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NEUROLOGICAL COMPLICATIONS OF HEMATOPOIETIC STEM CELL TRANSPLANTATION (HSCT)

A retrospective study in a HSCT center in Brazil

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Abstract – We present the neurological complications evaluated in a series of 1000 patients who underwent hematopoietic stem cell transplantation (HSCT). Central nervous system (CNS) neurological complications, particularly brain hemorrhages, were the most common, followed by seizures and CNS infections. An unusual neurological complication was Wernicke's encephalopathy. Less frequent neurological complications were metabolic encephalopathy, neuroleptic malignant syndrome, reversible posterior leukoencephalopathy syndrome, brain infarct and movement disorders. The most common neurological complication of the peripheral nervous system was herpes zoster radiculopathy, while peripheral neuropathies, inflammatory myopathy and myotonia were very rarely found.

KEY WORDS: neurological complications, hematopoietic stem cell transplantation, stem-cell transplantation.

Complicações neurológicas do transplante de células tronco hematopoiéticas (TCTH): estudo retrospectivo em um centro de TCTH no Brasil

Resumo – Apresentamos as complicações neurológicas avaliadas em uma série de 1000 pacientes submetidos ao transplante de células tronco hematopoiéticas (TCTH). As complicações neurológicas do sistema nervoso central foram as mais encontradas, particularmente as hemorragias encefálicas, seguidas por crises convulsivas e por infecções. Uma complicação peculiar foi a encefalopatia de Wernicke. Menos freqüentemente foram encontrados casos de encefalopatia metabólica, síndrome maligna neuroléptica, leucoencefalopatia posterior reversível, infarto cerebral e os distúrbios do movimento. Entre as complicações neurológicas do sistema nervoso periférico a mais encontrada foi a radiculopatia pelo herpes zoster, enquanto que raramente se observaram casos de polineuropatias periféricas, miopatia inflamatória e de miotonia.

PALAVRAS-CHAVE: complicações neurológicas, transplante de células tronco hematopoiéticas, transplante de precursores hematopoiéticos.

Allogeneic hematopoietic stem cell transplantation (HSCT) is an excellent therapy option for a variety of serious malignant and benign diseases, including leukemias and myelodysplastic syndromes, aplastic anemia, autoimmune diseases and inherited diseases, including hemoglobinopathies and pediatric genetic diseases[1-8].

There is, however, a relatively high incidence of transplant-related mortality (TRM) associated with complications arising from the procedure, which can be as high as 20 to 50%[1,2,4,5]. Neurological complications of HSCT have been reported to occur in 2.8 to 70% of patients in different series[1-6]. In 2005 Uckam et al. reported serious neurological complications in children who had received HSCT. The authors observed that 9.7% of the children developed neurological complications classified as serious (life-threatening). The main risk factors identified were the main risk status of the underlying disease, mismatched transplantation, previous diagnosis of advanced AML, older age and the presence of grade II or higher graft-versus-host-disease (GVHD)[9]. Denier et al. described the spectrum and prognosis of neurological complications after HSCT in a series of 361 patients. The authors concluded

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that neurological complications are common (16% of their patients), that their incidence can vary according to the primary disease and transplant type, and that they are associated with a worse prognosis[10].

Usually, neurological complications of HSCT are caused by several factors, which include pretransplant chemotherapy and/or radiotherapy, conditioning regimens used, infections caused by the transplant-related immune deficiency and adverse effects caused by the drugs used either to prevent or treat GVHD[1,2,3,5].

The neurological complications discussed in the present report were identified during a retrospective review of the data from the last 17 years of transplants in the HSCT Center at the Hospital de Clínicas, Federal University of Paraná, Curitiba, Brazil. The analysis was performed in three different stages: in the first stage 458 patients who had received HSCT were evaluated[11], in the second 662 patients[12] and in the third 1000 patients.

The objective of this study was to compare these complications with the main neurological complications reported in the literature to date.

