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CASE REPORT

Possible therapeutic effect of lipid supplementation on neurological complications in liver transplant recipients

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Summary

Neurological complications (NCs) represent a serious problem following liver transplantation and may develop either because of various peri-operative factors or the toxicity of immunosuppression. Although the causality assessment of NCs can be particularly difficult in the setting of organ transplantation, calcineurin inhibitors (CNIs) might influence NCs to a certain extent, regardless of the etiology. Therefore, minimizing the influence of CNIs could be a reasonable strategy for alleviating NCs. Based on our hypothesis that lipid supplementation prevents lipophilic CNIs from crossing the blood–brain barrier, soybean oil was administered to five liver transplant patients with NCs. In all of these patients, the neurological symptoms improved without discontinuing or reducing the dose of CNIs. Thus, lipid supplementation might be able to reduce the adverse neurological effects of CNIs.

Along with advances in surgical techniques, the administration of calcineurin inhibitors (CNIs) has significantly improved the outcome of organ and tissue transplantation [1,2]. However, these potent immunosuppressive drugs possess the capacity to cause toxic side effects. Central nervous system toxicity presents as a wide spectrum of mild-to-severe neurological and psychiatric disorders that have been observed in approximately 20–40% of liver transplant recipients treated with CNIs [3–6]. It has been reported that the risk factors for neurological complications (NCs) possibly include hypoglycemia, hypomagnesemia, hypocholesterolemia, elevated cyclosporine (CsA) and tacrolimus (TAC) blood levels, hypertension, acute renal failure, pre-operative hepatic encephalopathy, decreased liver function, and electrolyte disturbances such as hyper- or hyponatremia [7–10]. Generally, the symptoms of NCs can be reversed by discontinuing or reducing the dose of CNIs [7–13]. However, without appropriate immune monitoring, these strategies may, in turn, increase the risk of acute cellular rejection (ACR).

In this study, we describe our experience in treating 10 patients with NCs after living-donor liver transplantations (LDLTs). Between June 2000 and March 2006, 74 patients underwent LDLTs at Hiroshima University Hospital. Of the 74 patients, 45 had not experienced pretransplant NCs. These 45 patients included 27 males and 18 females; their ages ranged from 20 to 66 years (mean age ± SD, 50.9 ± 9.4 years). The primary diseases in these patients included hepatitis B/C virus-related cirrhosis in 30 patients (of these, 19 patients had hepatocellular carcinoma), primary biliary cirrhosis in five, autoimmune hepatitis in four, alcoholic cirrhosis in two and other diseases in four patients. The graft donors included 31 offspring, nine spouses, three siblings and two parents; their ages ranged from 18 to 61 years (mean age, 32.5 ± 12.1 years). The graft weight and graft-to-recipient body weight ratio (GRWR) ranged from 262 to 896 g

Table 1. Patient characteristics.

	Non-NC group ($n = 35$)	NC group ($n = 10$)	*P*-value
Age at LTx (years)	51.4 ± 1.6	49.1 ± 2.6	0.50
Sex (male/female) (*n*)	22/13	5/5	
Primary diagnosis (*n*)			
Cirrhosis	12	6	
HCC	16	3	
Others	7	1	
Operation time (min)	724.8 ± 22.7	685.4 ± 22.5	0.38
Time to extubation (days)	2.9 ± 0.5	2.2 ± 0.5	0.49
GRWR	0.99 ± 0.04	0.90 ± 0.07	0.29
CsA/TAC (*n*)	8/27	3/7	

NC, neurological complication; LTx, liver transplantation; HCC, hepatocellular carcinoma; GRWR, graft-to-recipient body weight ratio; CsA, cyclosporine; TAC, tacrolimus.
Data are expressed as mean ± standard error of mean.
Statistical differences were determined by unpaired Student's *t*-test. Differences with $P < 0.05$ were considered significant.

Table 2. Clinical parameters.

