >50% in distinct subgroups) than those with non-vascular CNSC, such as drug-related pathologies [7, 25, 26]. In children, CNSC other than CNI-associated neurotoxicity have been linked to reduced OS [25].

METHODOLOGY

Recommendations were developed according to the methodology published by the EBMT practice harmonization and guidelines committee [27]. Experts on hematology ($n = 16$), neurology ($n = 5$), infectious diseases ($n = 4$), microbiology ($n = 1$), and neuroradiology ($n = 1$), were invited to contribute. Experts from all these disciplines were responsible for preparing sections of the recommendations in advance based on their area of expertise. These sections were then presented and reviewed during a 2-day, in-person meeting held in Berlin (Germany) on Sept 29–30, 2025, where in-depth discussions to reach a consensus on best practice were performed.

The aim of this document is to establish best practice recommendations for the initial approach to CNSC in patients undergoing allo-HCT and to assist clinicians in the initial diagnostic evaluation. A companion paper in this issue addresses

complementary aspects of epidemiology, neuroimaging, and paediatric-specific considerations.

EBMT RECOMMENDATIONS

In allo-HCT recipients, new neurological symptoms should be initially considered potentially transplant- or disease-related and warrant a careful, systematic evaluation [2]. The assessment should incorporate the primary diagnosis, disease status at transplantation, risk of CNS relapse, prior/current exposure to neurotoxic agents, immune reconstitution status, the risk/presence of GVHD, cardiovascular risk profile, psychological state and any procedures or complications occurring before, during and after allo-HCT, together with the patient's overall medical history (Fig. 1).

Clinicians should evaluate the onset, severity, and progression of symptoms, noting whether they are new or not, and whether any 'red flag' is present (Table 1). Symptoms may present abruptly or follow a progressive course, with mono- or polysymptomatic patterns. CNS manifestations can be generalized or localized; the most common generalized symptoms are headache, seizures, and altered consciousness [4, 28, 29]. CNS infection should be suspected when new neurological signs occur with fever, although the absence of fever does not exclude infection [2].

When CNS are suspected, first-line diagnostic testing should include basic blood tests (complete blood count, coagulation profile, glucose, electrolytes, liver and renal function tests) and brain imaging (computed tomography (CT) or preferably contrast-enhanced brain magnetic resonance imaging (MRI)). Neurological examination is essential but often insufficient to exclude structural brain injury [2]. MRI remains the cornerstone for diagnostic clarification. In patients with sudden onset or rapidly progressive CNS symptoms, cranial CT can also be indicated in emergency settings, particularly to exclude haemorrhage, stroke, mass effect, or hydrocephalus. If seizures are observed or suspected, electroencephalography (EEG) should be performed (Fig. 2).

If a CNS infection is suspected, a lumbar puncture (LP) should be performed (provided that CT scan rules out any contraindication) for differential cell count, protein and glucose levels, Gram stain, fungal stain, culture, and pathogen-specific or multiplex PCR or antigen (such as pneumococcal or cryptococcal antigens) or, if available, next-generation sequencing (NGS) testing. First-line CSF PCR assays depending on the clinical and radiological pattern, may include bacterial, viral (HHV-6, EBV, CMV, HSV-1, HSV-2, VZV, JCV/BKV, adenovirus, enterovirus), fungal (*Aspergillus*, *Mucorales*, *Cryptococcus*) and parasitic (toxoplasmosis) agents. Additional investigations should be guided by the differential diagnosis, for example include tests for fungal markers (such as galactomannan) and mycobacteria. Broader viral or fungal testing should be based on the clinical, biological, and epidemiological context. In these cases, CSF NGS as a hypothesis-free approach to assay for a wide range of different infections may be considered [29].

Noteworthy, CNS in allo-HCT may present with atypical clinical, radiological, or CSF findings, underscoring the need for a high index of suspicion and a multidisciplinary diagnostic approach, including a neurological and an ophthalmological consultation.

