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Cyclosporine neurotoxicity: a review

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Cyclosporin A (CsA) induces neurological side effects in up to 40% of patients. A reversible posterior leukoencephalopathy syndrome is the most serious complication. Symptoms include headache, altered mental functioning, seizures, cortical blindness, and other visual disturbances, with hypertension. Neuroimaging studies show white matter changes in the posterior regions of the brain. Other neurological side effects of CsA include tremor, diffuse encephalopathy, cerebellar syndrome, extrapyramidal syndrome, pyramidal weakness, and peripheral neuropathy. Hypertension, hypomagnesemia, hypocholesteremia, and the vasoactive agent endothelin may all play a role in the pathogenesis of CsA neurotoxicty. Neurotoxicity is more frequent with high CsA blood levels, but levels may be within the therapeutic range. Dose reduction or withdrawal of CsA usually results in resolution of clinical symptoms and of neuroimaging abnormalities.

Key words Cyclosporine neurotoxicity · Reversible posterior leukoencephalopathy · Hypomagnesemia · Hypocholesterolemia · Endothelin

Introduction

Cyclosporine (CsA), a lipophilic, cyclic oligopeptide that modulates T-cell function, is a potent immunosuppressive agent. The use of CsA is associated with numerous side effects. Nephrotoxicity and hypertension are the most common, but hepatotoxicity, gingival hyperplasia, hypertrichosis, opportunistic infections, and B-cell lymphomas related to Epstein-Barr virus infection are also observed [21, 22, 31, 69]. Neurotoxicity was earlier less well-known, but with growing experience central nervous system side effects are now reported in up to 40% of patients [22, 31, 47, 52, 69, 71]. The most frequent neurological complication is tremor, which develops in 20–40% of patients treated with CsA. In a minority of transplanted patients severe and sometimes life-threatening toxicity occurs. Recent series state that one in ten patients treated with CsA experiences a CsA-related neurological complication requiring dose adaptation [39, 50, 71]. This paper reviews the incidence and spectrum of clinical manifestations of CsA neurotoxicity, together with potential mechanisms of toxicity and therapeutic implications.

Cyclosporine: the drug

CsA together with FK 506 (tacrolimus) and rapamycin belong to a new class of immunosuppressant drugs. The underlying molecular mechanism is based on binding of CsA to cyclophilin and of FK 506 and rapamycin to FK 506-binding proteins (FKBP), and together these proteins are characterized as the immunophilins [56, 57]. Drug-immunophilin binding results in the inhibition of the calcium-calmodulin activated phosphatase calcineurin. There is a close correlation between the degree of calcineurin inhibition and immunosuppressive activity. Calcineurin is widely distributed through the nervous system, and its distribution parallels that of FKBP and cyclophilin, and the amount of these immunophilins far exceeds that in the

immune system. Experimentally calcineurin inhibition leads to neuroprotective effects, including nitric oxide synthase blocking activity, blocking K^+-induced neurotransmitter release and NMDA-induced release of glutamate. In contrast, CsA and FK 506 greatly induce the release of these neurotransmitters at low concentrations [57].

Also, CsA protects mitochondria and neurons against hypoglycemic damage. These and other observations may help to explain that these agents may also have neuroprotective effects including regulation of nitric oxide regulation, neurotransmitter release, and neurotrophic effects. Most clinical experience with these immunosuppressive drugs so far is related to CsA, wich now belongs to the standard repertoire following transplantation of bone marrow (BMT) and other organs. It is administered broadly for the prevention of graft rejection of solid organ transplants, for BMT, and in various disorders involving the immune system.

The predominant effect of CsA on the immune system is inhibition of T-cell proliferation. It reversibly inhibits the activation of the primary T-helper cell and the subsequent release of many of its lymphokines, including interleukin-2. In contrast to these inhibitory effects, CsA spares T-suppressor lymphocytes. Thus, CsA causes immunosuppression by inhibition of helper-inducer and cytotoxic T-cell activities and promotion of suppressor cell function. T-cell independent, antibody-mediated immunity is spared [31]. It causes no myelosuppression.

In blood CsA is bound to cells and lipoproteins. Some 40–60% is bound to erythrocytes and leukocytes, the remaining part to cholesterol-containing lipoproteins, that is, high-density and low-density (LDL) lipoproteins. Less than 5% of CsA is present as free drug in plasma; this proportion is not correlated with the total blood level or with toxic effects. Because lipoproteins serve as a reservoir for CsA, lipid binding buffers its effects [21, 22, 31].

