Transplant International

Transplant International ISSN 0934-0874

ORIGINAL ARTICLE

Hepatic encephalopathy and post-transplant hyponatremia predict early calcineurin inhibitor-induced neurotoxicity after liver transplantation

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Keywords
acute graft rejection, calcineurin inhibitors, cyclosporine, early calcineurin inhibitor-induced neurotoxicity, hepatic encephalopathy, hyponatremia, liver transplantation, neurotoxicity, tacrolimus.

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Conflicts of Interest
None.

Received: 24 February 2011
Revision requested: 23 March 2011
Accepted: 4 May 2011
Published online: 7 June 2011

doi:10.1111/j.1432-2277.2011.01280.x

Summary

Early calcineurin inhibitor-induced neurotoxicity (ECIIN) is considered when neurological symptoms occur within 4 weeks after liver transplantation (LT). Risk factors and clinical outcome of ECIIN remain largely unknown. We sought to estimate the incidence, risk factors, and outcome of ECIIN after LT. We retrospectively evaluated 158 patients that underwent LT in a 2-year period and received immunosuppression with calcineurin inhibitors (CNI) and prednisone. ECIIN was considered when moderate/severe neurological events (after excluding other etiologies) occurred within 4 weeks after LT and improved after modification of CNI. Demographic and clinical variables were analyzed as risk factors. Twenty-eight (18%) patients developed ECIIN and the remaining 130 patients were analyzed as controls. History of pre-LT hepatic encephalopathy (OR 3.16, 95% CI 1.29–7.75, $P = 0.012$), post-LT hyponatremia (OR 3.34, 95% CI 1.38–9.85, $P = 0.028$), and surgical time >7 h (OR 2.62, 95% CI 1.07–6.41, $P = 0.035$) were independent factors for ECIIN. Acute graft rejection and infections were more frequent in the ECIIN group. In addition, length of stay was longer in ECIIN patients. In conclusion, pre-LT hepatic encephalopathy, surgical time >7 h, and post-LT hyponatremia are risk factors for ECIIN. Clinical complications and a longer hospital stay are associated with ECIIN development.

Introduction

Early complications after liver transplantation (LT) remain a significant cause of morbidity and mortality in a subset of recipients [1,2]. The central nervous system which may be functionally and morphologically altered in patients with cirrhosis is vulnerable to perioperative insults as well as prone to toxicity of immunosuppressive agents [3]. Adverse neurological events, most of them occurring within the first month after LT, may occur in up to 40% patients [4–6]. In this context, neurotoxicity because of calcineurin inhibitors (CNI) is thought to play an important role in the pathogenesis of these neurological events [4,6]. CNI-induced neurotoxicity occurs more commonly in liver recipients than in other solid-organ transplant recipients [5,7–9].

Early calcineurin inhibitor-induced neurotoxicity (ECIIN) is defined as adverse neurological events that occur within 4 weeks after LT [10]. This condition may develop in up to 28% of LT recipients within the first 4 weeks [10]. The majority of patients develop severe manifestations such as altered mental status, seizures, or focal neurological deficits [5,7,10]. ECIIN management requires CNI withdrawal or dose modification, a measure that may alter post-transplant outcome because of the risk of allograft rejection and infections. In addition, it impairs quality of life and many of its symptoms may persist after CNI conversion [10]. There is scarce data on the

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incidence, risk factors, and clinical course of ECIIN after LT [10,11]. Thus, adequate identification of these factors may help to prevent and to minimize the risks and complications in patients with LT [8]. The aim of this study was to assess the incidence and risk factors associated with ECIIN as well as the clinical outcome after LT.

Methods

Study patients and controls

We retrospectively evaluated 167 consecutive patients that underwent LT at our institution between January 2006 and December 2007. Patients that died within 2 weeks after LT ($n = 5$) and those who underwent simultaneous liver–kidney transplantation ($n = 4$) were excluded. Therefore, data on 158 patients were analyzed. The study protocol was approved by the Institutional Review Board of our hospital.