Table 1 summarizes the main symptoms suggestive of CNS in allo-HCT recipients and provides a structured framework for clinical assessment. For each symptom, clinicians should consider: [1] key questions regarding onset, evolution, severity and associated features; [2] relevant examination findings; [3] context-dependent factors related to transplant phase, comorbidities, or treatment exposures; [4] red flags indicating a possible neurological emergency; and [5] the principal differential diagnoses, including relapse, infectious, vascular, metabolic, toxic/iatrogenic, immune-mediated and psychological causes. Importantly, not all investigations are required in every

patient; rather, diagnostic testing should be individualized and guided by a dynamic differential diagnosis process that is continuously refined based on clinical evolution and initial results. This structured approach facilitates early recognition, proper prioritization of investigations, and timely management of CNS.

SPECIFIC NEUROLOGICAL SYMPTOMS OR SIGNS

Headache arises from pain-sensitive extracranial tissues (skin, muscles, vessels, sinuses, dental structures) or intracranial structures, including large arteries near the circle of Willis, venous sinuses, dura, and cranial nerves [30]. Acute, severe, or new-onset headache in patients without a prior history, for example of migraine, should promptly be evaluated for intracranial haemorrhage, infection, PRES or any other CNS involvement [5, 31, 32]. Orthostatic headache suggests low CSF pressure, often after LP or intrathecal chemotherapy; symptoms not improving with supporting measures warrant evaluation for venous sinus thrombosis or intracranial hypotension [33].

The clinical context is critical. A history of CNS disease, prior irradiation, or intrathecal chemotherapy raises concern for relapse or neurotoxicity; coagulopathy or thrombocytopenia predispose to intracranial bleeding; fever or neck stiffness should prompt evaluation for infectious or aseptic meningitis (although their absence does not formally exclude meningitis). Hypertension may suggest PRES, particularly in patients on CNI or Cushing triad with increased intracranial pressure [34]. On the other hand, a previous history of recurring migraine or tension headache might decrease the level of suspicion for other complications, especially if the headache is of mild or moderate intensity.

Seizures are relatively uncommon after allo-HCT [32, 35–38], occurring mainly within the first year, particularly during the first 100 days [35, 36, 39]. In a recent paediatric study, seizures were associated with a higher risk of long-term epilepsy (OR = 14; 95% CI = 2.87–68.97) [35]. The most frequent causes include drug-related neurotoxicity such as PRES, metabolic disturbances, cerebrovascular events, CNS infections, and leukemic or lymphomatous relapse. Agents such as certain β -lactam antibiotics (e.g. carbapenems), CNI, and busulfan may precipitate seizures [40]. Furthermore, antipsychotic medications can lower the seizure threshold [40, 41].

Generalized seizures account for about 65% of episodes, followed by focal seizures. In PRES, occipital lobe seizures, including those presenting with non-motor symptoms such as visual disturbances or amaurosis, and status epilepticus may predominate [37, 40], particularly in a paediatric population [35]. Early presentations may be subtle, with minor motor activity or focal non-convulsive signs such as gaze deviation, ocular clonus, visual hallucinations, or altered consciousness. EEG monitoring is critical for detection, as clinical signs may be subtle or nonspecific [42]. In critically ill patients with depressed level of consciousness, seizures should be excluded by early use of bedside long-term EEG monitoring, particularly in the presence of drugs such as cefepime or carbapenem that can mimic multifocal myoclonus and are known to lower seizure threshold [3, 43, 44] (Fig. 2). Distinguishing seizures from non-epileptic events can be challenging [45].

Motor weakness may arise from injury to any part of the motor pathway, including the cortex, spinal cord, peripheral nerves, neuromuscular junction, or muscle. CNS causes of focal weakness include ischemic or haemorrhagic stroke, PRES, and less commonly leukemic or lymphomatous relapse. Strokes induced by infection (e.g. VZV or fungi) should also be considered [13, 14, 29, 46]. Spinal cord involvement may present as paraparesis or quadriparesis with a sensory level and may result from infectious myelitis, radiation- or intrathecal-chemotherapy induced myelopathy, vascular aetiologies, or metabolic and

Table 1. Structured clinical approach to main neurological symptoms in allo-HCT recipients, detailing patient/relative history, targeted examination findings, appropriate context-based diagnostics, emergency red flags, and relevant neurological differential diagnoses.

