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REVIEW ARTICLE

Wolf O. Bechstein

Neurotoxicity of calcineurin inhibitors: impact and clinical management

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W.O. Bechstein
Department of Surgery,
Ruhr-University Bochum,
Knappschaftskrankenhaus Bochum-Langendreer, In der Schornau 23–25,
44892 Bochum, Germany
Tel.: +49-234-299-3201
Fax: +49-234-299-3209

Abstract Between 10%–28% of patients who receive the immunosuppressant cyclosporine (CsA) experience some form of neurotoxic adverse event. Both sensorial motoric functions may be adversely affected, and thus patients present with a wide range of neurological and psychiatrical disorders. Mild symptoms are common and include tremor, neuralgia, and peripheral neuropathy. Severe symptoms affect up to 5% of patients and include psychoses, hallucinations, blindness, seizures, cerebellar ataxia, motoric weakness, or leukoencephalopathy. Tacrolimus is associated with similar neurotoxic adverse events. Neurotoxicity may result in serious complications for some patients, particularly recipients of orthotopic liver transplants. Factors that may promote the development of serious complications include advanced liver failure, hypertension, hypocholesterolemia, elevated CsA or tacrolimus blood levels, hypomagnesemia, and methylprednisolone. Occipital white matter appears to be uniquely susceptible to the neurotoxic effects of CsA; injury to both the major and minor vasculature may cause hypoperfusion or ischemia and local secondary toxicity in the white matter. Calcineurin inhibition by CsA and tacrolimus alters sympathetic outflow, which may play a role in the mediation of neurotoxic and hypertensive adverse events. The symptoms of CsA- and tacrolimus-associated neurotoxicity may be reversed in most patients by substantially reducing the dosage of immunosuppressant or discontinuing these drugs. However, some patients have experienced permanent or even fatal neurological damage even after dose reduction or discontinuation. CsA-sparing and tacrolimus-sparing drug regimens that use the immunosuppressant mycophenolate mofetil, which has no neurotoxic effects, may reduce the incidence and severity of neurotoxic adverse events while maintaining an adequate level of immunoisuppression.

Key words Neurotoxicity · Immunosuppressant · Cyclosporine · Tacrolimus · Mycophenolate mofetil

Introduction

Many immunosuppressive drugs, including corticosteroids, methotrexate; OKT3 monoclonal antibody, antithymocyte globulin (ATG), and cyclosporine (CsA) are associated with, among other toxicities, neurotoxic adverse events [91] Causality assessment can be particularly difficult in the setting of organ transplantation since neurological complications may also be related to the pre-transplant status of the recipient, the type of organ transplant performed and postoperative complications related to the type of transplant. Moreover, causal-

ity assessment of drug-related neurotoxicity may become more difficult because of the tendency to use "cocktail-regimens" consisting of several agents. Under these circumstances, not only may there be additive effects of several drugs but pharmakokinetics of individual drugs may be substantially influenced, especially when new investigational agents are introduced in a trial setting. This review will focus on neurotoxic adverse events associated with the xenobiotic immunosuppressants CsA and tacrolimus.

Neurotoxicity associated with CsA and tacrolimus is a less common adverse effect than either their associated nephrotoxicity or hypertension, and thus is less well-known and less well-understood. However, it can result in serious complications for some patients, particularly recipients of orthotopic liver transplants (OLT). [13, 26, 59, 91, 94] Before a diagnosis of immunosuppressant-induced neurotoxicity can be made, a number of other possibilities must be excluded. Major psychiatric disturbances, identical to those also associated with immunosuppressant-induced neurotoxicity, are often present in patients who have undergone non-transplant-related major surgery and are therefore not receiving immunosuppressants.

These disturbances gradually resolve as the patient's metabolical and physical conditions improve. Furthermore, peripheral and autonomic neuropathy are commonly encountered conditions and may produce symptoms resembling neurotoxicity in diabetic patients who have received transplants. Peripheral neuropathy in these patients may be a consequence of their diabetes, but it may also be a symptom of drug-induced neurotoxicity. Finally, candidates for OLT may already have neural deficits because of the metabolic consequences of their hepatic failure. Objective measurements of neurotoxicities are not easily applicable in the immediate postoperative clinical environment, and thus the incidence of neurotoxicity is probably underestimated.

Overview of CsA-Associated neurotoxicity

Estimates of the overall frequency of CsA-related neurotoxic effects in transplant recipients vary from 10 %–28 % [26, 27, 91]. Both sensorial and motoric functions may be adversely affected in patients receiving CsA, [26, 59] and patients may also experience neuropsychiatric disorders.

Careful questioning of the patient is often required to identify neuropsychiatrical disorders and they may not be noted if a thorough examination is not performed. Consequently, patients may present with a wide range of mild to severe neurological and psychiatrical disorders. Clinical symptoms may include tremor, somnolence, mental status changes, peripheral neuropathy, cerebellar symptoms, Parkinson's syndrome, visual disturbances, cortical blindness, seizures, and coma (Table 1) [19, 26, 30, 70]. The mildly neurotoxic effects of CsA, eg, headache, tremor, neuralgia, and peripheral neuropathy, are common. Unfortunately, as many as 5 % of patients may develop a more severe syndrome characterized by an altered level of consciousness, confusion, psychosis, visual and auditory hallucinations, blindness, seizures, cerebellar ataxia, motoric weakness, or leukoencephalopathy [1, 12, 19, 35, 54, 70, 91, 94]. Patients may have been receiving CsA therapy for several months, or even years, before the neurotoxic complications of CsA first develop [9, 38, 92, 94].

Table 1 Severity grading of CsA-associated neurotoxicities

Mild	Moderate	Severe
Mental status changes	Visual disturbances	Altered level of consciousness
Tremor	Cortical blindness	Confusion
Headache		Psychosis
Neuralgia		Seizures
		Leukoencephalopathy
Peripheral neuropathy		Coma

Between 20 %–39 % of patients who develop CsA-related neurotoxicity experience tremor, making this the most commonly noted neurologic finding. [91]. In kidney and bone marrow transplant (BMT) recipients, the incidence of tremor is 21 % and 16 %, respectively [91]. Tremor is not particularly distressing for most patients and tends to diminish with time. Paresthesia, especially of the hands, is another common subjective complaint and is experienced by approximately 11 % of patients [91].