CsA is metabolized by isoenzymes of the hepatic cytochrome P-450 enzyme system [31]. The metabolites of CsA show substantially less immunosuppressive activity than the native drug, but they have toxic effects. Coadministration of drugs that interact with the cytochrome P-450 system affect CsA metabolism. Inhibitors of cytochrome P-450 such as ketoconazole, erythromycin, oral contraceptives, and methylprednisolone increase CsA levels. CsA levels are decreased by inducers of the system, for instance, phenytoin, carbamazepine, valproate, and rifampicin [22, 31].

Regular measurements of CsA concentrations in blood are essential to optimize immunosuppressive therapy. The therapeutic range of the concentration depends on the assay used. Unfortunately, neurotoxicity due to CsA can occur at normal and at high drug levels.

Clinical manifestations of cyclosporine neurotoxicity

A wide range of CsA-related neurological side effects have been reported with all kinds of transplantation and with primary immune-related disorders. Extensive experience has been obtained from studies in BMT and liver transplant recipients [20, 51, 71]. Recent trials on CsA and FK 506 provide prospective data on CsA neurotoxicity [36, 39, 49, 50].

Most of the neurological side effects of CsA concern the central nervous system, but peripheral nerves may also be affected. Less serious effects consist of tremors, agitation, insomnia, anxiety, amnesia, headache, and dysesthesia. More severe complications include confusion, disorientation, decreased responsiveness, hallucinations, delusions, seizures, cortical blindness, pyramidal motor weakness, aphasia, and ataxia.

Tremor

Postural tremor is reported in up to 40% of patients. This tremor is often mild and generalized, developing shortly after CsA therapy is initiated [31, 36, 44, 47, 49]. Intention tremor, as part of a cerebellar syndrome is less frequent [2, 59, 66]. A review of data collected on 3000 kidney transplant recipients and nearly 800 BMT patients, and a study of nearly 400 liver transplant patients revealed the incidence of tremor to be 12–21% [44, 71]. Tremor is more frequent with high CsA levels, but normal blood levels do not preclude the presence of tremor. Metabolic disturbances, especially with liver failure following liver transplant may aggravate the tremor. Since the tremor is usually mild, dose reduction is not always required.

Posterior leukoencephalopathy

CsA causes a reversible syndrome of headache, altered mental functioning, seizures, and cortical blindness associated with findings on imaging studies indicating leukoencephalopathy predominantly in the posterior regions of the cerebral hemispheres [16, 23, 27, 33, 52, 54, 55, 60, 62, 67, 72]. Most of the patients with this syndrome are hypertensive, and in more than half CsA levels are high. Low cholesterol and magnesium levels are found in over 50% of patients. The interval between the start of CsA therapy and the first symptoms averages 14 days. Hinchey et al. [26] proposed calling this syndrome “reversible posterior leukoencephalopathy (PLE).” PLE is also found in patients with acute hypertensive encephalopathy, eclampsia, and various kinds of immunosuppressive therapy. Hypertension is an important factor in the development of PLE. Clinical findings in the 15 patients of Hinchey et al. included headache, vomiting, confusion, lethargy, seizures, cortical blindness, and other visual disturbances such as homonymous hemianopia, blurred vision, and visual neglect. Hemiparesis formed part of the syndrome in five patients. Computed tomography (CT) and magnetic resonance imaging (MRI) show multifocal,

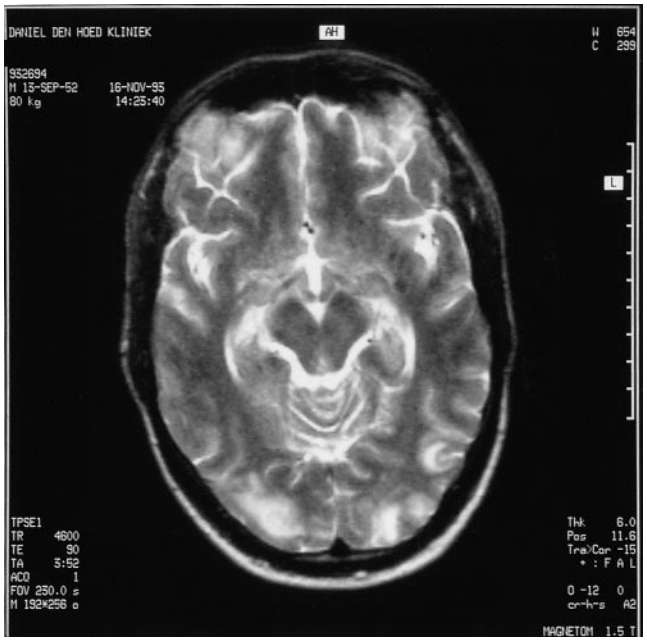

Fig. 1 Axial section of T2-weighted MRI of the head in a 40-year-old man with cortical blindness, headache, hypertension, and hypomagnesemia while treated with CsA after allogenic BMT. Hyperintense signals are located in both occipital regions

