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

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A major obstacle of allogeneic haematopoietic stem cell transplantation is graft-versus-host disease, an immune-mediated disorder that affects multiple tissues and organs with varying severity. Neurological complications of acute and chronic graft-versus-host disease are rare but can produce severe clinical problems with significant morbidity and mortality. In this article, we review neurological manifestations of chronic graft-versus-host disease that comprise immune-mediated neuropathies, myasthenia gravis and myositis in the peripheral nervous system and various cerebrovascular complications, demyelination and immune-mediated encephalitis in the central nervous system. The National Institutes of Health consensus on criteria for clinical trials in chronic graft-versus-host disease recommended that the diagnosis of chronic graft-versus-host disease of the nervous system can be made only when other organs are affected by graft-versus-host disease and frequent neurological differential diagnoses such as drug-induced toxicities or opportunistic infections are excluded. The Consensus Conference on Clinical Practice in chronic graft-versus-host disease, held in autumn 2009 in Regensburg, aimed to summarize the literature and to provide guidelines for the diagnostic approach in children and adults with neurological manifestations of chronic graft-versus-host disease. Moreover, we present therapeutic recommendations and their level of evidence for the management of these complications. Overlapping symptoms and comorbidities after allogeneic haematopoietic stem cell transplantation and the limited knowledge about the underlying biological mechanisms of chronic graft-versus-host disease affecting the nervous system emphasize the need for further experimental and clinical investigations.
Keywords: chronic graft-versus-host disease; allogeneic haematopoietic stem cell transplantation; neurologic manifestations; supportive care

Abbreviations: GBS = Guillain-Barré syndrome; GVHD = graft-versus-host disease; HSCT = haematopoietic stem cell transplantation; IDP = inflammatory demyelinating polyradiculoneuropathy; PNS = peripheral nervous system

Introduction

Chronic graft-versus-host disease (GVHD), a late complication occurring after allogeneic haematopoietic stem cell transplantation (HSCT), is characterized by pleomorphic clinical manifestations, affecting multiple tissues and organs with varying severity and clinical course (Filipovich et al., 2005; Ferrara et al., 2009).

Knowledge about the biological mechanisms leading to chronic GVHD is still limited. There is growing evidence that thymic damage is a major cause of chronic GVHD after allogeneic HSCT (Teshima et al., 2003). The thymus plays a central role in positive and negative selection of T cells during their development. The recovery of T cells following allogeneic HSCT results both from a thymus-dependent pathway, which involves the generation of naïve T cells from donor-derived haematopoietic stem cells, and from a thymus-independent pathway, which includes interleukin-7 driven peripheral expansion of graft-derived mature donor T cells (Chung et al., 2007; Sakoda et al., 2007; Zhang et al., 2007). Experimental data suggest that thymic damage caused either by the conditioning regimen, acute GVHD or age-related involution and atrophy can disrupt thymic education of T cells, mainly by impairment of medullary thymic epithelial cells (Sherer and Shoenfeld, 1998; Martin, 2008; Clave et al., 2009). Particularly, thymic destruction by alloreactive T cells might be a leading cause for the development of chronic GVHD, because chronic GVHD usually does not occur after autologous HSCT, where increased thymopoiesis and T cell renewal can be observed (Hakim et al., 2005; Muraro et al., 2005). Thymic dysfunction also interferes with the appropriate generation of immunosuppressive regulatory T cells, which play a major role in maintaining peripheral tolerance by controlling autoreactive T cells. Additional concepts of the pathophysiology of chronic GVHD include a T helper 1 to T helper 2 shift of the cellular immune response, replacement of antigen presenting cells of the host by antigen presenting cells of the donor leading to indirect antigen presentation of allo-antigens, donor-derived B cells producing auto- and allo-antibodies against the host and non-specific mechanisms of chronic inflammation as well as aberrant production of immunosuppressive factors such as transforming growth factor-β, which cause fibrosis of involved organs (Shlomchik et al., 2007; Martin, 2008).

Chronic GVHD often affects a variety of organs, including the skin, eyes, oral mucosa, lungs, intestinal tract and liver, and may mimic autoimmune diseases like systemic sclerosis or autoantibody-mediated thrombocytopenia. Severity of chronic GVHD is staged according to the number of organ manifestations and the severity of organ involvement (Filipovich et al., 2005).

Neurological manifestations of chronic GVHD are rare and can affect both the peripheral and central nervous system (PNS and CNS) (Openshaw, 2009). They usually occur several months to years after allogeneic HSCT, at a time after administration of multiple, potentially toxic drugs, when often infectious and metabolic complications have occurred. In the PNS, chronic GVHD can occur at different anatomic levels and involve the peripheral nerve, the neuromuscular junction or the muscle and adjacent fascia. Less clearly associated with chronic GVHD are CNS manifestations such as cerebral vasculitis, demyelination and encephalitis-like disease. According to the 2005 National Institutes of Health consensus criteria for chronic GVHD, myositis and polymyositis are the only ‘distinctive’ neurological manifestations of chronic GVHD, whereas peripheral neuropathies and myasthenia gravis are less established and therefore considered as ‘other’ or ‘associated features’ of chronic GVHD (Filipovich et al., 2005). Hence, diagnosis of neurological chronic GVHD can be made only in the presence of additional recognized manifestations of chronic GVHD, such as skin, mouth, gastrointestinal, lung or joint involvement. Not much is known about the pathophysiology of neurological manifestations of chronic GVHD and further research is urgently warranted.

Here, we review the different manifestations of chronic GVHD in the PNS and CNS, discuss the clinical picture of chronic GVHD-related neurological diseases and give guidance to diagnostic procedures and therapeutic considerations. The described diseases are in the context of chronic GVHD following allogeneic HSCT, and the discussion does not apply to or cover autologous HSCT or other forms of stem cell therapies.

This literature review and assessment was presented as part of the Consensus Conference on Clinical Practice in Chronic GVHD held in autumn 2009 in Regensburg, Germany (complete programme provided at http://www.gvhd.de), which summarized the currently available evidence for diagnosis, severity staging, immunosuppressive as well as supportive treatment of chronic GVHD and provided practical guidelines for the use of treatment modalities. The Consensus Conference was organized under the auspices of the German working group on bone marrow and blood stem cell transplantation, the German Society of Haematology and Oncology, the Austrian Stem Cell Transplant Working Group of the Austrian Society of Haematology and Oncology, the Swiss Blood Stem Cell Transplantation Group and the German-Austrian Paediatric Working Group on HSCT.