Visual hallucinations are less frequently reported than tremor [91]. Cortical blindness is an extremely rare complication [23, 27, 35, 83], the diagnosis of which is made based on exclusion, because multiple factors may produce blindness. Blindness has been reversed in most patients after dose reduction or discontinuation of CsA. However, one patient (a recipient of a kidney-pancreas transplant) developed sudden, complete, and permanent blindness within 36 h after administration of intravenous CsA. The onset of blindness in this patient coincided with a sudden elevation of CsA blood levels [27]. All graft recipients are at risk of developing seizures because of posttransplantation infection, metabolic derangement, and the occurrence of acute graft rejection along with its concomitant hypertension and fluid overload [91]. The incidence of seizures in kidney and BMT recipients has been reported at 1.5 % and 5.5 %, respectively [91]. Thus, CsA should be considered a possible causative or contributory factor if a patient devel-

ops seizures in the absence of any other obvious predisposing cause.

Published case reports have shown that individual patients, or a limited number of patients, have developed rare and severe neurotoxicity after treatment with CsA. One cardiac transplant recipient became paraplegic in the early postoperative period with concomitant sensory loss of the lower extremities distally [84]. The syndrome fully subsided 5 weeks later, after dose reduction. The symmetric polyneuropathy experienced by this patient was thought to be caused by axonal degeneration of the peripheral nerves. Another patient with idiopathic uveitis developed acute encephalopathy 2 weeks after beginning a combination regimen of CsA and methylprednisolone [58]. One OLT recipient developed a rapidly progressing irreversible neurotoxic syndrome with brain, kidney, and lung involvement that resembled thrombotic thrombocytopenia purpura (TTP) [6], while another developed late-occurring severe neurotoxicity including leukoencephalopathy [9].

The cerebellum appears to have been affected in a limited number of patients with CsA-associated neurotoxicity. Three patients with tremor, ataxia, confusion, amnesia, hyporeflexia, and weakness have been described; these symptoms resolved after CsA was discontinued [5]. Two patients were reported to have developed ataxia, weakness, and dysarthria followed by seizures and coma [90]. A single patient with cerebellar edema and secondary brainstem compression requiring decompressive craniotomy has been described [63].

Probably the best data available on neurotoxicity in renal transplant patients were obtained by the Canadian Neoral Renal Study Group [16]. A total of 1097 patients were entered into a randomized trial, 356 continued treatment with a conventional formulation of cyclosporin (CsA), while 737 were randomized to receive Neoral (CsA-ME), the microemulsion form of cyclosporine with increased bioavailability. During the first month of treatment, a significantly higher proportion of CsA-ME patients experienced neurological complications such as tremor, paresthesia, flushing, and headache, compared to CsA patients (21.7 % vs 15.2 %, $P < 0.05$).

However, this seemed to be transient. At 18 months no significant differences with regard to the incidence of neurological adverse events were observed. The incidences of specific adverse events for the respective groups CsA-ME vs CsA were headache: 19 % vs 17.4 %, paresthesia 4.9 % vs 3.7 % and tremor 2.7 % vs 2.0 % [16]. Nevertheless, one may cautiously interpret these data in the way that improved bioavailability of cyclosporine is accompanied by a tendency, albeit it not significant of increased neurological adverse events.

In a European multicenter trial, 448 renal transplant recipients were randomized to receive either CsA-based immunosuppression ($n = 145$) or tacrolimus-based immunosupprcssion ($n = 303$) [52]. Both groups received azathioprine and prednisolone in addition to the calcineurin inhibitors. A siginificantly increased incidence of tremor was noted in Tacrolimus-treated patients compared to CsA-treated patients (34.7 % vs 11.7 %, $P < 0.001$), while the incidences of insomnia (23.8 % vs 26.2 %) and headache (20.5 % vs 13.8 %) were not significantly different [52]. No serious neurological adverse events were observed.

Similarly, in a US trial, a total of 412 patients after renal transplantation were randomized to receive either tacrolimus-based immunosuppression ($n = 205$) or CsA-based immunosuppression [67]. In this trial also, tremor was significantly more often recorded in tacrolimus vs Cs-treated patients (54.1 % vs 33.8 %, $P < 0.001$) while the incidences of other neurological complications were not significantly different between treatment groups. In declining order of frequency, the following complications were noted (tacrolimus vs CsA): headache (43.9 % vs 37.7 %), insomnia (32.2 % vs 29.5 %), paresthesia (23.4 % vs 15.5 %), dizziness (19.0 % vs 15.5 %), anxiety (14.1 % vs 8.2 %) [67]. Again, no serious neurological adverse events were observed. Cortical blindness has been described in a patient following kidney transplantation [83], however this seems to be extremely rare after kidney transplantation.

Estimates of the incidence of neurotoxicity in bone marrow transplant (BMT) recipients receiving CsA range from as low as 4.2 % [70] to as high as 28.8 % [26]. The lower estimate was based on a retrospective review of 239 patients who received CsA-based prophylactic regimens. In that study, 10/239 (4.2 %) of patients experienced neurologic complications [70]. The higher estimate is based on the retrospective analysis of 625 patients with thalassemia who received CsA during prophylactic therapy to prevent graft-versus-host disease (GVHD) [26]. In that group, the overall incidence of neurotoxicity was 28.8 % and the incidence of convulsions was 10.1 %. In both studies, all neurological findings were reversible after temporary discontinuation of CsA. Specific symptoms of neurotoxicity in BMT recipients may include mental status changes, tremor, headache, severe visual disturbances, and cortical blindness [26, 70]. Eye movement abnormalities have been seen in some BMT recipients treated with CsA and ganciclovir [64]. One BMT recipient developed an ocular flutter 51 days after allogeneic BMT transplantation for acute myeloid leukernia [4]. Clinical symptoms resolved within 3 weeks of discontinuation of CsA; however, disturbances of motoric control appear to have persisted for more than 8 months because during that time the patient's electrooculogram was slightly abnormal.