bilateral white matter abnormalities, mostly in the parieto-occipital lobes but also in the temporal lobes, pons, thalamus, and cerebellum (Fig. 1). Treatment with antihypertensive agents or reduction or withdrawal of CsA has been reported to lead to resolution of neurological signs and neuroimaging abnormalities within weeks in all patients [26].

Encephalopathy

A mild encephalopathy due to CsA is reported in up to 30% of patients [23, 49, 50]. The conditioning regimen of transplantation, the operation procedure, metabolic disturbances and infections may all contribute to the development of encephalopathy [50, 51, 68]. Confusion and disorientation are often the first symptoms of PLE, but they are also reported without other features of PLE. Agitation, anxiety and insomnia are less serious frequently observed side effects of CsA. Relief of symptoms following cessation or reduction in dose indicates that CsA is an important factor. In mild encephalopathy dose reduction is not always needed as in most patients the complaints resolve spontaneously. Severe encephalopathy and coma are less frequent symptoms of PLE [7, 66]. Most cases involved heart or renal transplants, with high CsA levels and diffuse white matter changes. Consciousness returned within 24 h after cessation of CsA [7].

Headache

An intermittent, mild and diffuse headache without other signs of PLE is seen in up to 37% of patients on CsA [49, 52, 64]. Severe headache and migraine with or without aura are less frequent [18, 53, 59, 60]. Few patients before transplantation had migraine or a positive family history for migraine. The headache seems dose related, and reduction in CsA dose brings relief in the majority of patients. Others find relief of migraine with sumatriptan, while simple analgesia is often ineffective. The vasoactive properties of CsA may explain the headache [53, 59].

Seizures

Large series reported an incidence of CsA-related seizures of 1.5–6% [1, 5, 13, 30, 44, 61, 70]. Seizures are also frequent in PLE [26, 30, 67]. One author saw CsA-related seizures only in association with low magnesium levels, and correcting the hypomagnesemia controlled the seizures [61]. Interestingly, magnesium sulfate is widely used to prevent eclamptic seizures in pregnant woman with hypertension [35]. Others did not found an association between seizures and hypomagnesemia [33, 68, 70, 71]. Generalized tonic-clonic seizures often occur with high CsA levels. Most patients suffer a single seizure, without recurrence after dose reduction [12]. Focal seizures and complex partial seizures are less frequent, mostly in association with focal deficits such as hemiparesis [11, 23, 61, 65].

Status epilepticus is rare [33]. Appleton [1] described two renal transplant patients and one BMT patient with a complex partial status epilepticus consisting of confusion, regressive behavior, stupor, and focal motor seizure activity. The transplanted patient is at risk of developing seizures due to a number of factors, metabolic disturbances being the most important. Hyponatremia, hypocalcemia, and hypoglycemia are frequently observed and are considered to contribute to the development of seizures [1, 23]. Infections, graft rejection and its treatment with steroids, and pretransplant (hepatic) encephalopathy are cofactors in CsA-associated seizures. For these reasons liver transplant patients are particularly at risk [12, 51, 68, 70]. BMT has often been treated by intrathecal chemotherapy and total body irradiation as part of the conditioning regimen which lowers the seizure threshold [17, 20, 52]. In the individual patient the role of CsA is not easily determined, but must always be considered together with other predisposing factors.

Visual hallucinations and delusions

Visual hallucinations, delusions and memory deficits occur with or without other features of PLE [46, 60]. Complex

visual hallucinations have been observed both with normal and high levels and subsided after reduction or withdrawal of CsA [40, 58]. Abnormalities on CT or MRI are not seen.