METHOD

The HSCT Center at the Hospital de Clínicas, Federal University of Paraná, Curitiba, Brazil, has been active for the last 25 years and, according to its database, 1616 patients have received HSCTs at the center to date, 1493 of which were allogeneic and 123 of which autologous.

Neurological complications of HSCTs (NCHSCTs) can be divided into those involving the central nervous system (CNS) (the brain, cerebellum, brainstem and spinal cord) and those involving the peripheral nervous system (PNS) (the lower motor neuron, motor and sensory roots, dorsal root ganglia, nerve plexi, peripheral nerves, neuromuscular junction and muscles).

Central NCHSCTs were further classified as vascular diseases (intracranial hemorrhage, including intracerebral hemorrhage, subarachnoid, subdural and epidural hemorrhage, and brain infarction), CNS infections (encephalitis, meningitis, abscess) of several etiologies (bacterial, fungal, viral and parasitic, including toxoplasmosis and cysticercosis), epileptic seizures (irrespective of trigger factors), metabolic encephalopathy, reversible posterior leukoencephalopathy and neuroleptic malignant syndrome.

Peripheral NCHSCTs were classified as radiculopathies, peripheral neuropathies and myopathies.

The neurological diagnoses were performed according to international criteria and confirmed by different tests, including image scans (CT scans and MRI), Doppler (transcranial, carotid and vertebral arteries), electroencephalograms, electroneuromyography, CSF analysis and routine blood tests, including screening tests for infection in immunocompromised patients.

The charts of 1000 patients who had received HSCT at the center during the previous 17 years (1989–2006) and had developed neurological complications were evaluated retrospectively.

The most common diagnoses found in the series were aplastic anemia, chronic myeloid leukemia, acute myeloid leukemia, acute lymphocytic leukemia, Fanconi anemia, myelodysplastic syndrome and other hematological malignancies. There was also a small percentage of genetic disorder.

Patient age varied between 2 and 60 years, with a mean of 19.2, and the ratio of males to females was 60:40.

This study was approved by the Ethics Committee of the Hospital de Clínicas of Federal University of Paraná.

RESULTS

NCHSCTs were found in 31% of the patients in the present series (n=1000). Central NCHSCTs accounted for 70.3% of the cases, and peripheral NCHSCTs for 29.7%. Table summarizes the most frequent neurological complications and their respective incidence rates.

Central neurological complications accounted for 19% of the deaths in the patients studied.

The most important central NCHSCTs observed were intracranial hemorrhage (29%); epileptic seizures (15 %); CNS infections (11.3%) including encephalitis (6%), meningitis (3%), brain abscesses (1 %), cerebral toxoplasmosis (1%) and neurocysticercosis (0,1%); metabolic encephalopathies (9.5%); brain infarction (2.4%); reversible posterior leukoencephalopathy syndrome (1%); movement disorders (1%); Wernicke's encephalopathy (1%); and malignant neuroleptic syndrome (0.2%).

The most common peripheral complications were herpes-zoster radiculopathy (27%), peripheral polyneuropathy (2%), inflammatory myopathy (0.5%) and myotonia (0.2%).

Table. Neurological complications of HSCT – HC – FUPR.

CNS (70,3%)	Brain vascular disease = 31.4%	
	Intracranial hemorrhage = 29%	
	Brain infarct = 2.4%	
	Epileptic seizures = 15%	
	Infections: encephalitis: fungal. vírus = 6%	
	(11.3%)	Bacterial meningitis = 3%
		Brain abscess = 1%
		Brain toxoplasmosis = 1%
		Neurocysticercosis = 0.1%
	Metabolic encephalopathy = 9.5%	
	Wernicke encephalopathy = 1%	
	Reversible posterior leukoencephalopathy = 1%	
	Movement disorders = 1%	
	Malignant neuroleptic syndrome = 0.2%.	
PNS (29,7%)	Herpes zoster radiculopathy = 27%	
	Peripheral neuropathy = 2%	
	Inflamatory myopathy = 0.5%	
	Myotonia = 0.2%	

HSCT, hematopoietic stem cell transplantation; HC-FUPR, Hospital de Clínicas, Federal University of Paraná; CNS, central nervous system; PNS, peripheral nervous system.