One transplant center has reported that four recipients of heart transplants experienced serious CsA-associated neurotoxicity, including the following symptoms: coma, cerebral hemorrhage, hemiparesis and dysphasia,

confusion, and visual hallucinations [89]. Again, neurological effects were eliminated in most patients after discontinuation of CsA or a reduction in the dose. CsA-neurotoxicity in heart transplant recipients may cause a relative long-term decline in cognitive brain function [38]. Impaired brain function (measured objectively by cognitive P300 evoked potentials) was recorded in 55 heart transplant recipients compared with 55 age- and sex-matched healthy control subjects (359 ms at vertex vs 345 ms at vertex, respectively; $P < 0.01$). By 4 months posttransplantation, P300 measurements had normalized in these patients; however, they again declined at 12 months. The same patient group also scored abnormally in the psychometric Trail Making Test A (45 s data vs 31 s, $P < 0.01$) [38].

Neurotoxicity is a serious complication for all recipients of OLT [59] and may be induced by various postoperative events, including metabolic and circulatory disorders or graft rejection, or it maybe caused by immunosuppressant toxicity [13, 19, 20, 59]. Recipients of OLT experience the highest incidence of CsA-associated neurotoxicity; estimated at between 25 % [1] and 32 % [39] and is thus a significant cause of morbidity and mortality in this group of patients. The clinical symptoms of CsA-neurotoxicity vary greatly in OLT recipients. Neurotoxicity may begin either insidiously with confusion or abruptly with seizures [13]. The most frequent neurotoxic complications in OLT recipients are mental status changes (ranging from delirium to coma) and seizures [39]. Epileptic seizures, hemiparesis, dysphasia, delirium, and organic brain syndromes have been observed in 6 %–47 % of OLT recipients receiving CsA-based (or tacrolimus) immunosuppression [59]. Again, most OLT recipients quickly improve after discontinuation of CsA [19]; however, symptoms do not reverse in all patients. Three patients developed a severe form of CsA-toxicity with leukoencephalopathy [1]. One of these patients died 8 months after the onset of symptoms. Postmortem examination revealed cerebellar hemorrhage and progressive multifocal leukopencephalopathy.

Overview of tacrolismus-associated neurotoxicity

Many symptoms of tacrolimus-induced neurotoxicity are similar to those of CsA-induced neurotoxicity. [24, 94]. Symptoms of mild neurotoxicity include tremor, insomnia, nightmares, headache, vertigo, dysesthesia, photophobia, or mood disturbance. Symptoms of severe neurotoxicity include akinetic mutism, seizures, cortical blindness, focal deficits, psychosis, or encephalopathy [24].

The overall frequency of some neurological symptoms is greater in patients receiving tacrolimus compared with those receiving CsA; eg, headaches, tremor, and sleep disorders are observed more frequently with tacrolimus [31]. Moderate to severe neurotoxicity (including cortical blindness, tremor, seizures, and encephalopathy) has been reported in 21 %–32 % of patients [59, 94]. The frequency of neurological disturbances in transplantation patients receiving tacrolimus was determined in a retrospective study [24]. Symptoms ranged from a mild tremulousness (the most common finding) to major disturbances of neurological function (identified in 5.4 % of patients). In many patients, clinical symptoms were related to high plasma concentrations of tacrolimus. Although other studies have not demonstrated a clear relation between the level of tacrolimus and the development of neurotoxicity, reducing the dose of tacrolimus or discontinuing the drug usually leads to a regression of symptoms [94].

Compared with patients receiving CsA, the incidence of moderate or severe neurotoxicity is markedly higher in OLT recipients receiving tacrolimus in the early postoperative period (11.7 % vs 21.3 %, respectively) [59]. Table 2 summarizes the specific neurotoxic symptoms experienced by OLT recipients who received tacrolimus. These patients required additional medications to treat their neurotoxic symptoms. Current doses of tacrolimus are routinely lower than those used in this study; thus, neurotoxic side effects are less common. However, patients may still experience underlying psychiatric disturbances that may not be diagnosed without careful testing.

Compared with OLT recipients, recipients of heart and lung transplants appear to be less susceptible to the neurotoxic effects of tacrolimus; as few as 3.6 % of patients in these groups develop neurologic dysfunction [24].

Compared with adult kidney transplant recipients, severe tacrolimus-associated neurotoxicity may occur relatively infrequently in pediatric recipients, with an incidence of 7 % (1 of 14 patients) [62]. However, this pediatric population developed mild neurological complaints frequently; the most common symptoms were myalgias (7/14; 50 %); tremors (7/14; 50 %), and fatigue (5/14; 38 %). In contrast, a multicenter trial conducted in the United States showed that there were no significant differences in the overall incidence of neurologic events in pediatric OLT recipients treated with either CsA (21 patients) or tacrolimus (30 patients) [53]. However, only pediatric patients who received tacrolimus experienced major neurologic events. Specifically, one patient became comatose, two patients experienced encephalopathy, and four patients had convulsions while receiving tacrolimus. Minor neurologic events (headaches, insomnia, neuropathy, and tremor) occurred in both groups. Tacrolimus-treated patients also tended to have more insomnia (10 % vs 5 % for tremor), whereas CsA-treated patients had more neuropathy (20 % vs 10 %). Lastly, only patients who received tacrolimus experienced decreased coordination (1/30 patients) and parasthesia (2/30) [53]. Rare but severe neurotoxicities

Table 2 Early postoperative neurotoxicity in OLT-reciplents treated with tacrolimus[a]