Neurological Symptom	What to ask the patient/relatives?	What to look for clinically?	Which diagnostic studies may be considered?	Red Flags of Emergency	Neurological Differential Diagnosis to be considered (in alphabetic order)
Altered Mental Status (AMS)	■ Scale for cognitive assessment age appropriate ■ Preexisting cognitive impairment (MCI) or prior episodes ■ Alcohol, illegal drugs ■ Psychotropic medications use ■ Craniocervical trauma	■ Level of consciousness ■ Infection context ■ Associated tremor, asterixis, myoclonus, nystagmus ■ Signs of major organ dysfunction e.g. hypoxemia ■ Sedative medications	■ Capillary glucose ■ Basic blood test* ■ Ammonia level ■ Thiamin level ■ Drug levels (azoles, CNI, cefepime) ■ EEG ■ Brain imaging ■ CSF analysis**	■ Presence of focal symptoms/signs ■ Seizures ■ Sudden onset ■ High grade of severity ■ Early post-transplant period	■ Antitumor therapy CNS toxicity (e.g., TBI, chemotherapy, immunotherapy) ■ Brain hemorrhage ■ CNS GVHD ■ CNS infection ■ Encephalopathy ■ Major organ failure ■ Medications: antibiotics, psychotropic agents, opioids ■ Metabolic disorders (e.g., diabetic coma, hyponatremia) ■ PRES / MTA ■ Sepsis ■ Sleep deprivation
Aphasia	■ Native language	■ Fluency, comprehension, repetition, naming ■ Reading, writing abilities	■ Brain imaging ■ EEG ■ CSF analysis**	■ Abrupt onset	■ Cerebrovascular events ■ Encephalopathy ■ ICANS ■ CNS infection (encephalitis, abscess, PML, etc.)
Ataxia	■ Alcohol, drugs ■ Nutrition status	■ In the seated position and during gait ■ Romberg test ■ Trunk ataxia	■ Brain and spinal cord MRI ■ Vitamin B12 level ■ Paraneoplastic Ab ■ CSF analysis (e.g., exclusion CNS relapse)**	■ Abrupt onset ■ Early post-transplant period	■ Cerebrovascular ■ Cytarabine-induced cerebellitis ■ Encephalopathy ■ Focal posterior fossa mass ■ Post-infectious (e.g., VZV) ■ PRES ■ Rhombencephalitis ■ Sedative drugs
Blurry vision	■ Monocular or bilateral ■ Visual hallucinations ■ Eye pain ■ Alcohol deprivation ■ Drugs	■ HTA, bradycardia ■ GVHD evaluation	■ Brain imaging ■ Ophthalmology including fundoscopy ■ Infection screening (e.g., toxoplasma) ■ Thiamin level ■ Paraneoplastic/ autoimmune Ab panel	■ Associated headache ■ Papilledema ■ Early post-transplant period	■ Cerebrovascular ■ Eye infections: keratitis, chorioretinitis, uveitis ■ Fludarabine-induced neurotoxicity ■ GVHD ■ Intracranial hypertension ■ Optic neuritis ■ PRES ■ Steroid-induced cataract/glaucoma/lenticular edema ■ Voriconazole-induced visual hallucinations ■ Wernicke encephalopathy
Coma	■ Glasgow Coma Scale	■ Pupil diameter ■ Neck stiffness ■ Vital signs	■ Capillary glucose ■ Basic blood test* ■ Brain imaging + angiography ■ Toxic drug screen ■ Ammonia level ■ EEG ■ CSF analysis**	■ Always	■ See AMS