General considerations on the treatment of chronic graft-versus-host disease

Chronic GVHD often affects multiple organs and therefore requires a multidisciplinary approach involving expertise in haematology, gastroenterology, rheumatology, dermatology, ophthalmology and other clinical fields. In general, systemic and topic
immunosuppressants are given, along with appropriate supportive therapy.

The evaluation of evidence and the subsequent recommendations were graded according to the classification system used in supportive care of chronic GVHD (Couriel, 2008). Since the evidence of the majority of treatment options in chronic GVHD is sparse and therefore the strength of recommendation falls into category C, for most of the therapeutic options the category C and evidence level III were further specified, as shown in Tables 1 and 2. Where evidence from the use in chronic GVHD (hallmarked as ‘a’) was not available or insufficient, studies from the treatment of the general neurological condition (‘b’) were evaluated. All strength of recommendation and evidence levels were first rated by an expert panel and subsequently rated by all participants of the consensus process.

First-line treatment of chronic GVHD consists of corticosteroids (‘strength of recommendation’ A, ‘evidence level’ Ia) with or without combination with calcineurin inhibitors (C-1 IIa) and is based on controlled trials (Wolff et al., 2010a), whereas evidence of second-line treatment of chronic GVHD is less well defined (Wolff et al., 2010b). Agents being used for second-line treatment are prednisone (B III-1a), calcineurin inhibitors (C-1 III-1a), mammalian target of rapamycin inhibitors (C-1 III-1a), mycophenolate mofetil (C-1 III-1a) and photopheresis (C-1 Ila). A pulse of steroids (C-2 IIa) and rituximab (C-2 Ila) should be generally applied after second-line treatment but may be used earlier in special circumstances. Advanced line treatment options being proposed include methotrexate (C-2 III-1a), hydroxychloroquine (C-2 III-2a), clofazimine (C-2 III-2a), pentostatin (C-2 IIa), thoracoabdominal irradiation (C-2 III-2a) and imatinib (C-2 III-1a). Additional agents in advanced line treatment are azathioprine (C-3 III-1a) and thalidomide (C-3 Ila).

When neurological manifestations develop during the course of chronic GVHD, immunosuppressive treatment is applied as combination treatment consisting of two to three agents, including steroids. Since long-term application of steroids is associated with significant side effects, one of the major goals in second-line treatment is to spare steroids. A uniform feature of patients receiving immunosuppressive treatment for chronic GVHD is a significantly increased risk for infectious morbidity and mortality. Therefore, frequent screening and sufficient prophylaxis for viral reactivation and Pneumocystis jirovecii pneumonia is required. Moreover, antifungal prophylaxis should be considered in patients with a history of invasive fungal infections or additional risk factors.

Peripheral nervous system manifestations of chronic graft-versus-host disease

Myositis

Myositis is a rare but typical neuromuscular complication in patients who develop chronic GVHD (Table 3). Its incidence is ~2–3% after allogeneic HSCT (Openshaw, 2009) but has been reported to be less frequent in other cohorts (Oda et al., 2009). Chronic GVHD-related myositis appears to be similar to idiopathic polymyositis in its clinicopathological presentation (Parker et al., 1997; George et al., 2001; Couriel et al., 2002; Stevens, 2003), especially in juvenile polymyositis where maternal microchimerism has been demonstrated (Artlett et al., 2000; Reed et al., 2000).

Patients develop typical clinical symptoms between 3 and 69 months after allogeneic HSCT. These symptoms can be present either with or without other signs of chronic GVHD (Urbano-Marquez et al., 1986; Sato et al., 2002; Stevens et al., 2003). The most common symptoms are moderate to severe symmetrical weakness of proximal muscles, the neck flexors and limb girdle. Muscle pain is not always present but is a common feature. Dysphagia from involvement of the striated muscles of
the upper oesophagus and pharynx can occur. Respiratory muscle involvement is rare but is occasionally seen (Stephenson et al., 2001). Allo-autoimmune reactions can also involve the heart muscle, resulting in myocarditis, especially after donor-lymphocyte infusion or discontinuation of immunosuppressive drugs (Lin et al., 2005; Liu et al., 2007; Ahn et al., 2009). In rare cases, chronic GVHD-related myositis can mimic dermatomyositis presenting with a heliotrope rash on the eyelids, with oedema and erythema of the knuckles (Leber et al., 1993; Ollivier et al., 1998).

Creatine kinase is a sensitive serum enzyme for the diagnosis of myositis. Normal values may be found in those with mild or early disease, but in most patients creatine kinase levels are elevated 5–50 times above normal. Although other enzymes, including lactate dehydrogenase, transaminases and the highly sensitive aldolase, are also elevated in active myositis, creatine kinase is most reliable, correlating best with the clinical course (Greenberg, 2009). In juvenile myositis, however, all associated enzymes should be tested, because more than 20% of children have normal creatine kinase concentrations (Feldman et al., 2008).

Myositis-specific autoantibodies have not been described in patients with chronic GVHD thus far, whereas autoantibodies directed against the nucleus (antinuclear antibodies), smooth muscle cells or mitochondria were reported (Parker et al., 1996; Takahashi et al., 2000; Stephenson et al., 2001; Stevens et al., 2003; Lin et al., 2005). Distinct human leucocyte antigen types that are highly associated with idiopathic polymyositis, such as HLA-DR52, HLA-B8, HLA-DR3 (DRB*0301) and HLA-DQA1*0501, have been only infrequently reported in chronic GVHD-related myositis (Parker et al., 1997).

Similar to the idiopathic form, needle electromyography in patients with chronic GVHD-related myositis often shows the typical myopathic pattern with fibrillation potentials, positive sharp waves, short-duration and small amplitude motor unit action potentials and full interference patterns in weak muscles.

To confirm the diagnosis of myositis, a muscle specimen is usually taken. Muscle CT or MRI is helpful to identify a suitable muscle. In children with myositis, MRI is often used both to establish the diagnosis and to monitor disease activity (Maillard et al., 2004). The typical histopathological features of GVHD-associated myositis are segmental muscle fibre necrosis, muscle fibre regeneration and mononuclear cell inflammation. The lymphocytic infiltration found is composed of donor cells (Takahashi et al., 2000). Immunohistochemistry revealed equal numbers of CD4+ and CD8+ T cells in the perimysium, whereas cytotoxic CD8+ T cells infiltrated more predominantly in the endomyositis (Takahashi et al., 2000; Oda et al., 2009). Further studies demonstrated that highly restricted oligoclonal T cells accumulate and expand in affected muscles in allogeneic HSCT-related myositis, suggesting a specific stimulation by yet unknown muscle autoantigens (Kojima et al., 2002).