Patient[b]	Days postoperative onset (D) – Duration of symptoms	Neurological symptoms	Tacrolimus-dose reduction or with drawal	Additional treatment	Outcome
199	D4-persisting	OBS[c] (severe), dysphasia, hemiparesis	Withdrawal, switched to CsA[d]	Diazepam, haloperidol	Partial recovery, died13 months post LTX-violent death
196	1. D 14–4 months	1. OBS (severe)2.	1. Reduction	1. Haloperidol-Dexa methasone, neurosurgery	Near-complete recovery
	2.D4/5–6 months	Intracranial hemorrhage, hemiparesis, dysphasia, frontal lobe syndrome, akinetic mutism	2. Switched to CsA[d]		
175	D4–2 months	OBS (moderate), seizures, dysphasia, dysarthria	Withdrawal, switched to CsA[d]	Diazepam, phenytoin	Complete recovery
195	D1–3 weeks	OBS (severe)	Withdrawal, switched to CSA[d]	None	Complete recovery (died 5 months post LTX after HBV recurrence)
174	D2–6 weeks	OBS (severe) Parkinson syndrome, cerebellar syndrome	Withdrawal, switched to CsA[d]	Haloperidol, diazepam, levopromazine	Complete recovery
125	D2–2 weeks	OBS (moderate)	Reduction	Haloperidol	Complete recovery
230	D5–5 months	OBS (moderate), frontal lobe syndrome, hemiparesis	Reduction	Haloperidol, rivotril	Resolving hemiparesis, near complete recovery
131	D2–3 weeks	OBS (moderate)	Reduction	Haloperidol	Complete recovery
190	D4–2 weeks	OBS (moderate), myocloni, hyperreflexia	Withdrawal[e]; very low dose from D10	None	Complete recovery
111	D3–2 weeks	OBS (moderate)	Reduction	Haloperidol	Complete recovery
219	D7–3 weeks	OBS (moderate)	Reduction	None	Complete recovery
120	D3–2 weeks	OBS (moderate)	Unchanged	None	Complete recovery
192	D1–1 weeks	OBS (moderate), burning feet, hands, face	Reduction	Haloperidol	Complete recovery

[a] [Adapted from Mueller et al, 1994, Table 2 on page 157] [b]Patients were randomly assigned to tacrolimus-based immunosuppression. Early posttransplantation, they developed neurological symptoms of moderate to severe neurotoxicity; patients are listed in decreasing order of symptom severity [c] OBS, organic brain syndrome. The first 8 patients listed also had abnormal EEGs. [d]Switched to CsA due to neurotoxicity[e] Tacrolimus withdrawal due to nephrotoxicity on D1–3 and D8, D9

have also been described in tacrolimus-treated patients. Three patients developed a severe sensorimotor neuropathy shortly after administration of tacrolimus [95]. With the exception of marked sensory symptoms, the clinical picture in these patients resembled chronic inflammatory demyelinating polyradiculoneuropathy. Electrophysiological studies revealed primarily demyelinating neuropathies. One OLT recipient developed sudden-onset, fatal neurological complications 5 months after she underwent transplantation and treatment with tacrolimus [68]. Postmortem examination revealed multiple vasculitic lesions thought to be the result of a tacrolimus-mediated toxic effect on the cerebral vessels and consistent with the sudden onset of symptoms. Posterior leukoencephalopathy has been described in two OLT recipients receiving tacrolimus; symptoms in both patients were reversed after tacrolimus was discontinued [60]. Lastly, OLT recipients have developed peripheral neurotoxicity with the characteristic features of motoric axonal neuropathy [7].

Pathophysiology of neurotoxicity

The cellular basis for the neurotoxicity associated with either CsA or tacrolimus has not been conclusively

identified. CT findings from patients with CsA-associated neurotoxicity are similar to those described for patients receiving tacrolimus; both drugs may mediate neurotoxicity via a common mechanism [33]. Both CsA and tacrolimus mediate their immunosuppressive effects via inhibition of calcineurin [14, 75] and, thus, it is possible that some or all of their adverse effects (nephrotoxicity and hypertension, as well as neurotoxicity) are also mediated via calcineurin inhibition [73].

Calcineurin accounts for > 1 % of total protein in the brain, and the intracellular binding proteins for both CsA and tacrolimus (the immunophilins cyclophilin and FKBP-12, respectively) [14] are enriched in the central and peripheral nervous systems [50,73]. In the spinal cord, the distribution of protein and/or messenger RNA for FKBP-12, cyclophilin, and calcineurin appears to be heterogeneous and the majority of localizations neuronal [18]. In most brain regions, there is a striking colocalization of FKBP-12 and calcineurin, as well as between cyclophilin and calcineurin. However, cyclophilin is enriched in some brain areas that lack calcineurin. These findings suggest that, within the brain, the function of the inummophilins and calcineurin are related.

Alteration of sympathetic outflow

Inhibition of calcineurin by CsA and tacrolimus alters sympathetic outflow during CsA-mediated hypertension (a frequently occurring CsA-associated adverse event) [50, 73]. It is reasonable to suggest that further consequences of calcineurin inhibition may mediate the neurotoxic effects of both CsA and tacrolimus. Animal models have shown that only immunosuppressive drugs that inhibit calcineurin mediate sympathetic activation [50, 73]. In a rat model, elevations of blood pressure was accompanied by higher sympathetic nerve activity after treatment with CsA and tacrolimus, but not rapamycin. Rapamycin, like tacrolimus, binds to FKBP-12, but the rapamycin-FKBP-12 complex does not inhibit calcineurin. [14, 73]. Although the site of CsA's excitatory action in the sympathetic nervous system has not been precisely identified, it is likely that both the central neural and peripheral reflex mechanisms are involved [50]. Clinical studies also implicate the involvement of sympathetic activation in CsA-induced hypertension. [74, 76]; eg, elevated levels of muscle sympathetic nerve activity also have been reported in patients receiving CsA after combined heart-lung transplantation [76].