Table 1. continued

Neurological Symptom	What to ask the patient/ relatives?	What to look for clinically?	Which diagnostic studies may be considered?	Red Flags of Emergency	Neurological Differential Diagnosis to be considered (in alphabetic order)
Dysarthria	■ Dry mouth ■ Dysphagia ■ Mucositis ■ Alcohol, illegal drugs ■ Psychotropic medication	■ Speech pattern ■ Waxing/waning nature ■ Fatigability ■ Associated dysphagia (e.g, choking/coughing with liquids)	■ Basic blood test* ■ Brain imaging ■ CSF analysis (e.g. exclusion of CNS relapse)**	■ Abrupt onset ■ Early post-transplant period ■ Associated bulbar signs	■ Cerebrovascular ■ CNS relapse ■ Encephalopathy ■ GVHD ■ Infections (abscess, rhombencephalitis) ■ Neuromuscular (myasthenia) ■ Psychotropic drugs
Headache	■ Prior episodes ■ Type, rate, duration, onset ■ Responsive to medication ■ Severity ■ Recent intrathecal therapy/LP ■ Other symptoms ■ Severe anemia	■ Prior CNS disease ■ Neck stiffness ■ HTA, bradycardia, focal deficits, level of consciousness	■ Brain imaging ■ Fundoscopy ■ CSF analysis**	■ Abrupt onset ■ Meningeal signs ■ Focal neurological symptoms/signs ■ Early post-transplant period ■ Severity	■ Cerebral venous thrombosis ■ CNI toxicity / hypertension (HTA) ■ CNS infection ■ CNS relapse ■ Ischemic/hemorrhagic stroke ■ Post-lumbar puncture (positional headache) ■ PRES ■ Primary headache
Hemiparesis	■ Facial involvement ■ Severity ■ Sensory symptoms	■ Arrhythmia ■ Coagulopathy	■ Brain imaging +/- angiography ■ CSF analysis (e.g. exclusion of CNS relapse, infection such as PML etc)** ■ EEG	■ Abrupt onset	■ CNS relapse ■ Ischemic/hemorrhagic stroke ■ Parenchymal brain disease / abscess ■ PML ■ Strokes induced by VZV or fungi
Memory issues	■ Transient ■ Anamnesis with the family (e.g. personality/behavior change) ■ Prior TBI ■ Sleep quality ■ Alcohol, drugs ■ Psychotropic medication	■ Attentional deficits ■ Memory subtype (e.g. short term or anterograde amnesia) ■ Waxing/waning nature	■ Brain MRI ■ Neuropsychological test (MoCA) ■ EEG ■ CSF analysis** (e.g. HHV-6 DNA) ■ Thiamin, B12, folate level ■ Paraneoplastic/Autoimmune Ab panel	■ Abrupt onset	■ Anxiety ■ CRCI / TAME ■ Global transient amnesia associated with infusion of progenitor cells (DMSO) ■ GVHD / autoimmune encephalitis ■ HHV-6 encephalitis ■ Non-convulsive status ■ Toxic leukoencephalopathy ■ Wernicke encephalopathy
Monoparesis	■ Painless/painful ■ Sensory symptoms ■ Weight loss ■ Recent intervention ■ Severity of weakness	■ Anatomical topography ■ Muscle atrophy ■ Flaccid vs. spastic	■ Basic blood test* ■ Brain +/- spine imaging ■ NCS-EMG ■ Plexus MRI ■ Nerve ultrasound ■ CSF analysis (e.g. exclusion of CNS relapse)	■ Abrupt onset	■ Amyotrophic neuropathy ■ CNS relapse ■ Compressive mononeuropathy ■ Iatrogenic plexopathy ■ Ischemic/hemorrhagic stroke ■ Neuroleukemosis ■ Osteomyelitis/arthritis in children ■ Parenchymal brain disease / abscess ■ Psoas hematoma (coagulopathy)
Mood/Psychologic disorders	■ Prior history ■ Alcohol, drugs ■ Psychotropic medication ■ Sleep quality	■ Suicidality	■ Beck Test ■ MoCA ■ Psychiatric consult ■ TSH determination ■ Antidepressant/anxiolytic trial in mild cases ■ CNS imaging ■ CSF analysis (e.g. exclusion of CNS relapse)**	■ Acute suicidality ■ Confusion ■ Psychotic symptoms	■ CNS infection ■ CNS relapse ■ Drug-induced: levetiracetam, steroids ■ Sleep deprivation