There are no controlled studies evaluating specific treatments of chronic GVHD-related myositis. However, responses of chronic GVHD-related myositis to immunosuppressive therapy are similar to what has been observed in idiopathic polymyositis (Couriel et al., 2002). Since chronic GVHD-related myositis is regarded as a 'distinctive' manifestation of chronic GVHD, the recommendation and evidence of immunosuppression proposed for other manifestations of chronic GVHD also applies to treatment of chronic GVHD-related myositis. Corticosteroids are primarily used for the treatment of myositis (A 1a; A 1b). Although some patients may improve within days, improvement in others may be delayed for 4–6 weeks. The dosage of prednisone may then gradually be tapered until the lowest possible amount that controls the disease is reached. Combination with other immunosuppressive drugs, such as mycophenolate mofetil (C-1 III-1a), is often necessary for disease control and to reduce steroid doses. Other immunomodulating therapies used for combination therapy include cyclosporin (C-1 III-1a), methotrexate (C-2 III-3a) and cyclophosphamide (C-2 III-3a). In refractory cases of chronic GVHD-related myositis, intravenous gammaglobulin (C-2 III-3a; A 1b) can be administered (Cherin et al., 2002; Couriel et al., 2002; Dalakas, 2006). Furthermore, rituximab was demonstrated to have a beneficial effect in refractory cases of inflammatory myopathies (Mok et al., 2007; Sultan et al., 2008). In children, early aggressive

### Table 3 Neurological manifestations of chronic GVHD and differential diagnoses

<table>
<thead>
<tr>
<th>Chronic GVHD manifestation</th>
<th>Common differential diagnoses</th>
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<tbody>
<tr>
<td>PNS</td>
<td>Metabolic, endocrine, drug-induced (e.g. steroids) myopathies; fasciitis or perimyositis</td>
</tr>
<tr>
<td>Myositis† (typically polymyositis, rarely with myocarditis or dermatomyositis)</td>
<td>Other, non–immune-mediated polymyopathies (e.g. diabetic, toxic/ drug-induced); recurrence of haematological malignancy in spinal meninges, nerve sheaths or nerve plexus</td>
</tr>
<tr>
<td>Immune neuropathies§ (GBS, chronic IDP)</td>
<td>Lambert-Eaton myasthenic syndrome; congenital myasthenic syndromes in children</td>
</tr>
<tr>
<td>Myasthenia gravis§</td>
<td>Other, non–immune-mediated cerebrovascular diseases (e.g. haemorrhage, ischaemia) or vasculitis (e.g. drug-induced, infectious, post-infectious); leukoencephalopathy (e.g. microvascular dysfunction, irradiation, intrathecal chemotherapy, drug toxicity)</td>
</tr>
<tr>
<td>CNS</td>
<td>Other immune-mediated demyelinating diseases (e.g. multiple sclerosis, acute disseminated encephalomyelitis); leukoencephalopathy (see above), infectious diseases</td>
</tr>
<tr>
<td>Vasculitis§, angiitis§</td>
<td>Opportunistic infections (e.g. viral, fungal), post-transplant lympho-proliferative disorders; recurrence of haematological malignancy in the CNS; neurometabolic diseases</td>
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† Myositis represents a ‘distinctive feature’ of chronic GVHD, which is usually not found in acute GVHD. Myositis is not considered sufficient to establish a diagnosis of chronic GVHD without evidence of further organ involvement.

§ These manifestations are considered ‘associated features’ of chronic GVHD, which can be acknowledged as part of chronic GVHD if the diagnosis of chronic GVHD is confirmed and no other reason found.

It is controversial whether CNS manifestations are part of chronic GVHD or not.
treatment with high-dose methylprednisolone (30 mg/kg i.v. per day, maximum 1 g daily) in combination with low-dose oral corticosteroid (0.5 mg/kg/day), followed by methotrexate (15 mg/m²/week), is generally recommended to reduce cumulative steroid dose, to limit weight gain, to improve height velocity and to avoid calcinosis and other sequelae (C-1 IIIb) (Al-Mayouf et al., 2000; Ramanan et al., 2005).

Generally, patients with a good clinical response show substantial return of function in the first 2–7 months of treatment (Couriel et al., 2002). However, when patients experience a worsening of weakness after an initial positive response to corticosteroids, a relapse of the inflammatory process or a corticosteroid myopathy must be considered.

Steroid myopathy

All synthetic glucocorticoids can cause a corticosteroid myopathy, but the incidence is higher in patients treated with the 9-alpha fluorinated corticosteroids, such as triamcinolone, betamethasone and dexamethasone, which are typically not applied in chronic GVHD. Doses equivalent to 30 mg/day or higher of prednisone and dexamethasone, which are typically not applied in chronic fluorinated corticosteroids, such as triamcinolone, betamethasone and dexamethasone, are frequently with alternate day regimens (Bowyer et al., 2001). However, immune-mediated neuropathies to axonal variants such as the Miller–Fisher syndrome (Hughes and Cornblath, 2005). In the context of chronic GVHD, all variants of GBS have been described (Wen et al., 1997; Bulsara et al., 2001; Rodriguez et al., 2002; Rabinstein et al., 2003; Ostronoff et al., 2008).

Clinically, GBS is characterized by a rapidly progressive symmetrical ascending motor weakness, numbness and hypo- or areflexia. Cranial nerves, most frequently the facial nerves, are involved in a significant proportion of patients. Respiratory insufficiency can develop, and weakness of the respiratory muscles requires artificial ventilation in up to 25% of cases. Autonomic involvement is common and can cause urine retention, ileus, hypertension, cardiac arrhythmia and postural hypotension. Peak disease is reached within 2–4 weeks in nearly all patients (Hughes and Cornblath, 2005).

Nerve conduction studies play an important role in diagnosis and subtype classification of GBS. The disease is further confirmed by CSF analysis, usually displaying an albumino-cytological dissociation with regular cell numbers and elevated protein concentrations (Hughes and Cornblath, 2005). Lumbosacral MRI is not specific for GBS but may reveal gadolinium enhancement of spinal nerve roots in up to 90% of patients. MRI should be performed especially in young patients with acute or subacute paraparesis to exclude spinal compression (Rabie and Nevo, 2009).