CsA and tacrolimus may modulate the activity of both excitatory (N-methyl-D-aspartic acid [NMDA]) and inhibitory (γ-aminobutyric acid [GABA]) amino acid receptors via calcineurin. Calcineurin may modulate glutamatergic neurotransmission via both pre- and postsynaptic sites of action [73]. Studies with dissociated rat hippocampal neurons have shown that the CsA-cyclophilin complex interferes with GABA-mediated responses, suggesting that calcineurin may regulate desensitization of GABA receptors [51].

Tacrolimus has been shown to elicit inhibition of NMDA-induced neurotransmitter release and augmentation of depolarization-induced neurotransmitter release; both events are mediated via alteration of the phosphorylation state of calcineurin substrates [36]. Both CsA and tacrolimus can affect synaptic activity in the rat hippocampus; both drugs inhibit NMDA receptor mediated potentials but have no effect on depotentiation [48]. Interestingly, tacrolimus also inhibits the induction of long-term potentiation, which is widely accepted as being involved with memory acquisition.

Considerable evidence suggests that changes in the phosphorylation states of neuronal proteins are correlated with learning [10]. The peptidyl-prolyl-cis/trans-isomerase (PPIase) activity of a cyclophilin appears to be a requirement for successful memory formation in chicks [10].

Therefore, inhibiting various protein kinases may disrupt memory formation. When administered intracranially to day-old chicks, CsA disrupts memory formation assessed in a single-trial passive avoidance task [11]. A role for cyclophilin in memory is supported by the evidence that protein biosynthesis, which involves protein folding, is essential for long-term memory in many species [17].

Of recent interest is the finding that the mammalian retina contains cyclophilins. The main function of these novel cyclophilins (which have reduced PPIase and CsA-binding activities compared with other known cyclophilins) appears to be facilitation of protein folding or intracellular transport of opsins. [28, 29] These observations suggest new directions of investigation of the role of cyclophilins in CsA-induced cortical blindness.

Novel mechanisms

Recent in-vitro experiments have suggested novel mechanisms to explain the neurotoxic effects of CsA and tacrolimus; eg, selective toxicity of glial cells [82] and induction of apoptosis of oligodendrocytes [54]. In-vitro toxicity studies have shown that CsA is selectively toxic for glial cells in culture [82]. After being cultured with CsA, glial cells developed intracytoplasmic inclusions that were identified as lysosomes containing neutral lipids, whereas control cultures remained unaffected. The temporal development and severity of these changes was correlated with the length of exposure to CsA. It is particularly interesting that this selective toxicity correlates with the typical reversible changes within the white matter revealed by computed tomography

(CT) scans and cranial magnetic resonance imaging (MRI).

CsA may cause neurotoxicity by inducing apoptosis of oligodendrocytes and neurons [54]. In mixed cultures of mouse neuron and glial cells, CsA caused neuronal death characteristic of apoptosis. Oligodendrocytes, with the highest concentration of calcineurin, were the most sensitive to CsA-induced apoptosis, whereas astrocytes, which have little calcineurin, were relatively resistant. Although exciting, it is not known to what extent these data reflect the clinical syndrome of CsA- and tacrolimus-induced neurotoxicity.

In-vitro studies have also raised some concern about potential neurotoxicity of rapamycin and have prompted the suggestion that special attention should be paid to the neurological side effects of this drug. The toxic effects of rapamycin on astrocyte metabolism are equivalent to those of CsA and tacrolimus [77, 78].

Morphologic changes in the brain

Brain lesions in patients with CsA-associated neurotoxicity have been visualized using cranial MRI and CT scans.Some of the pathological changes are reversible with discontinuation of the drug [20, 26, 35, 42, 70]. It is generally agreed that the occipital white matter is uniquely susceptible to the neurotoxic effects of CsA [54, 88], but some studies have revealed evidence of more extensive and irreversible brain injury [54]. Parietal or occipital hyperintense T2 lesions have been located primarily at the gray-white junction and affect both gray and white matter.

CsA-associated pathological changes observed using MRI appear similar to those attributed to hypoxic injury or centrally centered vasculitis [8, 42]. Specifically, lesions have a distinct anastomotic border zone distribution, but they do not develop anastomotic border zone infarction. Injury to both the major and minor vasculature may cause hypoperfusion or ischemia, and local secondary toxicity may produce lesions in the white matter [8].

CT has shown that patients with either CsA- or tacrolimus-associated neurotoxicities develop similar pathologic changes [33]. Other pathological changes may be unique to tacrolimus-mediated neurotoxicity; these include multiple hemorrhages and decreased attenuation in the thalami. Vascular toxicity may also play a role in mediating the neurotoxic effects of tacrolimus that are known to produce vascular injury in experimental animals [31]. Injury to the occipital white matter can result in reversible changes in visual acuity and, if the injury is severe, may cause reversible cortical blindness [88]. T2-weighted MRI scans of one patient with CsA-associated cortical blindness revealed increased signal intensity in two focal areas (bilateral and symmetrical) in the medial surface of the occipital lobes [30].

The characteristic pathological findings in cases of CsA-associated fatal convulsions are cerebral edema and focal necrosis, indicating disruption of the blood-brain barrier [54, 81]. These changes are probably the result of CsA-induced damage to the vascular basement membrane. All OLT recipients who have been treated with CsA may have cortical hyperintensity on their MRI scans. This most commonly involves the cingulate gyrus and the occipital lobe, and less commonly involves the parietal lobe and the frontal cortex [42]. Pathological changes consist primarily of fine linear (laminar) cortical hyperintensities and are most apparent on proton density-weighted images, but are difficult to discern on T2-weighted images.

Concomitant factors in the development of CsA- and tacrolimus-induced neurotoxicity

Many factors appear to predispose patients treated with either CsA or tacrolimus to develop drug-related neurotoxicial adverse events. Some of these factors are advanced liver failure [20], hypertension [26], hypocholesterolemia [19], elevated CsA- or tacrolimus blood levels [12], hypomagnesemia [86], intravenous administration of drug [19, 24, 69], and administration of other drugs that inhibit CsA and tacrolimus metabolism (including high-dose methylprednisolone) [49, 58].