Table 1. continued

Neurological Symptom	What to ask the patient/relatives?	What to look for clinically?	Which diagnostic studies may be considered?	Red Flags of Emergency	Neurological Differential Diagnosis to be considered (in alphabetic order)
Movement Disorders /tremor	- Personal/family history - Alcohol deprivation - Severity - Drugs: CNI, opioid prokinetics, SSRIs withdrawal	Hyperthermia	- Capillary glucose - Basic Blood Test* - Brain imaging - EEG - CK determination - TSH determination - CSF analysis (e.g. exclusion of CNS relapse)**	- Severe hyperthermia - Loss of consciousness	- CNI-induced tremor - CNS relapse - Drug-induced (e.g., metoclopramide) - Hyperglycemia-induced hemiballismus - Malignant neuroleptic syndrome (rigidity) - Opioid intoxication (myoclonus) - Progression of the pre-existing metabolic CNS disease (children) - Severe muscle atrophy
Para/tetraparesis	- Sensory level - Painful/painless - Sphincter dysfunction - Severity - Prior intrathecal therapy	- Cutaneous vesicles - Concurrent or prior infection	- Brain + Spinal cord imaging - NCS + EMG - CSF analysis** - Paraneoplastic/Autoimmune Ab - CK determination	Rapidly progressive	- CNS infection - CNS relapse - GBS / CIDP, GVHD - Myelitis (e.g., VZV) - Myelo-/radiculoneurotoxicity (MTX, Ara-C) - Neuromuscular complications - Nutritional myelopathy - Radiculitis (e.g., CMV) - Spinal cord compression (e.g., spondylodiscitis, vertebral fracture, epidural neoplastic disease) - Steroid myopathy
Paresthesia	- Prior or current neurotoxic drugs - Autonomic signs (e.g., bladder dysfunction) - Painful/painless - Diabetes - Alcohol	Anatomical topography	- Basic blood test* - CNS/spinal cord imaging - NCS-EMG - CSF analysis (e.g. exclusion of CNS relapse)**	Other focal neurological signs	- Cerebrovascular - CNS infection (abscess or VZV) - CNS malignant disease - Drugs: CNI-toxicity, CIPN - GBS - Myelitis - Nerve compression
Seizures	- Prior history of seizures, family history of seizures - Prior AEDs (withdrawal, non-compliance) - Prior trauma - Alcohol, illegal drugs	- HTA - Type of seizure - Duration - Organ dysfunction	- Capillary glucose - Basic blood test* - Drugs (e.g.CNI, cefepime, AEDs) levels - Ammonia level - Brain imaging - EEG - CSF analysis**	- Non recuperation of consciousness - Status epilepticus	- CNIs, busulfan, carbapenem antibiotics & other drugs - CNS GVHD - CNS infection - CNS relapse of the underlying disease - Ischemic/hemorrhagic stroke - Metabolic disturbances - PRES / TA-TMA

* Basic blood test should include total blood count, coagulation, glucose, sodium, calcium, magnesium, phosphate, liver function, renal function.

** CSF Low threshold for performing LP in patients with fever.

Ab Antibody, AEDs antiepileptic drugs, Ara-C Cytarabine, CIDP Chronic Inflammatory Demyelinating Polynuropathy, CIPN Chemotherapy-Induced Peripheral Neuropathy, CK Creatine Kinase, CMV Cytomegalovirus, CNS Central Nervous System, CNI Calcineurin Inhibitor, CRCI Cancer-related cognitive impairment, CSF Cerebrospinal Fluid, DMSO Dimethyl Sulfoxide, ECG Electrocardiogram, EEG Electroencephalogram, GBS Guillain-Barré Syndrome, GVHD Graft-versus-Host Disease, HHV6 Human Herpesvirus-6, HTA Hypertension, ICANS Immune Effector Cell-Associated Neurotoxicity Syndrome, LP Lumbar Puncture, MoCA Montreal Cognitive Assessment, MRI Magnetic Resonance Imaging, MTX Methotrexate, NCS-EMG Nerve Conduction Studies – Electromyography, PCR Polymerase Chain Reaction, PML Progressive Multifocal Leukoencephalopathy, PRES Posterior Reversible Encephalopathy Syndrome, SSRIs Selective Serotonin Reuptake Inhibitors, TA-TMA Transplant-Associated Thrombotic Microangiopathy, TAME Transplantation-Associated Altered Mentation, TBI Total Body Irradiation, TSH Thyroid-Stimulating Hormone, VZV Varicella-Zoster Virus.

Symptoms are listed in alphabetic order.