Myelopathies, diseases of the lower motor neuron, dorsal root ganglion diseases, plexopathies or neuromuscular junction diseases were not found in the series.

CNS complications

Vascular diseases of the brain (hemorrhage and infarction) – Intracranial hemorrhages were the most common neurological complications found in this series and were associated with thrombocytopenia. These complications were divided into intracerebral hemorrhage (the most common) and, more rarely, subarachnoid, subdural and epidural hemorrhages. There were a small number of brain infarctions in our series.

Epileptic seizures – In this group of patients had an incidence of 15% and were related to drugs (for example, busulfan and imipenem); brain hemorrhage or infarction; CNS infections (fungal, bacterial viral or protozoan); and metabolic encephalopathy. Patients with status epilepticus (SE) evaluated at the HSCT unit had a high mortality rate of about 90%.

CNS infections – CNS infections were secondary to many agents such as bacteria, fungi and parasites. These infections usually occur during periods of higher immunosuppression (e.g., the neutropenic phase and the first year of transplant). Case 1 represents a patient with an intense inflammatory reaction of racemose form of neurocysticercosis, after HSCT:

Case 1 – Male, 33 years old, with a previous diagnosis of neurocysticercosis (with hydrocephaly secondary to a cysticercus cyst in the fourth ventricle). He was submitted to a ventriculoperitoneal shunt followed by a posterior craniotomy with removal of the cyst. The patient remained asymptomatic for many years, during which period he developed idiopathic aplastic anemia and received an allogeneic HSCT. At engraftment, with the increasing number of peripheral blood leukocytes, he developed signs of neurological dysfunction: headache, vomiting, diplopia, bilateral ophthalmoparesis, bilateral horizontal and vertical nystagmus, gait ataxia, truncal ataxia and somnolence. MRI revealed intense inflammatory reaction at the cysts located in the basal cisterns and around the brainstem (Figure). CSF exam showed inflammatory reaction with a prevalence of mononuclear infiltrate. The patient progressed with ischemic areas of the brainstem, probably secondary to vasculitis, and died. Diagnosis was confirmed by autopsy (racemose form of neurocysticercosis).

Metabolic encephalopathies – These were characterized clinically by the presence of consciousness disturbances and epileptic crisis and were commonly secondary to water-electrolyte imbalance, particularly sodium and calcium disturbances. Also common were acid-base disturbances, hepatic and renal insufficiency, and hypoxia or ischemia. In some cases we observed metabolic encephalopathy associated with terminal events in HSCT patients with multiple complications and GVHD.

Wernicke's encephalopathy (WE) – This represented an important neurological complication in this series and is rarely reported in the international literature related to HSCT. Case 2 is an example of WE after HSCT.

Case 2 – Male, 36 years old, with a diagnosis of chronic myeloid leukemia. He received allogeneic HSCT and did not have any complications. He was on TPN (total parenteral nutrition) in accordance with the protocol used in the center when he developed a clinical picture of metabolic acidosis, and while on investigation for this condition he suddenly developed gait ataxia and bilateral ophthalmoparesis with no disturbance in consciousness. The picture was highly suggestive of WE, and IV thiamine repletion (100 mg attack dose followed by maintenance) resulted in a full recovery in 3 days. This clinical diagnosis allowed the cause of death of eight previous cases with similar features to be clarified retrospectively. These diagnoses were then confirmed by autopsy, and the cases were confirmed to have been caused by an iatrogenic deficiency of thiamin in the TPN.

Reversible posterior leukoencephalopathy syndrome (RPLS) – This was observed in eight patients whose cases were previously published elsewhere.