Early calcineurin inhibitor-induced neurotoxicity was defined as previously described [8,10]. This definition was considered when moderate or severe neurological events (visual disturbance, altered level of consciousness, confusion, psychosis, seizure, leukoencephalopathy, and/or coma) appeared in the absence of central pontine myelinolysis, central nervous system infection, stroke, or hemorrhage within the first 4 weeks after LT and symptoms improved after dose modification of CNI therapy [8,10]. A cohort ($n = 130$) of patients from the same time period without neurological complications within 3 months after LT was analyzed as a control group.

Data collection

Prespecified data were collected from hospital records and our transplantation database where pretransplant, perioperative, and post-transplant data for every liver transplant is prospectively included. Pre, peri, and post-transplant variables were analyzed as risk factors of ECIIN. Pretransplant variables included age, gender, underlying liver disease, Model for End-stage Liver Disease (MELD) score, retransplantation, serum creatinine, serum sodium, and previous history of hepatic encephalopathy (HE). History of HE was considered if patients had at least one episode of HE (grade 2 or more, West-Haven criteria) before transplantation. Perioperative variables included cold ischemia time, duration of surgery, and need for reoperation within 4 weeks after the LT. Postoperative variables included type of CNI, serum creatinine, serum magnesium, serum cholesterol, and serum sodium. Serum levels of magnesium, total cholesterol, glucose, bilirubin, and ALT were evaluated at diagnosis in the ECIIN group and between 7 and 10 days (mean value) after LT in the control group. Median serum sodium levels within 7 days after LT were estimated in both groups. Hyponatremia in the pre and postoperative periods was defined as serum sodium concentration lower than 130 mEq/l [12,13]. Similarly, median values of serum creatinine within 7 days after LT were used to estimate the kidney function in the early postoperative period. Renal insufficiency was considered when median values of serum creatinine were >1.5 mg/dl [14]. The rate and type of infections, acute graft rejection, need for boluses of steroids, length of hospital stay, and mortality between the ECIIN group and the control group were also collected. Acute graft rejection was evaluated on the basis of Banff criteria [15]. Moderate and severe graft rejections were treated with 1 g of methylprednisolone three times daily intravenously. All patients were followed after LT until the last outpatient visit or death.

Immunosuppression protocol

Standard immunosuppression in our center included administration of tacrolimus or cyclosporine and prednisone. All patients received methylprednisolone (500 mg intravenously before the surgery and after graft reperfusion) followed by a daily taper from 200 mg to 20 mg of prednisone over 5 days. This dose was maintained until 1 month after transplantation. If there were no signs of graft rejection, prednisone was then tapered progressively and stopped within 6–12 months after transplantation. Tacrolimus was started the first day after transplantation at a dose of 0.1 mg/kg/day and then adjusted to maintain blood levels between 8 and 15 ng/ml within the first 3 months. Cyclosporine was started at 10 mg/kg/day to achieve blood levels between 150 and 300 ng/ml during the first 3 months. In patients with serum creatinine levels ≥1.7 mg/dl before transplantation, tacrolimus or cyclosporine administration was delayed until a reduction in serum creatinine below 1.5 mg/dl was observed. In the meantime, patients were treated with prednisone and mycophenolate mofetil at a dose of 1 g/12 h.

Prophylaxis for infections

All patients received a preoperative intravenous dose of 2 g of ceftazidime plus 400 mg of teicoplanin. Oral trimethoprim-sulfamethoxazole (160/800 mg) was administered every 48 h during the first year after transplantation as prophylaxis for *Pneumocistis jiroveci*. Daily oral nystatin suspension was administrated during the first 3 months. In patients with a donor–recipient cytomegalovirus (CMV) serology mismatch (D+/R−), anti-viral prophylaxis with valganciclovir (900 mg/day) was maintained for 12 weeks. The CMV infection was monitored weekly by means of pp65 anti-genemia from week 2 to week 8 after

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LT and twice monthly until the fourth month post-transplantation.