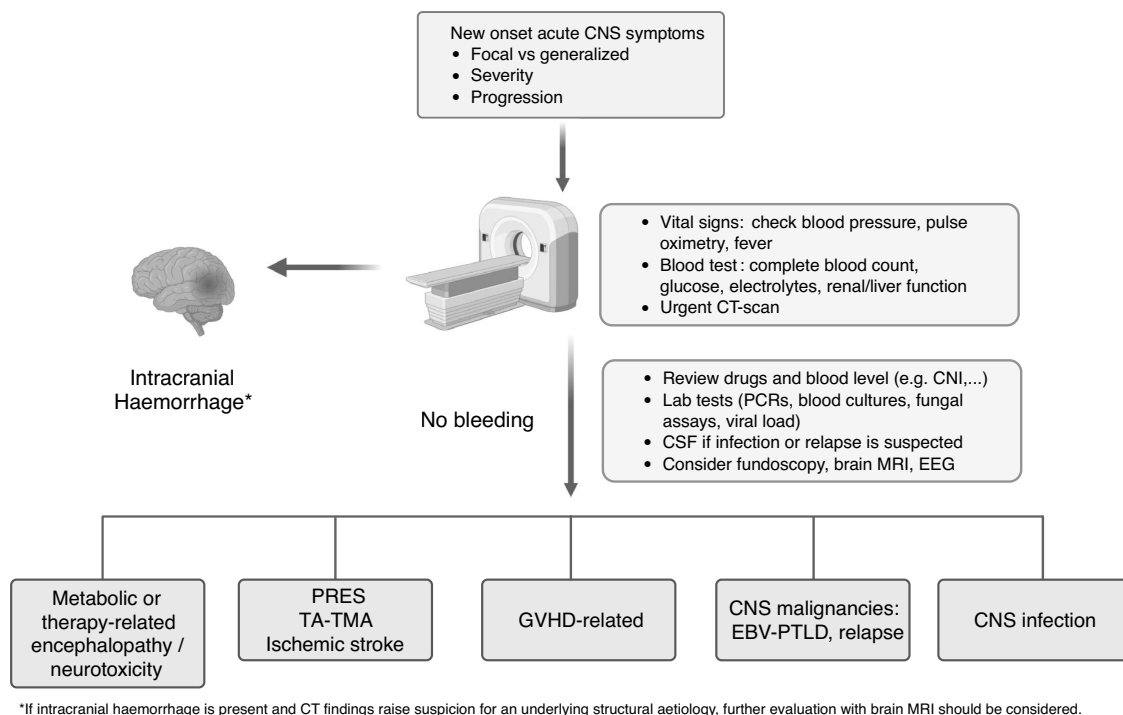


Fig. 2 Algorithm for management of acute neurological symptoms. CNS Central nervous system, CT Computed tomography, CNI Calcineurin inhibitor, PCR Polymerase chain reaction, CSF Cerebrospinal fluid, MRI Magnetic resonance imaging, EEG Electroencephalography, PRES Posterior reversible encephalopathy syndrome, TA-TMA Transplant-associated thrombotic microangiopathy, GVHD Graft-versus-host disease, EBV Epstein-Barr virus, PTLT Post-transplant lymphoproliferative disorder, EBV-PTLD Epstein-Barr virus-associated post-transplant lymphoproliferative disorder.

nutritional deficiencies (e.g. cobalamin or copper deficiency) affecting the corticospinal tract [47].

There are also several peripheral nervous systems-related causes of motor weakness, including chemotherapy-induced neuropathy, immune-mediated neuropathies, compressive mono-neuropathies, corticosteroid-induced myopathy, and GVHD-associated neuromuscular disorders.

Dizziness may manifest as vertigo, disequilibrium, (pre) syncope, or light-headedness, each pointing toward different vestibular, neurologic, cardiovascular, or functional causes [48]. A comprehensive evaluation integrating neurologic, otologic, infectious, systemic, cardiovascular and metabolic assessments is essential [49].

Ataxia is a gait disturbance due to impaired coordination or loss of proprioception (sensory ataxia), and may result from neurotoxicity, metabolic imbalance, infectious, post-infectious or immune-mediated mechanisms, or secondary complications of prolonged hospitalization and systemic illness. Cytarabine is the most frequent chemotherapeutic cause, which can sometimes result in dysarthria, limb and truncal ataxia, as well as nystagmus, particularly in older patients or in those with renal impairment [50, 51]. CNIs can induce reversible cerebellar dysfunction through direct toxicity or during PRES. Infectious rhombencephalitis should also be considered in immunosuppressed patients. Thiamine deficiency may present with acute ataxia, ophthalmoplegia, and confusion. Immune-mediated causes, including autoimmune cerebellitis related to GVHD or immune reconstitution, are rare but recognized [50, 52]. Sensory ataxia may arise from nutritional disorders such as vitamin B12 deficiency causing subacute combined degeneration or copper deficiency myeloneuropathy [53], occasionally linked to prolonged parenteral nutrition or excess zinc intake [54]. Infectious, immune-mediated or methotrexate-induced myelopathies may also be considered [50, 52].