Cerebellar syndrome

CsA-related dysarthria and cerebellar ataxia have been reported [2, 6, 42, 61, 68]. PLE with white matter changes predominantly in the cerebellar lobes seems a rare neurological complication of CsA therapy [4, 6, 42]. Most patients have undergone BMT or liver transplantation. The interval between the start of CsA therapy and the first symptoms is relatively long, in only two patients within 1 week while in all the others symptoms developed after 1–6 months of CsA treatment. Symptoms consisted of ataxia, tremor, and dysarthria with additional symptoms of seizures, confusion, depression, paraparesis, corticospinal tract signs, dysphagia, or polyneuropathy. One study described a case of acute cerebellar edema and brainstem compression requiring bilateral decompressive suboccipital craniectomy [42]. CsA levels are normal in all cases; low magnesium levels have been reported only by Thompson et al. [61]. Blood pressure has been mentioned only in a single case [68].

Extrapyramidal syndrome

A syndrome of subacute onset of dysarthria leading to mutism with normal oral and written comprehension is another rare complication of CsA. This developed in four liver transplant patients 4–9 days after starting CsA therapy [65]. Additional symptoms and signs were hypokinesia, severe dysphagia, and orolingual apraxia. MRI showed no abnormalities. The syndrome was reversible in all after withdrawal of CsA, although mild dysarthria remained for several months. Bird et al. [9] described three patients with a similar syndrome, one with severe orofacial dyskinesia. After improvement of mutism, two patients developed features of pseudobulbar palsy with severe dysarthria, dysphagia, and mild cerebellar ataxia. MRI revealed white matter lesions in the pons, with and without lesions elsewhere. The pontine lesions resemble those seen in PLE [9, 15]. Speech apraxia and an action myoclonus type of speech, with normal language function was seen in 3 of 46 patients with CsA neurotoxicity in one series of 430 consecutive liver transplant patients [71].

Pyramidal weakness

Hemi-, para-, and tetraparesis is generally seen in association with other signs and symptoms of PLE [16, 23, 46]. Eight patients have been reported to have developed pyramidal weakness between 13 days and 8 months after starting CsA [2, 28, 33, 34, 66]; three had a hemiparesis, two a paraparesis, and three a quadriparesis. Lane et al. [33] described a cardiac transplant patient who developed a paraparesis after doubling the CsA dose for chronic graft rejection. Levels were just above upper limits; after withdrawal a slow but complete recovery occurred.

Peripheral neuropathy

Burning palmar and plantar paresthesias are often reported, although the incidence is not well known [39, 49, 70, 69]. McDiarmid et al. [36] found an incidence of 20%. A more serious motor polyneuropathy with acute areflexic tetraparesis was observed by Guarino et al. [24] in 4 of 19 patients after liver transplantation. Two patients underwent electromyography which revealed demyelinating and axonal damage, confirmed by sural nerve biopsy. Plasma levels of CsA were high when symptoms developed. After cessation of CsA all patients recovered within 2 months. A case of polyneuropathy has been reported with facial weakness resembling Guillain-Barré syndrome which resolved within 3 weeks after withdrawal of CsA [46]. CSF examination was normal; electromyography showed an axonal neuropathy. Groen et al. [23] described a reversible polyneuropathy together with seizures and cortical blindness following liver transplantation.

Miscellaneous

Asymptomatic optic disc edema and elevated intracranial pressure, resolving after discontinuation or lowering of the CsA dose, has been reported in six allogenic BMT patients [3]. O'Riordan found an ischemic retinopathy with multiple cotton wool spots, macular stars, and retinal edema in three patients after allogenic BMT, all with impaired visual function [43]. Ischemic lesions of the optic disc were found in 13 of 127 BMT patients, all treated with total body irradiation as part of the conditioning regimen and with CsA to prevent graft-versus-host disease. Ten patients had decreased visual acuity; symptoms were reversible in nine [8]. Ischemic disc lesions were observed only in patients who received allogenic BMT. The conditioning regimen with total body irradiation might have been an important causative cofactor, although a similar retinopathy developed with busulfan without total body irradiation as conditioning therapy [8, 43].

Laboratory findings

Cerebrospinal fluid (CSF) analysis is normal in most patients [13, 19, 27, 28, 42, 52], but in some an elevated protein concentration is present [2, 5, 33, 40]. Pleiocytosis is rare and suggests another diagnosis [2, 5, 46, 54].

Electroencephalographic findings are not specific. Most commonly reported are diffuse and focal slowing [1, 16, 23, 46, 52, 54] and epileptiform discharges [1, 2, 38, 60].