Hypocholesterolemia and previous hepatic failure may predispose patients with advanced liver failure to develop CsA-associated neurotoxicity [19, 20, 27]. CsA is a highly lipophilic molecule; thus, hypocholesterolemia may cause rises in the level of unbound CsA by enhancing its diffusion across the blood-brain barrier [27, 33]. Furthermore, advanced liver failure may disturb the blood-brain barrier, increasing the uptake of CsA into the brain [20, 33]. Tacrolimus is also highly lipophilic; thus, it is conceivable that a similar mechanism leads to its increased neurotoxicity in OLT recipients. The results of one study do not, however, support this hypothesis; investigators did not find any clear relation between hypocholesterolemia and neurotoxicity [24].

Intravenous administration of either CsA or tacrolimus may contribute to the development of neurotoxicity, possibly as a result of the increase drug levels in the blood [19, 24, 69]. However, one study has shown that in some OLT recipients receiving either tacrolimus or CsA, drug blood-levels were within their low therapeutic ranges prior to, and after the onset of, neurological symptoms. Furthermore, patients who received only oral medication have also developed neurologic symptoms [59].

Drugs that inhibit the metabolism of CsA or tacrolimus (increasing their blood levels) may increase the

risk of neurotoxicity [37, 40, 56, 65, 66]. Methylprednisolone inhibits metabolism of CsA in the liver [58]. The occurrence of GVHD with concomitant use of high-dose corticosteroids is the single predisposing factor in the occurrence of convulsions in BMT recipients [26]. Other case reports suggest drugs that inhibit CsA metabolism may also enhance the risk of neurotoxicity. One patient developed severe tremors and myoclonus while receiving concomitant CsA and high dosage liposomal amphotericin B; symptoms resolved with the discontinuation of CsA [25]. Another report suggested that the combination of CsA with ganciclovir might produce transient brainstem- or neuromuscular dysfunction with abnormal eye movement in occasional patients [64].

Seizures may be associated with hypomagnesemia [86]. However, a retrospective analysis of 625 BMT recipients was unable to show a clear relation between magnesium levels and development of seizures [26]. At the moment of seizure, 30 % of patients had low magnesium levels (< 1.7 mg/dl), 57 % had normal levels (1.7 to 2.5 mg/dl), and 13 % had high levels (> 2.5 mg/dl). Clearly, prospective studies are needed to quantify the relative risk of all potential risk factors discussed to better enable physicians to minimize the risk of neurotoxicity.

Clinical impact of CsA- and tacrolimus-associated neurotoxicity

As well as decreasing patients' quality of life (QOL), drug-related neurotoxicity has a negative impact on both the morbidity and mortality of transplant recipients receiving either CsA or tacrolimus. Recipients of OLT appear to be more adversely affected, compared with recipients of other organ transplants.

OLT recipients with moderate/severe late-onset neurotoxicity are at an increased risk of dying, compared with patients with less severe manifestations of neurotoxicity [59]. Late neurotoxicity is strongly associated with severe infections and multiple organ failure; these factors are associated with a lethal outcome in more than 50 % of patients. Also, the incidence of epileptiform activity after OLT is reported to be 5-fold higher in patients with a fatal outcome compared with those who survive [96].

Heart transplant recipients who develop CsA-associated neurotoxicities may face a severe decline in their QOL. The relative long-term decline in cognitive brain function experienced by some patients [38] may be the most distressing feature of CsA-associated neurotoxicity and significantly impair their QOL. Furthermore, these observations suggest that long-term psychological testing may be necessary in patients who receive calcineurin inhibitors.

Discontinuation of CsA or tacrolimus does not reverse the symptoms of neurotoxicity in all patients. Patients who continue to experience clinical manifestations of neurotoxicity have a poorer long-term outcome. For example, one OLT recipient experienced only partial improvement after CsA was discontinued [15]. At the 1-year follow-up examination, this patient remained blind although other neurological symptoms had either disappeared or greatly improved. Patients with thrombotic thrombocytopenic purpura (TTP) associated with tacrolimus or CsA also have a much poorer outcome despite discontinuing imunnosuppressant therapy, and they often require intensive support [85]. A 17-year-old patient developed occular flutter 51 days after transplantation [4]. Subtle neurologic abnormalities with a pathologic electrooculogram persisted in this patient for at least 10 months.

The effective management of seizures in patients who are receiving CsA or tacrolimus is complicated by potential drug-drug interactions (eg, with concomitant immunosuppressants such as corticosteroids) and hypertension (a common side effect of CsA and tacrolimus therapy) [26]. The occurrence of GVHD, with the concomitant use of high-dose corticosteroids, is the single predisposing factor in the occurrence of convulsions in BMT recipients. Hypertension was shown to be an independent risk factor for seizures; 25.7 % (38/148) of hypertensive patients developed convulsions compared with 2.5 % (25/274) of those without hypertension. Neurotoxic adverse events may result in a transplant recipient becoming less compliant with regard to their immunosuppressant drug regimen, thus, increasing the risk of inadequate immunosuppression and the risk of graft rejection.

Management of neurotoxicities

The pathogenesis of CsA- and tacrolimus-associated neurotoxicities (as well as the many factors favoring their development) is still not completely understood and, therefore, it is difficult to prevent this adverse event. In treating drug-related neurotoxicities, the physician may be required to manage an extremely wide range of symptoms, including tremor, paresis, hallucinations, and coma. Some of the rare symptoms of neurotoxicity may be unpredictable and difficult to manage. For example, any abnormalities in behavior and/or stupor in patients receiving CsA may be a manifestation of complex partial status epilepticus [3]. It has, therefore, been suggested that any CsA-treated patient who develops an encephalopathy should have an electroencephalogram performed at the time of abnormal behavior.

Discontinuation of therapy

Most cases of CsA- and tacrolimus-associated neurotoxicity have occurred at high doses of either drug [7, 24, 39, 72]. Therefore, the first step in the treatment of drug-related neurotoxicity is to discontinue the immunosuppressant, correct electrolyte abnormalities, and control hypertension [5, 46, 85]. In many cases, discontinuation or dose reduction results in resolution of symptoms; unfortunately, this approach has not been successful in all patients [4, 15].