Movement disorders in allo-HCT recipients include tremor, chorea, athetosis, myoclonus, and asterixis [55], and often reflect drug-induced neurotoxicity, metabolic disturbances, or secondary CNS relapse. Tremor is the most frequent manifestation, usually related to CNI-based immunosuppression [56]. Although more common with elevated CNI levels, it may occur within the therapeutic range [56, 57]. Corticosteroid-induced tremor resolves with dose tapering [51, 58].

Myoclonus may occur in metabolic encephalopathy, drug toxicity [59] or infectious and immune-mediated CNS. Although often reversible, it may signal serious encephalopathic processes that require prompt recognition and treatment. Non-ketotic hyperglycemia-associated chorea is an uncommon metabolic complication [60]. Several drugs used in the allo-HCT setting may induce acute dystonia, parkinsonism, or tardive dyskinesia, including CNI [5, 61], dopamine-blocking antiemetics (metoclopramide), and antipsychotics commonly used for post-transplant delirium (haloperidol, risperidone) [62].

Altered mental status (AMS) refers to a disturbance of consciousness, attention, cognition, or perception, ranging from mild confusion to deep coma, and reflects dysfunction of cortical and/or brainstem components of the CNS [63]. Impairment of attention and concentration is an early hallmark of global cerebral dysfunction. The American Society for Transplantation and Cellular Therapy (ASTCT) recently proposed a new diagnostic framework to better characterize the acute neurocognitive changes after HCT: Transplantation-Associated Altered Mentation and Encephalopathy (TAME) [64]. AMS is a common and sometimes multifactorial neurological potential emergency in allo-HCT [50, 65]. Delirium is frequently related to metabolic or toxic causes, and is associated with longer hospitalization, higher rates of intensive care unit admission and poor outcomes [66].

Dysarthria and aphasia Aphasia reflects a language-processing disorder caused by cortical involvement of the dominant

hemisphere, whereas dysarthria results from motor impairment of speech due to cerebellar, brainstem, or neuromuscular dysfunction [67]. In allo-HCT recipients, aphasia may occur acutely due to ischemic or haemorrhagic stroke, thrombotic microangiopathy, infection, or PRES. Less commonly, CNS relapse of the underlying hematologic malignancy, viral encephalitis, or metabolic encephalopathies may produce aphasic symptoms. Blinatumomab can also cause aphasia in the setting of ICANS [47].

Dysarthria may result from cerebellar toxicity due to cytarabine [51], brain lesions associated with PRES, stroke, or infection, or cranial neuropathies secondary to viral reactivation, disease relapse, or immune-mediated processes. CN1 neurotoxicity can also produce slurred or ataxic speech [68]. Metabolic abnormalities such as hyponatremia or hypomagnesemia, and sedative drugs (e.g., benzodiazepines, opioids), can also induce dysarthria. GVHD-associated myasthenia gravis may present with fluctuating dysarthria [69].

Visual disturbances Blurry vision may arise from ocular or neurological disorders, and can be caused by infectious, vascular, or medication-related factors. In PRES, visual disturbances may include blurred vision, visual field defects, or even cortical blindness. Ischemic or haemorrhagic stroke (including from infections) or CNS relapse involving the occipital lobes may also impair vision acutely. Other causes include optic neuropathies related to radiation, infection, immune-mediated processes, or disease relapse. Rarely, they are a manifestation of fludarabine-associated neurotoxicity, and can even present long after fludarabine has been discontinued [50, 70, 71]. Diplopia suggests oculomotor nerves involvement, which may result from infiltrative, infectious, vascular, or immune-mediated causes, brainstem lesions, or GVHD-associated myasthenia gravis. Post LP intracranial hypotension can cause horizontal diplopia [3].