In most cases, acute immune-mediated neuropathies after allogeneic HSCT are associated with antecedent infections (Mudad et al., 1995; Hernandez-Boluda et al., 2005; Naslowska-Adamska et al., 2006). Frequent pathogens in GBS are coxsackie viruses, cytomegalovirus, Chlamydia pneumoniae, Mycoplasma pneumoniae and Campylobacter jejuni. Other triggers are Epstein–Barr virus, hepatitis C virus and varicella. Male patients with active cytomegalovirus infections are at particularly high risk of developing GBS (El-Sabrout et al., 2001), often associated with involvement of the cranial nerves (Visser et al., 1996). Immune responses to these infective organisms are elicited by a panel of innate immune receptors that recognize a set of conserved molecular structures, so-called pathogen-associated molecular patterns. Molecular mimicry between microbial antigens and neural antigens is regarded as a leading mechanism underlying the triggering of GBS by antecedent infections. Strong evidence implicates autoantibodies to gangliosides as the cause of the axonal subgroups of GBS (Hughes and Cornblath, 2005). Autoantibodies against GM1 are usually associated with a C. jejuni infection, whereas autoantibodies against GM2 can be present in cytomegalovirus-associated GBS (Khali-Shirazi et al., 1999). In contrast, in axonal variants of GBS, T cell mediated immunity against myelin antigens is the major mechanism, resembling many features of experimental autoimmune neuritis (Hughes and Cornblath, 2005).

For the treatment of idiopathic GBS in adults, plasma exchange (A lb) is generally recommended. Intravenous gammaglobulin administration showed an efficacy similar to plasma exchange in several controlled clinical trials and is the preferred method in children (A lb) (Hughes and Cornblath, 2005; Agrawal et al., 2007; Hughes et al., 2007; Vucic et al., 2009). Plasma exchange or intravenous gammaglobulin are also the preferred treatment modality in patients with GBS after allogeneic HSCT (C-1 III-2a)
(Bulsara et al., 2001). If standard therapy fails, treatment with rituximab (C-2 III-3a), a chimeric monoclonal antibody directed against the B cell surface marker CD20, has been identified as beneficial in patients with chronic GVHD (Ostronoff et al., 2008). In some patients, the course of GBS and GVHD seemed to run in parallel, with an improvement in the neuropathy only after GVHD control (Amato et al., 1993). Corticosteroids are not beneficial in idiopathic GBS (D ib) (Hughes et al., 2010).

Apart from acute inflammatory neuropathies, subacute or chronic inflammatory demyelinating polyradiculoneuropathies (IDPs) with an onset phase lasting from 4 to 8 weeks or more than 8 weeks, respectively, have been described in patients after allogeneic HSCT (Lorenzoni et al., 2007; Wada et al., 2008). As a variant, chronic immune-mediated axonal polyneuropathy following HSCT can occur (Mulrooney et al., 2003).

The clinical course of a chronic IDP may be progressive or relapsing. Weakness usually involves both proximal and distal muscles. Sensory symptoms consist of numbness and tingling, sometimes also painful paraesthesia. Many patients have impaired balance due to proprioceptive deficits. Deep tendon reflexes are usually absent or weak. Autonomic and respiratory insufficiency occurs infrequently in comparison with GBS. Although uncommonly, some patients present with micturitional disturbances (Saperstein, 2008).

Similar to GBS, electrophysiological studies to confirm the diagnosis of a neuropathy and CSF analysis show an elevated protein concentration are performed (Hughes et al., 2006; Rajabally et al., 2009). Sural nerve biopsy may be helpful in excluding other aetiologies, such as amyloidosis, vasculitis and toxic neuropathies. However, in cases where clinical features, CSF protein concentration and nerve conduction studies are consistent with chronic IDP, information obtained from sural nerve biopsy usually does not add any additional diagnostic benefit (Molenaar et al., 1998).

Antecedent infections occur less often in chronic IDP than in GBS. Accordingly, there are no reports of autoantibodies in childhood and only low rates in adults. Chronic inflammatory neuropathies seem to be predominantly T cell mediated (Bosboom et al., 1977). These patients have to be carefully monitored because severe exacerbations of chronic IDP leading to quadriplegia and a fatal outcome have been reported after HSCT (Openshaw et al., 1991). Furthermore, chronic IDP can also develop 2–10 weeks after initiation of an immunosuppressive therapy with tacrolimus (Wilson et al., 1994).

Treatment of chronic GVHD-related chronic IDP does not differ from treatment of idiopathic chronic IDP. In the latter case, randomized controlled trials have demonstrated the efficacy of plasma exchange (A Ib), intravenous gammaglobulin (A Ib) and oral corticosteroids (A Ib) (Effimov et al., 2009). Cyclosporin (C-2 III-2b), mycophenolate mofetil (C-2 III-2b) and methotrexate (C-2 III-2b), as well as pulse cyclophosphamide therapy (C-2 III-2b), have all been reported to be beneficial in patients with chronic IDP not tolerating or not responsive to first-line agents (Saperstein, 2008; Brannagan, 2009; Donofrio et al., 2009). Interferon-β1a has also been used in idiopathic chronic IDP with some success (C-2 Ib), but since it may trigger GVHD (Posthuma et al., 2004), it should be applied only with caution after allogeneic HSCT.

Other conditions may coexist in patients with cancer that can lead to peripheral nerve damage. In addition to immune-mediated neuropathies after allogeneic HSCT, toxic neuropathies resulting from direct injury of the PNS by chemotherapeutic agents used for cancer treatment or the conditioning regimen are common. Moreover, immunosuppressive drugs such as cyclosporin, tacrolimus or thalidomide, used for the treatment of chronic GVHD, can induce nerve damage. Most drug-induced toxic neuropathies are axonal, sensory-motor polyneuropathies with a typical dying back pattern. Patients complain of numbness and tingling of the hands and feet. Peripheral nerve toxicity is a dose-dependent phenomenon that should prompt a dose reduction or discontinuation of the drug. In cases of cyclosporin-induced neuropathy, a switch to tacrolimus or another immunosuppressant should be considered. Usually, drug-induced neuropathy improves spontaneously after cessation of the responsible drug.