Recognition of factors that contribute to the development of neurotoxicity

The physician should be aware of any signs that herald the onset of neurotoxicity. Prolonged CsA therapy, after appearance of neurologic symptoms, may result in nonreversible neurotoxicities [15]. Specific patient groups, such as children and patients with a history of renal toxicity or hypertension who may have a predisposition to develop neurotoxicity, must be carefully monitored during immunosuppressant therapy [23, 58]. In addition, posttransplant patients who develop hypertension must be carefully followed since they are at an increased risk for developing seizures [26].

Other factors appear to increase the risk of neurotoxicity in patients treated with either CsA or tacrolimus. Advanced liver failure may slow the rate of clearance of parent drug, increasing the risk of neurotoxicity [87]. Transplant recipients are at an increased risk of infections, and therefore often receive antiinfective agents in addition to other immunosuppressants [45]. Many of these other medications (eg, high-dose methylprednisolone) [58] can inhibited metabolism of CsA or tacrolimus by the liver and increase the risk of adverse events, including neurotoxicity [37, 40, 66].

The development of severe micoangiopathic hemolytic anemia requiring clinical intervention may be the strongest predictive factor for neurotoxicity in BMT recipients [70]; visual disturbances can precede subsequent severe neurotoxicity, including seizures [30, 70]; and epileptiform activity in electroencephalograms of OLT recipients suggests a poor prognosis [96].

Therapeutic drug monitoring

As discussed, current strategies to manage neurotoxicity are based on the assumption that most, if not all, symptoms are dose-related and only occur at elevated blood levels of either CsA or tacrolimus. If this were the situation in all patients, regular measurement of drug levels in the blood would be of great value in preventing neurotoxicity by ensuring that they do not rise above therapeutic concentrations. Unfortunately, the development of neurotoxicity does not always correlate with a simple dose effect, and not all neurotoxicities can be reversed with discontinuation of CsA or tacrolimus [4, 13, 15, 46, 59, 85, 94], or be clearly correlated to the dose of immunosuppressant [26, 94]. Even careful monitoring of drug levels will not be of any use in either preventing neurotoxicity or managing patients experiencing some forms of neurotoxicity; eg, the occurrence of isolated cerebellar syndrome in children is not related to the dose of CsA [72]. Furthermore, there appears to be no correlation between serum CsA levels and the occurrence of seizures in BMT recipients [26]. Lastly, one study has shown that OLT recipients who received tacrolimus and CsA had blood levels of both drugs that were within their low therapeutic ranges prior to, and after the onset of, their neurological symptoms [59].

A simple-dose response correlation may not be adequate to predict all CsA- and tacrolimus-induced neurotoxicity; cumulative CsA dosage may be of greater importance in some patients [38] while in others it may be a serum concentration in excess of 1000 ng/ml [54, 71].

Therapeutic drug monitoring is best performed at the patient's bedside, and results should be interpreted by the attending physician. It is clear that strict adherence to therapeutic drug monitoring is insufficient to prevent the development of neurotoxicities, in part because of the high degree of variance between individuals. Lastly, susceptibility to neurotoxicity may be related to personality type. [Personal observation]

Monitoring CsA metabolites. The neurotoxic effects of CsA (and tacrolimus) possibly are mediated by metabolites. CsA and its metabolites can apparently cross the blood-brain barrier [46]; high levels of CsA metabolites have been found in cerebrospinal fluid [13]. Impaired hepatic function may affect CsA metabolism and lead to decreased clearance of both parent drug [87] and metabolites with an increased risk of neurotoxicity. Thus, monitoring of the major CsA metabolite M 17 concentration has been proposed as a strategy to reduce the risk of severe neurotoxicity [26, 87]. In the absence of data to the contrary, this proposal should not be ignored.

Treatment of seizures

The treatment of CsA-induced seizures can be problematic; they have been managed by a combination of reduction in CsA dosage with anticonvulsant therapy [13, 91]. However, the anticonvulsants phenytoin, phenobarbital, and carbamazepine should be avoided. All three drugs decrease CsA blood levels and make it difficult to maintain CsA at therapeutic levels. Such difficulties maybe avoided by treating patients with valproic acid

[91]. Lastly, any possible precipitating factors, such as hypertension [26] and hypomagnesia [86] should be corrected.

Usefulness of MRI

Regular visualization of the cranial lesions using MRI may be useful in managing severe neurological disorders, especially seizures [42]. Furthermore, it may support the clinical suspicion of CsA toxicity in patients who develop seizures, disturbed consciousness, cortical blindness, or speech disorders in the early postoperative period [42]. Some investigators recommend that a cerebral MRI be performed as soon as severe CsA-induced neurologic toxicity is suspected [15, 34]. Early radiological examination may be useful in monitoring patients receiving tacrolimus and high-dose corticosteroids and who are at risk of developing TTP [85]. Data from MRI scans should, however, be carefully interpreted because the validity of this approach has not been confirmed by prospective study. In one recent study of 44 OLT recipients, 5 patients had extrapontine myelinolysis and central pontine myelinolysis (CPM) characteristic of CsA toxicity. MRI scans revealed abnormal signal intensity within the pons well as in the subcortical white matter in the bilateral parieto-occipital regions. However, the extent of pontine abnormality in these patients was variable and did not correlate with the severity of neurological deficits [34]. Furthermore, two patients with indistinguishable CPM presented with different clinical settings; one had "locked in" syndrome and the other had less severe manifestations. Lastly, brain CT of 17 recipients of BMT (with moderate to severe neurotoxicity) revealed density changes in several areas (most frequently in the occipital lobe); however, these changes were not specific and transient on subsequent examination [26]. In the absence of clinical neurotoxicity, no abnormal findings can be detected by imaging methods such as conventional MR, MR perfusion maps and SPECT perfusion scans [80].