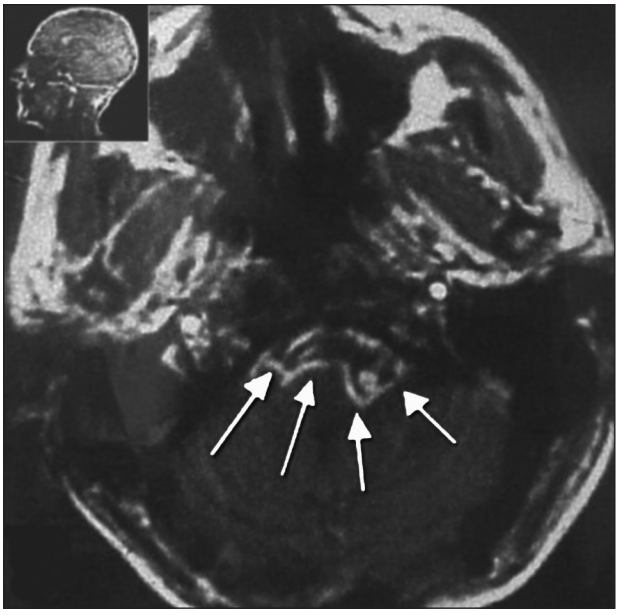

Figure. Cranial MRI (T1-weighted axial magnetic resonance scan) showed intense inflammatory reaction at the cysts located in the posterior fossa (basal cisterns, around the brainstem).

Movement disorders (MD) – We evaluated a small number of MD cases, which were classified as parkinsonism and hyperkynesias such as hemiballism/chorea, myoclonus, tremor and cerebellar ataxia.

Parkinsonism was detected in one 46-year-old male patient with toxoplasmosis encephalitis following HSCT. Cranial CT scan showed hypodense areas in the frontotemporal region in both hemispheres. CSF exam was inconclusive. Levodopa was administered, but the patient failed to respond and progressed to death. Autopsy revealed generalized toxoplasmosis with CNS involvement.

The clinical picture of hemichorea/ballism was observed in a child who developed pulmonary infection and cardiorespiratory arrest after receiving HSCT. The patient was resuscitated and had a good recovery except for the neurological symptom of hemichorea/ballism in the left side. Cranial CT scan of the brain was normal.

In one case, in the same center, generalized myoclonus was diagnosed in a patient with metabolic encephalopathy.

In another case, a child developed cerebellar ataxia in association with severe GVHD after being submitted to HSCT. Neuroimaging exams (CT and MRI) and CSF were normal.

Malignant neuroleptic syndrome – This is a rare complication of neuroleptic drugs and was found in only two cases in the present study.

The first case was a patient who developed severe vomiting after receiving conditioning and was medicated with high-dose haloperidol. He then developed rigidity, somnolence and hyperthermia and had elevated creatine-phosphokinase (CK) levels, although no infectious source was identified. Malignant neuroleptic syndrome was diagnosed, and therapy with bromocriptine (an ergoline dopamine agonist) was instituted with good response.

Peripheral nervous system complications

We observed radiculopathy caused by VZV infection (herpes zoster) – usually in the intercostal space – in 28% of the cases. Other complications found were polyneuropathy (2%), inflammatory myopathy (0.5%) and myotonia (0.2%).

In addition, one case of peripheral neuropathy secondary to vasculitis was recently observed in an HSCT patient with GVHD.

DISCUSSION

In general terms, the main neurological complications in our series were similar to the pathological findings reported in 2000 in a study by the pathology department of the same center[13] of 180 autopsies of patients who had undergone HSCT.

Intracranial hemorrhage – particularly intracerebral hemorrhage – was the most common complication observed. In 2002 Bleggi-Torres et al. examined the results of 58 autopsies of patients who had received HSCT and had developed intracranial hemorrhage[18] . The authors reported that 40 patients had intracerebral hemorrhage, 35 subarachnoid hemorrhage and eight subdural hemorrhage[14]. In 16 cases bleeding was extensive and directly related to death[14].