Other mechanisms have to be considered in the differential diagnosis of peripheral neuropathies in patients after allogeneic HSCT for malignant disorders. Weakness in a nerve root distribution can occur in patients with persistent leukaemia or lymphoma resulting from lymphomatous infiltration of the nerve sheaths or the nerve plexus. Polyradicular syndrome or cauda equina syndrome may occur in the course of the disease, suggesting spinal leptomeningeal metastases or extramedullary cord compression.

**Muscle cramps**

Transient painful contraction of single muscles or muscle groups is a rarely reported, but frequent, complication of chronic GVHD in clinical practice (Filippovich et al., 2005). Muscle cramps seem to be closely associated with moderate and severe chronic GVHD (Mumm et al., 2008). Whether muscle cramps are related to toxicity of long-term immunosuppression or represent an ‘associated’ symptom of chronic GVHD remains to be determined.

True muscle cramps are characterized by rapid onset, visible and palpable contractions, repetitive firing of motor unit action potentials (up to 150/s) on electromyography, and occasionally subsequent soreness, swelling and creatine kinase elevation (Miller and Layzer, 2005). The aetiology of cramps is manifold and includes exercise-induced cramps, lower motor neuron disorders and neuropathy, metabolic disorders, medications and autoimmune mechanisms (Miller and Layzer, 2005).

Generally there is insufficient data from the general condition (unless otherwise stated) and no data from chronic GVHD to draw therapeutic conclusions, thus recommendations are merely expert-based. Usually, cramps are terminated by stretching the affected muscle, and stretching exercises three times daily may also be an effective preventive measure (C-1 III-3a; C III-2b) (Miller and Layzer, 2005; Katzberg et al., 2010). Prophylactic pharmacotherapy aiming to reduce hyperexcitability of peripheral nerves
with channel-blocking agents such as quinine (C-3 III-3a; A Ib), diltiazem (C-2 III-3a; C III-1b), carbamazepine, oxcarbazepine, levetiracetam or gabapentin (all C-2 III-3a) may be tried in patients not responding to magnesium supplementation (C-1 III-3a) (Miller and Layzer, 2005; Couriel et al., 2006; Katzberg et al., 2010). Sometimes muscle relaxation (C-2 III-3a)—for example, with tetracepam, tolperisone or cyclobenzaprine for short-term use and baclofen for longer treatment courses—may be beneficial.

**Myasthenia gravis**

Myasthenia gravis is an antibody-mediated autoimmune disorder of the neuromuscular junction (Meriggioli and Sanders, 2009). It occurs with a frequency of <1% as a late complication ~22–60 months after allogeneic HSCT (Tse et al., 1999). Myasthenia gravis is usually associated with the presence of other manifestations of chronic GVHD and is therefore regarded as an ‘associated’ manifestation of chronic GVHD (Shimoda et al., 1994; Zaja et al., 1995). Occasionally, it may occur without other symptoms of chronic GVHD (Baron et al., 1998). Patients often present with myasthenic symptoms after discontinuation or tapering of their immunosuppressive drugs (Bolger et al., 1986; Dowell et al., 1999). Myasthenia gravis can also be associated with other autoimmune complications after allogeneic HSCT such as glomerulonephritis and polymyositis (Haslam et al., 1993; Tse et al., 1999). Patients with aplastic anaemia prior to allogeneic HSCT seem to have an increased risk for developing myasthenia gravis after transplantation (Nelson and McQuillen, 1988).

The clinical hallmark of myasthenia gravis is fatigable weakness. Patients can have varying degrees of ptosis, diplopia, dysarthria, dysphagia, facial weakness or fatigable limb or axial weakness. Pure ocular weakness is a common initial manifestation of myasthenia gravis, but myasthenia gravis can also present as a generalized disease from the beginning (Grob et al., 2008).

The factors that predispose to the development of myasthenia gravis following allogeneic HSCT are not known. Patients at high risk for developing myasthenia gravis after allogeneic HSCT have been shown to express specific HLAs, particularly HLA-Cw1, HLA-Cw7 and HLA-DR2, whereas idiopathic myasthenia gravis is associated with HLA-DR3, HLA-DQ2 and HLA-B8 (Mackey et al., 1997). There are no reports of thymoma, a common cause of idiopathic myasthenia gravis, in the allogeneic HSCT setting. Although the aetiology is probably different between thymoma-associated myasthenia gravis and myasthenia gravis after allogeneic HSCT, similar mechanisms might lead to an incomplete deletion of ‘self’-specific T cells and an insufficient formation of regulatory T cells. Recently, a complete lack of the autoimmune regulator, a transcription factor that plays a key role in the maintenance of central tolerance and a reduced expression of the transcription factor FoxP3 in intratumoural T cells have been described in patients with thymoma and a GVHD-like enterocolonopathy (Offerhaus et al., 2007).

The most commonly used immunological test for the diagnosis of myasthenia gravis measures the amount of serum antibody that precipitates skeletal muscle acetylcholine receptor. In most cases of myasthenia gravis and chronic GVHD, elevated titres of pathogenic autoantibodies directed towards the acetylcholine receptor can be detected (Shimoda et al., 1994). However, a limiting factor is that these antibodies are usually found with higher frequency in patients with allogeneic HSCT as compared with other autoantibodies and can be recognized early after HSCT in up to 40% of the patients that do not develop clinical evidence of myasthenia gravis (Leffert and Bjorkholm, 1987; Smith et al., 1989). Passive transfer of autoantibodies resulting in myasthenia gravis is rare, because donors with a history of significant autoimmune disorders are generally excluded from donation (Tse et al., 1999). In a few patients, other non-acetylcholine receptor components of the postsynaptic muscle endplate, such as the muscle-specific receptor tyrosine kinase or anti-striated muscle antibodies (e.g. Titin) might serve as targets for autoantibodies (Mackey et al., 1997; Hon et al., 2004; Atassi and Amato, 2008).

The diagnosis of myasthenia gravis is supported by electrophysiological tests. In myasthenia gravis, repetitive nerve stimulation with low frequency (2–5 Hz) produces a progressive decrease in the amplitude or the area under the curve of the compound muscle action potential.