Visual hallucinations can arise from metabolic encephalopathies, CNS infections, vascular lesions, or medication-related neurotoxicity. CN1s may cause visual hallucinations in PRES; high-dose corticosteroids, opioids, and antibiotics can also precipitate visual disturbances or psychotic symptoms. Among antifungals, voriconazole-induced hallucinations is an early concentration-dependent adverse event, which may resolve in some patients if delivery is switched from intravenous to oral [72].

Sensory disturbances may present as paresthesia (abnormal sensations without external stimulation) and dysesthesia (abnormal sensations evoked by a normally nonpainful stimulus) in allo-HCT patients [73]. A sensory level suggests myelopathy, which may result from infectious, vascular, or immune-mediated causes, or from metabolic and nutritional deficiencies, particularly vitamin B12 or copper deficiency affecting the posterior columns. Radiation- or intrathecal chemotherapy-induced myelopathy or leukemic/lymphomatous spinal infiltration may also occur, producing ascending sensory disturbances [50].

Trigeminal neuropathy should be considered in patients presenting with facial numbness or hypoesthesia, as it may result from CNS infection, leptomeningeal disease, or immune-mediated mechanisms related to chronic GVHD. Leukemic or lymphomatous infiltration of the bone marrow, or local infection should also be considered [50]. Other peripheral neuropathies should likewise be considered but fall outside the scope of this review.

Memory disturbances after allo-HSCT range from mild forgetfulness to severe amnesic syndromes [74]. High-dose chemotherapy, total-body irradiation (TBI), immunosuppressive agents and corticosteroids may damage hippocampal-limbic structures and induce reversible cognitive or mood-related memory deficits [58]. Posttransplant acute limbic encephalitis (PALE), usually presenting with anterograde amnesia and mild CSF/EEG abnormalities, is most often related to HHV6 infection [3, 20, 75, 76]. Wernicke encephalopathy due to thiamine deficiency causes AMS, ataxia and/or oculomotor disturbances, although the triad is often incomplete [77, 78]. GVHD, prolonged

or imbalanced parenteral nutrition, and treatment-related gastrointestinal toxicity predispose to this condition. Thiamine must be administered immediately at first suspicion to prevent progression to Korsakoff syndrome with irreversible anterograde amnesia [77]. Chronic GVHD, anaemia, metabolic disturbances and psychological factors such as depression, anxiety and fatigue also contribute to memory problems.

Psychological and Mood disorders are frequent. In the pre-transplant phase, patients often experience anxiety and depression related to fear of death, uncertainty about outcomes, and separation from family. In the early post-transplant period (0–100 days), depression and anxiety are common, frequently driven by isolation, immunosuppressive medications such as corticosteroids and CN1s, and infection risk. In the late post-transplant phase (>100 days), patients may develop chronic depression or post-traumatic stress disorder, persistent fatigue, cognitive impairment, and loss of social or occupational roles [79–81]. Chronic GVHD, particularly when severe, has been associated with adverse psychological outcomes and lower quality of life [82–84]. Neurological causes, including CNS infections, are rare.

CONCLUSION

As allo-HCT continue to increase and survival improves [85], heightened clinical vigilance and early recognition of CNSC remain essential to optimizing outcomes. Initial evaluation prioritizes accurate syndrome definition and the selection of targeted, cost-effective diagnostic studies. Neurological consultation with an experienced specialist is strongly recommended, as it aids not only in identifying common complications but also in detecting subtle early or atypical manifestations. Distinguishing among the many potential causes is challenging and often requires rapid, coordinated multidisciplinary diagnostic efforts to ensure timely and appropriate management to prevent irreversible neurological injury.

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AUTHOR CONTRIBUTIONS

RV, MSH, OP, DA, and JS conceptualized the review and developed the methodology according to the practice harmonization and guidelines committee [27]. All authors contributed to the literature search; RV, MSH, and JS screened and selected the included studies and extracted key data. RV, MSH, and JS wrote the first draft. IY-A formatted the final draft. All authors contributed to the interpretation of the evidence and edited subsequent versions. RV, MSH, OP, DA, and JS supervised the project and provided critical revisions. All authors approved the submitted manuscript and agree to be accountable for all aspects of the work.

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COMPETING INTERESTS

The authors declare no competing financial interests related to this work.

ADDITIONAL INFORMATION

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