	Non-NC group ($n = 35$)	NC group ($n = 10$)
	(Averaged data of POD7)	[Averaged data at the time of development of NC (POD 6.9 ± 4.3)]
Total bilirubin (mg/dl)	5.2 ± 0.7	6.2 ± 0.9
AST (IU/l)	81.0 ± 8.6	82.0 ± 20.1
ALT (IU/l)	246.0 ± 28.5	178.1 ± 44.7
Ammonia (μmol/l)	34.3 ± 1.8	33.1 ± 4.8
CsA trough (ng/ml)	204.3 ± 26.5	221.1 ± 64.5
TAC trough (ng/ml)	9.3 ± 1.8	11.1 ± 1.7
Total cholesterol (mg/dl)	97.5 ± 4.7	73.5 ± 5.8

NC, neurological complication; POD, post-operative days; AST, aspartate aminotransferase; ALT, alanine aminotransferase; CsA, cyclosporine; TAC, tacrolimus.
Data are expressed as mean ± standard error of mean.

(mean weight, 593.2 ± 150.4 g) and from 0.49% to 1.92% (mean ratio, 0.97% ± 0.27%), respectively. The basic immunosuppressive regimen after LDLT comprised TAC/CsA and methylprednisolone with/without basiliximab. Of the 45 patients, 11 received CsA-based immunosuppressive therapy, while the remaining 34 received TAC-based immunosuppressive therapy. The choice between CsA and TAC was left to the surgeon. The target blood levels of CNIs were achieved in all the 45 recipients in this series. The trough whole blood levels of TAC were maintained between 8 and 15 ng/ml in the first few post-operative weeks and between 5 and 10 ng/ml thereafter; those of CsA were maintained between 150 and 250 ng/ml in the first few postoperative weeks and between 100 and 150 ng/ml thereafter.

Of the 45 patients, 10 presented with a wide range of neurological and psychiatric disorders (NC group). The remaining 35 patients did not show any symptoms of NC (non-NC group). The characteristics of these patients are listed in Table 1. No significant differences were observed between the NC group and the non-NC group with respect to age, sex, operation time, time to extubation, GRWR, or the type of CNIs used for immunosuppression. The mean onset of symptoms was after 6.9 ± 4.3 post-operative days. When NCs developed, the serum levels of neurotoxic substances – such as bilirubin or ammonia – in the NC-group patients were comparable with those in the non-NC group patients on the 7th post-operative day (Table 2). No clear relationship was observed between the blood levels of CNIs and the incidence of NCs. No significant difference was observed in the pretransplant serum cholesterol values between the NC group and the non-NC group (145.1 ± 17.9 and 135.3 ± 8.8 mg/dl, respectively; unpaired Student's *t*-test). Notably, when NCs developed, serum cholesterol values were remarkably lower in the patients with NCs when compared with those in patients without NCs on the 7th post-operative day (Table 2).

In the patients suffering from NCs (Table 3), the first two patients (cases 1 and 2) recovered after the dose of CNIs was reduced. The next three patients recovered after TAC was withdrawn and the basal immunosuppressant

Table 3. Characteristics of patients suffering from neurological complication.

Case	Age (years)	Sex	Indication for LTx	CNI	Onset of NC	Neurological symptoms	Immunosuppressive treatment for NC	Duration of symptoms (days)	Pre. T.cho	Onset. T.cho	Post. T.cho
1	46	F	Alcoholic cirrhosis	TAC	POD3	Mental status change	Dose of TAC reduced	9	89	60	65
2	57	M	HBV cirrhosis/HCC	CsA	POD6	Mental status change	Dose of CsA reduced	4	204	80	88
3	52	M	PBC	TAC	POD7	Confusion, seizures	TAC withdrawn, switched to CsA	5	142	63	77
4	32	F	AIH	TAC	POD3	Altered level of consciousness	TAC withdrawn, switched to CsA	3	59	50	58
5	38	M	HBV cirrhosis	TAC	POD7	Headache, tremor	TAC withdrawn, switched to CsA	2	228	76	89
6	59	F	HCV cirrhosis	CsA	POD10	Altered level of consciousness	CsA unchanged + lipid supplementation	2	98	65	71
7	54	F	HCC	TAC	POD7	Mental status change	TAC unchanged + lipid supplementation	2	159	52	63
8	52	M	HCV cirrhosis	CsA	POD6	Altered level of consciousness	CsA unchanged + lipid supplementation	2	197	90	92
9	51	F	PBC	TAC	POD18	Neuralgia	TAC unchanged + lipid supplementation	1	101	99	121
10	50	M	HBV cirrhosis/HCC	TAC	POD4	Mental status change	TAC unchanged + lipid supplementation	1	174	100	102