Treatment in patients with myasthenia gravis consists of oral cholinesterase inhibitors that increase the amount of acetylcholine available for binding in the neuromuscular junction, and response to these drugs is also used as a diagnostic criterion. Pyridostigmine bromide is the most commonly used cholinesterase inhibitor (Meriggioli and Sanders, 2009). Most patients with HSCT-related myasthenia gravis have a good symptomatic response to the treatment. If symptoms cannot be adequately controlled by cholinesterase inhibitors, prednisone (A Ib) is generally used to affect disease progression (Schneider-Gold et al., 2005). For long-term immunotherapy of myasthenia gravis, additional steroid-sparing agents like cyclosporin (C-2 IIb) and cyclophosphamide (C-2 IIb) should be given. Other immunosuppressants such as mycophenolate mofetil (C-2 III-1b) and tacrolimus (C-2 III-1b) can be considered as well, although there is no clear evidence from randomized clinical trials of benefit in combination with corticosteroids (Hart et al., 2009). In cases of refractory myasthenia gravis, rituximab (C-2 IIb) may be used (Lebrun et al., 2009).

Although myasthenia gravis is a rare complication after allogeneic HSCT, life-threatening or fatal complications related to the disease or its treatment have been described (Mackey et al., 1997; Koski et al., 1998). Myasthenic symptoms usually aggravate during acute infections and with certain medication (e.g. aminoglycosides, fluoroquinolones, beta blockers, neuromuscular blocking agents), requiring special attention. For short-term treatment of myasthenia gravis exacerbations (e.g. myasthenic crisis) intravenous gammaglobulin (A Ib) (Gajdos et al., 2008) has been established to achieve a rapid clinical response. Many case series studies also report short-term benefit from plasma exchange (C-1 III-1b) in myasthenia gravis, especially in myasthenic crisis (Gajdos et al., 2002).

Although not yet described as a complication of chronic GVHD, Lambert-Eaton myasthenic syndrome has to be considered as a differential diagnosis in patients with allogeneic HSCT presenting with proximal weakness and usually autonomic disturbances. Diagnosis is supported by electrophysiological studies demonstrating an increase in compound muscle action potential.
amplitude >100% in a distal muscle after high-rate repetitive nerve stimulation (>10 Hz) or 10 s of maximal voluntary contraction. The laboratory diagnosis of Lambert-Eaton myasthenic syndrome depends primarily on detection of specific anti-voltage-gated calcium channel antibodies that are responsible for this presynaptic neuromuscular transmission disorder.

Central nervous system manifestations of chronic graft-versus-host disease

General considerations

Involvement of the CNS is less common than lesions to the PNS and only a few cases have been reported (Openshaw, 2009). Therefore, it is important to distinguish common neurological complications of HSCT (Padovan et al., 1998; Barba et al., 2009), e.g. drug-associated side effects, from the rare chronic GVHD of the CNS. The latter affects the brain or spinal cord and results from cerebral vasculitis, demyelination or diffuse infiltration of inflammatory cells. It is not known whether these manifestations reflect different aetiologies or are various clinicopathological presentations of an underlying common immune-mediated mechanism.

Owing to its rarity, no controlled studies investigating the incidence and time course of chronic GVHD of the CNS exist. In a review combining 18 cases, median age was 32 years without gender bias and onset after HSCT was 2–31 months (Kamble et al., 2007; Openshaw, 2009). Patients may present with stroke-like episodes (Padovan et al., 1999; Campbell and Morris, 2005), seizures and encephalopathy (Kamble et al., 2007), myelopathy (Openshaw et al., 1995), optic neuritis (Openshaw et al., 1995; Matsuo et al., 2009) or other focal neurological deficits. Often symptoms occur during or after a tapering of immunosuppressive therapy (Openshaw et al., 1995; Shortt et al., 2006; Matsuo et al., 2009; Sostak et al., 2010).

There is a long-standing debate about whether CNS manifestations of chronic GVHD are a clinical entity on their own or merely result from complications of the many procedures and therapies in the course of HSCT (Rouah et al., 1988; Openshaw, 2009). Hence, CNS manifestations were not included in the 2005 National Institutes of Health Consensus Criteria for Chronic GVHD (Filipovich et al., 2005), and it is controversial whether they represent an ‘associated feature’ of chronic GVHD or not.

Recently, Openshaw (2009) described diagnostic criteria for chronic GVHD of the CNS and suggested that all six criteria must be fulfilled to make the definite diagnosis. Since some CNS manifestations, such as limbic encephalitis mediated by antineuronal antibodies (Kishi et al., 2004), may lack abnormalities on brain MRI, CSF studies or standard brain histology, we suggest that pathological findings in these procedures are only facultative criteria. Likewise, response to immunosuppressive therapy is indicative of chronic GVHD of the CNS, but its absence cannot disprove involvement of the CNS. Therefore, we propose that for clinical purposes, the diagnosis of ‘possible’ chronic GVHD of the CNS can be made when both mandatory and at least two facultative criteria are met (Table 4).

Cerebrovascular disease

Various cerebrovascular complications associated with chronic GVHD have been described, presenting as large or small vessel disease (Padovan et al., 1999; Ma et al., 2002; Campbell and Morris, 2005). Histopathologically, multifocal inflammatory peri-vascular lesions, in particular around small to medium-small arteries in the meninges and the parenchyma, were found in some patients (Padovan et al., 1999; Ma et al., 2002; Sostak et al., 2010). The infiltrating cells mainly consisted of CD3+ and CD8+ cytotoxic T cells and, to a lesser degree, CD68+ monocytes/macrophages, partially expressing cell adhesion molecules such as chemokine receptor-5 (CCR5) and CD11a (Sostak et al., 2010). Donor origin of infiltrating cells was demonstrated in two patients (Ma et al., 2002; Sostak et al., 2010). Sometimes perivascular lymphomonocytic cuffs occurred together with focal demyelination (Padovan et al., 1999; Sostak et al., 2010), and there is a striking histological similarity to perivenous demyelination, as seen in acute demyelinating encephalomyelitis (Young et al., 2010). Further support for the existence of a cerebral manifestation of chronic GVHD comes from an experimental mouse model, which demonstrated parenchymal lymphocytic inflammation, microglia activation and mild cerebral angiitis after allogeneic HSCT (Padovan et al., 2001). However, while 29 of 109 consecutive post-mortem brain examinations from patients with HSCT showed cerebrovascular lesions, including haematomas, haemorrhagic necrosis and ischaemic infarcts, only two cases of CNS vasculitis were found (Mohrmann et al., 1990).