Intracerebral hemorrhage usually has a different evolution from that caused by systemic arterial hypertension, which is usually monophasic. Intracerebral hemorrhage observed in HSCT patients secondary to severe thrombocytopenia can have a slow but progressive clinical evolution because of the increase in the size of the hematoma, followed by mass effect, intracranial hypertension and transtentorial herniation. Difficulties with platelet replacement, persistent thrombocytopenia and problems recommending surgery because of the condition of the patients frequently cause intracranial hypertension with herniation refractory to treatment followed by brain death.

It is interesting to note that intracranial hemorrhages were more frequent (29% of cases) than brain infarctions in this series, a finding that differs from those reported in the literature[1,15]. Davis and Patchell describe a similar incidence of brain infarction and intracerebral hemorrhage in patients who received HSCT[1]. Another interesting aspect of reports in the literature is that the presence of brain infarction is generally related to infectious endocarditis or even marantic endocarditis, a diagnosis not observed in our patients despite thorough investigation[1,15].

The small number of brain infarctions observed in our series were mainly related to fungal infection, particularly by *Aspergillus sp*.

Coplin et al, evaluated the incidence, etiology and prognosis of strokes in patients after HSCT. Of 1245 patients who received HSCT, 2.9% had stroke, of which the most common causes were intracerebral hemorrhage related to thrombocytopenia (38.9% of cases) and the presence of brain infarction and hemorrhage secondary to fungal infection (20% of cases)[15].

CNS bacterial infection is estimated to be present in between 1.3 and 5.3 % of cases. Among the most common causes of bacterial meningitis are *Listeria monocytogenes*, *Streptococcus pneumoniae*, *Klebsiella pneumoniae*, *Escherichia coli* and *Alpha streptococcus*[1].

Brandi et al., in a study of 865 HSCT patients, identified the infections that were found most frequently in HSCT patients in our center. In their series neurological complications were observed in 27.6% of the cases, and 9.4% of the cases were caused by infection[16]. Of all the cases with infections, 70.7% were due to infection of the peripheral

nervous system caused by the Varicella-zoster virus, with intercostal radiculopathy, and 29.2% to infection of the CNS caused by various infectious agents. The most common of these were fungal (Aspergillus) and viral infections and toxoplasmosis encephalitis, followed by abscesses of different etiologies, and neurocysticercosis. A total of 53.6% of the patients had graft-versus-host disease[16].

Among the encephalitis, the most common etiologies are viral (herpes virus, cytomegalovirus and varicella-zoster virus) and fungal infections caused by *Aspergillus sp*.[1, 10,16,17].

Medeiros et al. investigated the main CNS infections that occur after HSCT in an autopsy study of 27 cases. They found encephalic infections in 15% of the cases and fungal infections, particularly those caused by *Aspergillus sp*, followed by *Candida sp* and species of Fusarium, in 60% of the cases. *Toxoplama gondii* encephalitis was found in 8 cases and bacterial abscesses in 2% of the cases[18].

Jantunem et al. studied diagnostic aspects of invasive infections caused by Aspergillus in patients who received HSCT. They concluded that the lungs were the most commonly affected organs (90% of cases), followed by the CNS (41%)[19]. Thus, methods for early detection of fungal infections are extremely important for early diagnosis of this condition, and patients suspected of having this type of infection should start anti-fungal therapy at the same time as the diagnostic process is under way[19].

Human herpesvirus type 6 (HHV-6) infections are emphasized in the literature as being an important cause of viral encephalitis in HSCT patients[20]. HHV-6 is a neurotropic virus, which often leads to a picture of encephalitis, particularly in immunocompromised hosts, such as HSCT patients[20]. The diagnosis of encephalitis caused by HHV-6 has become easier because PCR techniques can now be used in CSF. However, no HHV-6 infection was detected in our series, suggesting that among our patients this infection is not as important as the literature indicates.