Neuroimaging

In patients with signs of encephalopathy CT and MRI may show typical abnormalities. On CT nonenhancing areas of hypodensity are seen predominantly in the white matter of the occipital regions [1, 6, 7, 11, 23, 28, 52, 64]. MRI is more sensitive and demonstrates decreased signals on T1-weighted and hyperintense signals on T2weighted images in the same areas [6, 15, 29, 45, 52, 55, 64]. This explains the term for the CsA-related syndrome PLE. However, extension into the parietal areas is common. White matter lesions in the temporal and frontal lobes or in the cerebellum and pons are less frequent [4, 6, 9, 15, 42]. Contrast enhancement or blood may be seen in the involved areas. Cortical involvement is sometimes observed as well. Jansen et al. [29] recently described the MRI of six patients with hyperintensity of several cortical gyri on proton density weighted images, resembling changes resulting from cortical hypoperfusion. There is not a good correlation between the findings on neuroimaging and clinical symptoms. Similar reversible white matter changes, consistent with brain edema, are seen in hypertensive encephalopathy and eclampsia. Severe CsA neurotoxicity has been reported with normal CT or MRI [5, 16, 33, 60, 61].

Risk factors for developing cyclosporine neurotoxicity

Transplant patients are at risk for neurological complications regardless of whether they receive CsA [20, 39, 47, 50, 70]. Intensive pretransplant chemotherapy, intrathecal chemotherapy, total body irradiation, drug interactions, metabolic disturbances, and graft malfunctioning may all have synergistic toxic effects [17, 32, 31, 52, 68]. Methylprednisolone [13, 32, 52] hypertension and fluid overload [5, 16, 30, 46], hypocholesterolemia [9, 11, 21, 52], hypomagnesemia [61], and aluminum overload in renal transplant patients [60, 63, 69] are other risk factors for CsA neurotoxicity. Drugs that interfere with CsA metabolism may cause toxic levels of CsA or its metabolites [22].

Mechanisms of cyclosporine neurotoxicity

Autopsy studies

Few postmortem examinations have been carried out in patients who died with presumed CsA-related neurotoxicity. No specific histological substrate is known. Ischemic infarctions, edema, reactive astrocytosis, neuronal loss, hemorrhagic foci, diffuse neuronal damage, and demyelinization are nonspecific features [34, 52, 66]. One report described diffuse myelin and axonal loss throughout the entire spinal cord sparing the anterior horn cells in a patient who died with paraplegia. The brain was normal [34]. Experimentally it has been observed in cortical cultures that CsA may induce neuronal apoptosis and selective oligodendrocyte death [37].

Adrenergic receptors

In CsA neurotoxicity predominantly the posterior regions of the brain are involved. The reason for this site of predilection is not clear. A relationship with the regional density of adrenergic receptors on intracranial vessels has been suggested by Schwartz et al. [55]. Perivascular sympathetic nerves are stimulated by hypertension, resulting in increased vascular resistance protecting the brain from marked increases in intravascular pressure. Because the vertebrobasilar system and its branches have little sympathetic innervation, increased perfusion and disturbance of autoregulation may lead to edema in this territory.

Endothelin

A recent hypothesis is that CsA causes ischemic disturbances in the brain by endothelial damage and vasoconstriction [32, 48, 52, 64, 67]. Nephrotoxicity with increased serum creatinine concentrations, fluid overload, and hypertension are the most common CsA-related complications. One postulated mechanism is that CsA alters the balance of the vasodilator prostacyclin and its vasoconstrictor antagonist tromboxane A in renal tissue, leading to renal vasoconstriction and intima proliferation [10, 22, 31]. Other proposed mechanisms include enhanced sympathetic tone and activation of the renin-angiotensin system. The possible role of the potent endothelial cell-derived vasoconstrictor endothelin-1 has recently drawn interest [10, 67]. CsA damages endothelial cells, with a subsequent release of vasoactive agents such as endothelin-1 [10, 25]. Release of other substances may also play a role in the vasoconstructive properties of CsA. Endothelin-1 causes similar vasoconstriction and vasospasm in cerebral vessels, initiating mild, reversible ischemia and white matter edema [64, 67]. Specific binding sites for endothelin have been identified in several areas of the human brain, including the cerebellum, hippocampal formation, diencephalon, and choroid plexus [64].