Clinically, patients with large to medium vessel vasculitis may present with hemiparesis, aphasia or other focal neurological signs in cases of ischaemic or haemorrhagic stroke. Small vessel cerebral vasculitis is characterized by multifocal symptoms such as headache, cognitive impairment and seizures and typically has a relapsing progressive course. Additionally, the clinical presentation of small vessel vasculitis in children frequently includes the systemic

<table>
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<tr>
<td>1. Occurrence with chronic GVHD affecting other organs</td>
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<tr>
<td>2. Neurological signs of CNS involvement without other explanation</td>
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<tr>
<td>3. Corresponding brain MRI abnormality</td>
</tr>
<tr>
<td>4. Abnormal CSF studies (pleocytosis, elevated protein or immunoglobulin G, oligoclonal bands)</td>
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<tr>
<td>5. Pathological brain biopsy or post-mortem examination</td>
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<td>6. Response to immunosuppressive therapy</td>
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Source: Adapted from Openshaw (2009).

1 and 2 are mandatory, 3–6 are facultative criteria. To make the definite diagnosis of chronic GVHD of the CNS, all six criteria must be met; for a ‘possible’ chronic GVHD of the CNS, both mandatory and at least two facultative criteria have to be met.
features fever, malaise or flu-like symptoms (Elbers and Benseler, 2008).

When a cerebrovascular event is suspected, immediate CT to exclude cerebral haemorrhage and subsequent diffusion-weighted MRI to detect ischaemia are mandatory. Large vessel stenosis or occlusion should be ruled out by either CT/magnetic resonance angiography or by ultrasound of extra- and intracranial arteries. For cerebral vasculitis, further tests to detect encephalopathy and the inflammatory vasculopathy are needed. These include EEG, neuropsychological testing, CSF analysis (including culture and serology), gadolinium enhanced MRI and angiography. MRI frequently shows multifocal or confluent white matter signal changes and ischaemic lesions of different age and also occasionally small haemorrhages (Padovan et al., 1999). Angiography often remains negative (Padovan et al., 1999; Benseler et al., 2005; Openshaw, 2009). Brain biopsy may be required to ultimately confirm vasculitis; however, its sensitivity is probably not >50% (Birnbaum and Hellmann, 2009). To optimize the diagnostic yield, lesional biopsies including both white and grey matter, as well as leptomeninges, should be taken.

Treatment of biopsy-confirmed cerebral vasculitis consists of corticosteroids (1 mg/kg prednisone) (C-1 III-2a), usually in combination with cyclophosphamide (C-2 III-2a), for 3–6 months until induction of remission (Padovan et al., 1999; Birnbaum and Hellmann, 2009; Sostak et al., 2010). Since cyclophosphamide can have severe side effects, rituximab (C-2 III-3a) may be an additional option (Cutler et al., 2006; Jones et al., 2009). The induction phase with corticosteroids and cyclophosphamide is commonly followed by maintenance treatment with oral mycophenolate mofetil (preferred in children), methotrexate or azathioprine (all C-2 III-3b) (Elbers and Benseler, 2008; Birnbaum and Hellmann, 2009). Importantly, occupational and physical therapies should be given.

The differential diagnosis of immune-mediated cerebral vasculitis includes, but is not limited to, reversible vasoconstriction syndrome and evoked inflammatory, infectious, post-infectious, paraneoplastic and drug-induced aetiologies. Moreover, immunosuppressive drugs such as tacrolimus can induce angiitis (Pizzolato et al., 1998). White matter lesions are a common finding after HSCT, occurring in ~50% of patients (Sostak et al., 2003; Siegal et al., 2007). Often the exact reasons are unknown, but damage through a combination of mechanisms involving microvascular dysfunction (e.g. post-transplant microangiopathy), irradiation, chemotherapy-induced toxicity from systemic or intrathecal application and neurotoxicity from calcineurin inhibitors has to be considered. The latter can accumulate in the posterior reversible encephalopathy syndrome, which should lead to prompt cessation of the calcineurin inhibitor. Calcineurin inhibitor drug levels should be routinely monitored (Couriel et al., 2006). Moreover, cognitive deficits are associated with previous calcineurin inhibitor and intrathecal methotrexate treatment; therefore, follow-up neuropsychological testing could be considered every 12 months (Couriel et al., 2006). In some patients with cognitive deficits impeding work or daily activities, referral for neuropsychological evaluation and subsequent rehabilitation is needed.

### Demyelinating disease of the central nervous system

Demyelination is caused by myelin-specific antibodies or T lymphocytes, which coordinate an immune-mediated attack against the myelin sheath or by non-immune mechanisms such as infectious and toxic agents, various drugs and biochemical or genetic alterations.

During chronic GVHD, demyelination was reported to occur in single cases affecting the optic nerve with or without the spinal cord (Openshaw et al., 1995; Matsuo et al., 2009; Sostak et al., 2010), the cerebral white matter (Matsuo et al., 2009), the spinal cord (Sakai et al., 2006; Matsuo et al., 2009) or simultaneously the CNS and PNS (Solaro et al., 2001).

To our knowledge, no histology is available from patients with demyelinating chronic GVHD of the CNS. Some cases with predominating angiitis additionally showed sporadic focal demyelination and microglial activation in the white matter (Padovan et al., 1999; Sostak et al., 2010). Recently, in a report of histopathological findings of patients with multiple sclerosis who had allogeneic HSCT for co-incident haematopoietic malignancy, Lu et al. (2010) surprisingly found an increase in diffusely infiltrating CD3+ and CD8+ cytotoxic T cells and CD68+ microglia/macrophages in control allogeneic HSCT brains as well as multiple sclerosis brains. However, there was no indication of demyelination or other tissue damage in the non-multiple sclerosis brains.

Typically, demyelination during chronic GVHD takes a relapsing-remitting course similar to multiple sclerosis (Openshaw et al., 1995; Solaro et al., 2001; Sakai et al., 2006; Matsuo et al., 2009). The diagnosis is based on the demonstration of white matter lesions in the CNS with gadolinium enhancement during active disease and an inflammatory CSF with one or more of the following findings: mild pleocytosis, mild protein elevation, immunoglobulin G elevation and oligoclonal bands. The registration of evoked potentials (visual, somatosensory, acoustic) and transcranial magnetic stimulation can help to verify central nerve conduction slowing, a sign of demyelination. Brain biopsy is usually not necessary, since the symptoms rapidly improve on steroid therapy, which further supports the diagnosis of CNS demyelination.