CsA- and tacrolimus-sparing regimens

Concern is growing that the greatest beneficial effect of CsA seems to be limited to the early posttransplant period. This, the unknown effects of CsA and tacrolimus toxicity over the long term has prompted many investigators to attempt to withdraw CsA after the early posttransplant period [43]. The use of immunosuppressant therapies in novel combinations may permit the use of CsA (or tacrolimus) in much lower dosages than have been used conventionally, while still maintaining adequate immunosuppression and preventing allograft rejection [2]. CsA and tacrolimus are both calcineurin inhibitors; [14, 75] thus, any alternative immunosuppressant, such as mycophenolate mofetil (MMF), must have a different mechanism of action. Drug regimens based on this principal are described as "CsA-sparing" or "tacrolimus-sparing".

For patients showing symptoms of CsA-associated nephrotoxicity, these sparing regimens have yielded significant improvements in renal function with no increase in rejection rate. In a Canadian study, 10 kidney transplant recipients who showed symptoms of CsA-associated nephrotoxicity were switched from a regimen of CsA/prednisone to one of MMF/prednisone [41]. After conversion, patients did not experience any incidences of acute rejection; furthermore, renal function (assessed by serum creatinine and creatinine clearance) significantly improved after a mean follow-up period of 12 months. Weir et al. [93] reported a study involving 28 kidney transplant recipients with progressive deterioration of renal function. The dosage of CsA was reduced by 50%, and azathioprine (AZA) was replaced with MMF. After a mean follow-up time of 6 months, this CsA-sparing regimen resulted in a significant improvement in renal function. In a study of six patients with biopsy-proven CsA-nephrotoxicity, CsA was withdrawn completely and AZA was replaced with MMF [21]. At a mean follow-up time of 12 months, these patients experienced a significant improvement in renal function as measured by serum creatinine levels. Although these studies are small and short-term, they show that reducing or removing CsA and replacing it with MMF reduces nephrotoxicity; therefore, it is logical to predict that neurotoxicity will also be reduced. Similar trials have been carried out combining tacrolimus with MMF after renal transplantation [57].

Although there is limited data regarding the use of MMF after liver transplantation, a regimen of MMF/prednisone may be a possible replacement for CsA. Four OLT recipients were successfully converted from CsA to MMF/prednisone [32]. The initiation of MMF/prednisone therapy reversed rejection episodes in all four patients; only one patient developed a recurrent rejection episode requiring additional ininumosuppression. An open prospective study of 20 OLT recipients has shown that MMF appears to be a safe and potentially useful adjuvant immunosuppressive agent for rescue and maintenance therapy that will not increase the risk of neurotoxicity [44]. Patients in this study experienced reduced nephrotoxicity and hepatoxicity after the dosages of CsA or tacrolimus were reduced. Primary combination therapy of tacrolimus and MMF following liver transplantation has recently been reported [22].

Economic cost of neurotoxicity

Prolonged hospitalization is required for patients with severe forms of neurotoxicity and may pose a significant financial burden; eg, OLT recipients who develop neurotoxicity are at an increased risk of developing infections as well as multiple organ failure [59].

At present, MRI is considered the best modality to identify the pathology of lesions and some investigators consider that MRI should be performed as soon as any unusual neurological symptoms develop after transplantation [34]. Unfortunately, MRI is a very expensive procedure; in 1995, the mean allowed charge of an MRI scan was $993 [61]. However, MRI may reveal lesions in a patient with a normal CT scan [35].

The accumulating costs associated with therapeutic drug monitoring are an underestimated financial consequence of CsA- and tacrolimus-induced neurotoxicity. The cost of a single test is approximately $ 35. However, tests must be repeated frequently-initially on a daily basis, then weekly, biweekly, monthly, and quarterly to establish a maintenance dosage. Thereafter, measurements are required periodically for the duration of therapy; cumulative charges can rise quickly [79]. New "intelligent dosing systems" (IDS) may be useful in accurately predicting doses of tacrolimus required to achieve target drug levels [55]. A reproducible IDS could minimize the risk of all drug-related toxicities (including neurotoxicity), reduce duration of hospitalization, and reduce financial costs.

As discussed above, prospective studies have not been conducted to show the effect of CsA-sparing and tacrolimus-sparing on the incidence and severity of drug-related neurotoxicity.

However, such regimens, particularly those that employ MMF as the calcineurin inhibitorsparing immunosuppressant, do significantly reduce costs associated with drug-related nephrotoxicity (by reducing the number of rejection treatments and dialysis sessions) [47]. Therefore, it is reasonable to predict that MMF-based regimens can also reduce costs associated with neurotoxicities.

In light of the observation that different personality types may show varying susceptibility to neurotoxic side effects, psychological assessment of patients may be a factor in determining the best drug regimen to use in order to avoid neurotoxic adverse events. The additional cost of psychological testing could be offset by cost savings resulting from the prevention or reduction of neurotoxic adverse events.

Conclusions

CsA- and tacrolimus-associated neurotoxicities can have a significant impact on the morbidity of transplant recipients, especially in OLT recipients. CsA- or tacrolimus-induced neurotoxicity should always be considered in transplant recipients who develop neurological complications, especially in the absence of other clinical entities or drug reactions that could explain their development. Most of the time, the symptoms of drug neurotoxicity are reversible after a substantial dose reduction or drug discontinuation; but there are well-documented cases of patients who experience permanent or even fatal neurological damage. Levels of CsA and tacrolimus in the blood are usually, but not always, elevated at the time of the manifestation of neurological side effects. Thus, there is a real need for alternative immunosuppressive regimens that include reduced dosages of both CsA and tacrolimus. The encouraging results of MMF-based CsA- and tacrolimus-sparing regimens on the incidence of nephrotoxicity hold promise that similar regimens will reduce the incidence and severity of neurotoxic effects. Improvements in patient morbidity, mortality, and QOL should follow, as should a reduction in the financial costs associated with neurotoxicity.

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