Thrombotic microanglopathy

Endothelial damage can also cause hemolysis, thrombosis, and local ischemia [48]. Allogenic BMT may lead to

thrombotic microangiopathy [73]. This syndrome consist of intravascular hemolysis with massive red cell fragmentation and elevated lactate dehydrogenase, platelet aggregation with thrombocytopenia, renal insufficiency, hypertension, and neurological complications due to cerebral edema and ischemia [32, 48, 52, 55, 73]. CsA-induced endothelial damage has been related to BMT-induced thrombotic microangiopathy. Other predisposing factors are HLA-mismatched grafts, total body irradiation, conditioning with chemotherapy, graft-versus-host disease, and corticosteroid use. An increased incidence of CsA-related neurotoxicity in patients with thrombotic microangiopathy has been observed [4, 32, 48, 52, 55, 73]. Reece et al. [52] suggest that endothelial damage, reflected by microangiopathic blood changes, leads to disruption of the blood-brain barrier with increased concentrations of CsA in the brain aggravating the neurotoxicity.

Hypomagnesemia

CsA causes intracellular migration and renal wasting leading to hypomagnesemia [41, 67]. Thompson et al. [61] suggested an association between CsA neurotoxicity and the development of CsA-induced hypomagnesemia. Their seven patients with seizures had no recurrences after magnesium supplementation. Magnesium sulfate is superior to phenytoin for prevention and treatment of eclamptic seizures [35]. Both eclampsia and CsA neurotoxicity are related to PLE. Two patients with aphasia also completely recovered after magnesium replacement despite continuation of CsA. In this regard the effect of magnesium on the vascular tone is interesting. Magnesium has a vasodilator effect, and hypomagnesemia can lead to cerebral vasospasm [14, 67]. This vasoactive effect of magnesium may play an additional role in CsA neurotoxicity. However, hypomagnesemia is not a prerequisite for CsA-induced neurological complications [6, 16, 60, 68].

Hypocholesterolemia

CsA is a highly lipophilic drug, 40–60% being bound to cholesterol containing lipoproteins, especially LDL. The highest concentrations of CsA are found in liver, endocrine glands, kidneys, and adipose tissue, and the lowest are found in intestine and brain [21, 31]. A similar distribution has been described for the LDL receptor [21]. Groen et al. [21] hypothesized that cellular uptake of CsA occurs through transmembrane diffusion or by binding of CsA containing LDL particles to the LDL receptor. Native CsA is then released into the cytoplasm where it binds to intracellular proteins. Low cholesterol levels lead to increased concentration of CsA in LDL particles and thereby increased uptake of CsA in cells expressing LDL receptors. Low cholesterol levels also lead to an increase in the amount of LDL receptors expressed on the cell membranes [21, 23]. In the brain the LDL receptor is expressed primarily by cells of the arachnoid and astrocytes, the predominant cells of the white matter. Under normal conditions the blood-brain barrier transport of CsA is considerably restricted [21, 31]. CsA itself may alter the function of the blood-brain barrier by endothelial damage or by interference with astrocytes, which modulate the function of the barrier [21].

Clinical implications of cyclosporine neurotoxicity

In general, the prognosis of CsA neurotoxicity is good. Even severe complications such as PLE resolve with dose reduction or withdrawal of the drug [2, 6, 9, 33, 46, 61]. Rechallenge at a lower dose is well tolerated [9, 28, 33, 71]. Some authors report recovery of their patients without a change in CsA dose [1, 16]. Because blood levels are not always reliable, the dose should be reduced when there is significant suspicion of toxicity. Seizures usually respond to anticonvulsants. However, the use of phenytoin and other anticonvulsants may interfere with CsA metabolism.

If neurological complications develop following BMT or other organ transplantation many causes may be responsible including infectious, metabolic, or toxic factors. Differential diagnosis of CsA neurotoxicity includes:

- Metabolic encephalopathy
  - Hypomagnesemia
  - Hypertensive encephalopathy
  - Hypocholesterolemia
  - Common causes: hypo-/hypernatremia, hypercalciemia, hypoxemia, organ dysfunction (hepatic, renal, endocrine, etc.), sepsis
- Leptomeningeal metastasis/leukemia/lymphoma
- Meningitis: bacterial, viral, fungal, aseptic
- Encephalitis: bacterial, viral, fungal
- Graft-versus-host disease
- Progressive multifocal leukoencephalopathy
- Toxic encephalopathy
  - Drug induced: intrathecal or systemic chemotherapeutic agents, opioids, amphotericin B, etc.
  - Radiotherapy (late effects)
- Vascular
  - Subdural/intracerebral hemorrhage
  - Cerebral venous and sinus thrombosis
  - Disseminated intravascular coagulation
  - Vasculitis

Previous and ongoing medical treatment should be carefully reviewed, particularly the use of CsA. This includes its current dose and drug level together with concomitant factors such as hypertension, magnesium, and cholesterol levels.

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