Distinction of chronic GVHD-related CNS demyelination from other immune-mediated demyelinating disorders, such as multiple sclerosis or acute disseminated encephalomyelitis by clinical findings may be impossible. Hence, the diagnosis should be considered only when additional systemic signs of chronic GVHD are present. If recurrent optic neuritis and myelopathy are the only findings, neuromyelitis optica should be considered as a differential diagnosis by investigation of serum anti-aquaporin-4 antibodies.

In children, the diagnosis of chronic GVHD of the CNS with or without demyelination should be considered with even greater caution, since (i) the developing CNS in childhood is particularly vulnerable to myeloablative therapy; (ii) viral infections or reactivation of common viruses appear to be more frequent in paediatric patients than in adults; and (iii) in children transplanted for neurometabolic diseases, CNS processes may be difficult to distinguish from progression of the underlying disease.
CNS demyelination should be treated with a corticosteroid pulse (e.g. intravenous methylprednisolone 1 g for 3–5 days) (C-1 III-3a) under gastric ulcer and thrombosis prophylaxis (Matsuo et al., 2009; Sostak et al., 2010). In the absence of remission, the corticosteroid pulse can be repeated (C-2 III-3a) or plasma exchange (five times) (C-2 III-3a) applied (Openshaw et al., 1995; Soloro et al., 2001). In progressive cases, an increase of immunosuppressive therapy (C-2) or rituximab (C-3) may be beneficial.

Immune-mediated encephalitis

Immune-mediated encephalitis is a heterogeneous group of disorders characterized by pathological infiltration of immune cells or humoral factors, in particular antibodies, in the CNS tissue, causing functional and neuropsychological deficits.

Several post-mortem studies investigated immune-mediated encephalitis during chronic GVHD, which was characterized by perivascular and parenchymal infiltration of lymphocytes, widespread activation of microglia with HLA-DR expression and diffuse degeneration of the white matter (Marosi et al., 1990; Iwasaki et al., 1993; Saad et al., 2009). In a case with a solitary white matter lesion, infiltration of CD4+ T cells of donor origin was found (Kamble et al., 2007). Perivascular and parenchymal infiltration of cytotoxic CD8+ T cells was shown in two other patients (Kamble et al., 2007; Saad et al., 2009).

The clinical presentation consists of signs of encephalopathy such as altered level of consciousness, neuropsychological deficits, focal neurological deficits and seizures (Marosi et al., 1990; Iwasaki et al., 1993; Shortt et al., 2006; Saad et al., 2009). MRI showed diffuse or focal white matter abnormalities and the CSF signs of inflammation in the few available cases (Shortt et al., 2006; Kamble et al., 2007; Saad et al., 2009). Therapy has been reported for three patients, with nearly complete response upon corticosteroid pulses (C-1 III-3a) in two of them (Shortt et al., 2006; Kamble et al., 2007; Saad et al., 2009).

Obviously, opportunistic infections should be excluded on the basis of CSF cell count, serology, culture and polymerase chain reaction for viral, bacterial or fungal DNA. Common infections include herpes simplex virus, varicella zoster virus, cytomegalovirus, human herpes virus-6, Epstein–Barr virus, JC virus and toxoplasmosis. Long-term antiviral prophylaxis to prevent herpes simplex virus and varicella zoster virus infection should be considered in patients with chronic GVHD while on immunosuppressive drugs, and at least post-exposition therapy should be given (Gea-Banacloche and Boeckh, 2009). Epstein–Barr virus–related post-transplant lymphoproliferative disorders may show similar clinical and imaging features as chronic GVHD of the CNS and can be distinguished by histology, which usually shows predominant B cell infiltration and Epstein–Barr virus infection (Novoa-Takara et al., 2005). A distinct neurological syndrome consisting of anterograde amnesia, inappropriate antiidiuretic hormone secretion and EEG abnormalities, and termed post-transplant acute limbic encephalitis, has been observed in some patients with human herpes virus-6 reactivation in the CSF (Seeley et al., 2007). Sometimes, when clinical presentation and MRI are highly suspicious of an infection, but serology and polymerase chain reaction from CSF remain negative, biopsy of the lesion is required. This particularly holds true for chronic fungal and viral infections, such as progressive multifocal leukoencephalopathy (Kharfan-Dabaja et al., 2007). Finally, relapse of the neoplastic process should be considered and ruled out by biopsy.

Conclusions

Neurological manifestations of chronic GVHD are rare, especially in paediatric patients, but can have a major impact on the disease course and survival after allogeneic HSCT. Early recognition of neurological complications is of high importance for appropriate treatment and avoidance of potentially life-threatening events.

Considering the complex differential diagnosis of neurological manifestations of chronic GVHD, referral to an experienced neurologist is recommended. In addition, it may be beneficial for high-risk patients, defined as those with pre-existing neurological disorders, intense prior neurotoxic treatment such as intrathecal chemotherapy, irradiation of the CNS or both, and disorders with increased risk for neurotoxicity like long-lasting diabetes, to undergo neurological evaluation prior to allogeneic HSCT, including patient history, complete physical examination and laboratory parameters (Table 5). Baseline clinical and electrophysiological tests are particularly helpful in patients with pre-existing polyneuropathy to determine the degree of nerve damage before allogeneic HSCT and to recognize changes in the pathological pattern during the treatment course. To assess possible CNS complications after allogeneic HSCT, baseline cerebral MRI including T1/T2-weighted images, fluid attenuated inversion recovery sequences and a time of flight magnetic resonance imaging should be performed (Openshaw et al., 1995). In progressive cases and with lack of complete response to corticosteroid pulse (C-1 III-3a) or rituximab (C-3), plasma exchange (five times) (C-2 III-3a) may be beneficial.

Table 5 Diagnostic workup of patients with suspected chronic GVHD of the nervous system

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angiography may also be considered. This is of special importance in patients with prior radiotherapy, local chemotherapy in the CSF or history of infectious CNS complications. Cerebral imaging prior to allogeneic HSCT may help to define whether chronic GVHD of the CNS is a real entity or not.

To ensure optimal care of patients with neurological chronic GVHD-related diseases, a close collaboration between haematologists, radiologists, neurologists, neurophysiologists and physiotherapists is important. Moreover, more effort is needed for research on pathophysiology and risk factors of neurological complications in chronic GVHD.

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References