Diagnosis of toxoplasmosis in patients submitted to HSCT was not common until some years ago, and its low prevalence in these patients compared with that in other immunocompromised patients (e.g., those with AIDS) was the subject of much debate. However, in the series published by Maschke et al, investigated the presence of opportunistic infection in 655 patients after HSCT, and 4% of the patients were found to have infections, and 74% of these had toxoplasmosis encephalitis[21]. Denier et al. found CNS infections in 4.2 % of their cases, with a predominance of toxoplasmosis, (1.4% of cases)[10]. Toxoplasmosis cases observed at our HSCT center were difficult to diagnose and were only confirmed by pathology analysis (cerebral biopsy or autopsy). These patients usually had nonspecific neurological clinical manifestations suggestive of encephalitis, or, less frequently, had granulomas or abscesses[22].

Neurocysticercosis cases diagnosed post-HSCT are very rare, and in our series we had only one case (the racemose form). The patient, who had a previous history of surgical therapy, had had a cyst removed from the fourth ventricle and a ventricular-peritoneal shunt implanted to correct hydrocephaly. After HSCT due to aplastic anemia, this patient developed an intense inflammatory reaction to racemose cyst in the CNS, associated with severe vasculitis.

Wernicke encephalopathy is a neurological complication to which little importance is attributed in the international literature regarding neurological complications after HSCT. Majolino et al. reported the case of a patient who had a clinical picture compatible with WE after the use of busulfan. The authors questioned the involvement of busulfan in the causality of thiamin deficiency[23].

However, in our study, eight patients with iatrogenic WE were described. The disease was caused by the lack of thiamin in the TPN formulation although this was supposed to contain this vitamin. This problem was caused by the pharmaceutical company that supplied the formulation. Clinical symptoms varied, and the characteristic triad of ataxia, confusion and ophthalmoparesis was not always present. In most of the cases we observed disturbances in consciousness, characterized by somnolence, torpor and coma; metabolic acidosis; and an uncommon form of optical neuritis. The mortality rate was high, and all cases were confirmed by autopsy[24]. After a 25-year-old patient who had a very suggestive clinical picture of WE had been diagnosed with thiamin deficiency, the remaining patients in this WE series were diagnosed retrospectively. This 25-year-old patient had a dramatic response to IV thiamin replacement (case 2).

Posterior reversible leukoencephalopathy (PRL) has been described in patients with renal insufficiency; patients with eclampsia; and patients with hypertensive encephalopathy, which is possibly related to the cytotoxic effects of drugs such as cyclosporine used in immunosuppressive therapy on the vascular endothelium[25]. In 2001, Teive et al reported eight patients who had received cyclosporine after HSCT and developed RPL[25].

Movement disturbances (MD) in patients after HSCT have not been the subject of publications to date. However, a case of cerebellar ataxia in a child who developed severe GVHD after HSCT raised the possibility of brain involvement secondary to GVHD. Despite the absence of specific confirmation, the patient recovered partially from ataxia after high-dose steroid treatment. There is no consensus in the literature about the possibility of brain involvement (encephalopathy or vasculitis) secondary to GVHD[1,26].

Peripheral neurological system complications are generally less frequent after HSCT[1-3,5-9]. There have been reports of cases of peripheral neuropathy secondary to chemotherapy, radiculopathy secondary to VZV infections and myositis related to chronic GVHD[1,2,27,28]

In 1997 Zétola described the pre- and post-HSCT neurological evaluation of 43 patients using clinical neurological exams and nerve conduction studies[29]. The objective of the study was to investigate the possibility of peripheral nerve damage as a result of conditioning and immunoprophylaxis regimens used for HSCT (busulfan, cyclophosphamide, cyclosporine and methotrexate). However, the author failed to find any evidence that these drugs were toxic to the PNS in the patients studied[29].

More recently, a case of a patient with chronic inflammatory demyelinating polyradiculoneuropathy in chronic graft-versus-host disease following allogeneic hematopoietic stem cell transplantation was reported[30].

In conclusion, the authors present neurological complications in 1000 patients who underwent HSCT. CNS neurological complications, particularly brain hemorrhages, were the most common, followed by seizures and CNS infections.

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