LTx, liver transplantation; M, male; F, female; HBV, hepatitis B virus; HCV, hepatitis C virus; HCC, hepatocellular carcinoma; PBC, primary biliary cirrhosis; AIH, autoimmune hepatitis; POD, post-operative day; for other abbreviations see footnotes to Tables 1 and 2.
Mental status changes include psychosis, paranoia, restlessness, etc. Altered levels of consciousness include disorientation, confabulation, fixation, obsession, hallucinations, etc.

was switched from TAC to CsA (cases 3, 4, and 5). However, one of these patients subsequently suffered from ACR that probably occurred because of the reduction in the dose of CNIs (case 3).

It is well known that both CsA and TAC are highly lipophilic; moreover, the lipophilic nature of both the substances implies that they do not rapidly enter the brain tissue [10,13]. In blood, approximately 40% of CsA is taken up by erythrocytes. Most of the remaining 60% is bound to the lipoprotein fractions, which include triglycerides, phospholipids, free cholesterol, cholesterol esters and apolipoproteins. It appears that <10% of CsA is not bound to lipoproteins or erythrocytes [8,14,15]. In the presence of hypolipidemia, unusually large amounts of CNIs may remain unbound or free. If the blood–brain barrier is impaired, the unbound CNIs might be able to cross it, leading to their increased uptake in the brain. In addition, there exists strong evidence suggesting that the average level of FK-binding proteins (FKBP) in brain tissues is 10–40 times higher than that in the immune tissues [16]. A combination of high FKBP levels in the brain and increased TAC content in the brain tissues might result in local TAC-associated toxicity. Based on this concept, we hypothesized that exogenously supplied lipids can prevent lipophilic CNIs from crossing the blood–brain barrier. A previous report, which has demonstrated that the anti-proliferative effect of CNIs is enhanced when they are bound to low-density lipoproteins [17], encouraged us to apply this idea in a clinical setting. After obtaining approval from the ethical committee of our institute, we preliminarily tested lipid supplementation in five patients with NCs (cases 6, 7, 8, 9, and 10). We continuously administered 20% soybean oil (Intralipos®; Otsuka Pharmaceutical Factory Inc., Naruto, Japan) at a dose of 0.1–0.2 ml/kg/h for 2–3 days. The neurological symptoms of all the five patients improved remarkably after the initiation of the treatment with i.v. injections of soybean oil without discontinuing or even reducing the dose of CNIs. During the observation period, neither adverse effects caused by the soybean oil treatment nor an episode of ACR was encountered in these patients. In the context of the other risk factors known to be related with NCs such as hypertension, fluid overload, high-dose methylprednisolone concomitant therapy, and administration of other drugs that inhibit CNIs metabolism, we have not observed significant differences between the patients with NCs treated with lipid supplementation and those treated with dose reduction of CNIs. In addition, we have not seen observed remarkable changes in those above-mentioned risk factors before and after lipid supplementation in the five patients. Hypomagnesemia might also be a possible risk factor in NCs. Although we have not routinely monitored the serum levels of magnesium, it is unlikely that the soybean oil

treatment affects those levels because soybean oil does not contain magnesium.

The mechanism underlying NCs has not been clearly elucidated. Several investigators have suggested the presence of some disturbance in the blood–brain barrier [8,12,13]. The analysis of cerebrospinal fluid after liver transplantation has demonstrated the presence of CNIs and their metabolites; further, high-dose corticosteroids that are administered during transplantation inhibit the metabolism of CNIs in the liver. Both these observations suggest a direct toxic effect of CNIs on neural tissues. The CNIs may gain access to the neural tissues either directly due to membrane toxicity or indirectly through the disruption in the blood–brain barrier that is associated with severe hepatic failure. However, we could not precisely differentiate NCs from the dementia/mental derangement associated with hepatic coma – a common complication in patients with acute liver failure. Thus, the causality assessment of NCs can be particularly difficult after liver transplantation. Nevertheless, CNIs might influence the development of NCs to a certain extent, regardless of the etiology. Therefore, minimizing the influence of CNIs could be a reasonable strategy to alleviate NCs. Our experience suggests that the exogenous supply of lipid supplementation might be able to reduce the adverse neurological effects of CNIs without the risk of insufficient immunosuppressive therapy.

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