Evaluation and management of ECIIN

An electroencephalogram (EEG), brain computerized tomography (CT), or magnetic resonance imaging (MRI) was performed in patients who presented seizures or a rapid change in mental status. All patients underwent a detailed history/physical exam and a spinal tap as part of the work up. In these patients, CNI were discontinued and replaced by oral mycophenolate mofetil. CNI were restarted after 48–72 h of the resolution of the episode. Anti-epileptic drugs were administered after any seizures and were continued for 6–12 months. In the remaining patients who developed other moderate/severe neurological symptoms, CT scan or MRI were performed and the dose of CNI was reduced by 50% or held for 12–24 h.

Infections

The following infections were considered: bloodstream infections, pneumonia (upper respiratory tract infections were excluded), deep surgical wound infections, febrile urinary infections, and other infections requiring hospital admission. CMV disease was defined according to the guidelines proposed by Ljungman *et al.* [16]. CMV viral syndrome was diagnosed when compatible clinical symptoms were present and evidence of CMV replication in the blood was detected by the presence of a positive pp65 anti-genemia test. CMV end-organ disease was considered only when a biopsied specimen revealed typical histopathological findings of CMV infection and positive immunohistochemical staining. Fungal infections were defined according to the EORTC/Mycosis Study Group [17].

Statistical analysis

Statistical analysis was performed using SPSS statistical packages (version 15.0; SPSS, Inc., Chicago, IL, USA). Continuous variables were summarized as means (and SD) or medians (range), depending on their homogeneity. Categorical variables were compared using the chi-square or the Fisher exact test when appropriate. Continuous variables were compared using the Student's two-tailed *t*-test or Mann–Whitney *U*-test. Analysis of factors independently associated with ECIIN was performed using binary logistic regression that included predictors with $P < 0.10$ in univariate analysis. The probability of remaining free of clinical complications with 90 days after LT for each group were calculated by using the Kaplan–Meier method and compared by using the log-rank test. Associations are given as odds ratio (OR) with a confidence interval (CI) established at 95%. A two-sided *P*-value <0.05 was considered to be significant.

Results

Twenty-eight (17.7%) of 158 patients developed ECIIN after LT (ECIIN group). In the control group ($n = 130$), none of the patients developed any neurological complications within 1 year after LT. The baseline characteristics of both groups are outlined in Table 1. History of pre-LT HE and pre-LT hyponatremia were more common in the ECIIN group. In addition, patients from the ECIIN group were older than controls, developed more post-LT hyponatremia and had a longer surgical time. Post-LT hyponatremia was more frequent in patients with pre-LT hyponatremia (16/21, 72.2%) compared to normonatremic patients (6/137, 4.4%) before LT ($P < 0.0001$). There were no differences in serum creatinine levels at the time of LT between both groups. Post-LT serum creatinine levels >1.5 mg/dl were also similar between both groups. The development of ECIIN was similar in patients taking either CNI [tacrolimus: 20/115 (17.4%) vs. cyclosporine: 8/43 (18.6%), $P = 0.85$].

Clinical features and management of ECIIN

Altered mental status (stupor, coma, confusion, agitation, and/or psychosis) was the main presentation of ECIIN in 17/28 (60%) patients. Seven patients (25%) developed generalized seizures. Other presentations were aphasia (one patient), dysarthria (one patient), visual disturbance (one patient), and right hemiparesia (one patient). All patients with altered mental status and three patients with seizures had concomitant tremor. Mean time between LT and the diagnosis of ECIIN was 7.5 days (range: 1–26 days). Seizures developed sooner after LT than other presentations (5.4 vs. 8.1 days, $P = 0.29$). High CNI levels (tacrolimus >15 ng/ml; cyclosporine >300 ng/ml) were present in 6/28 (21.5%) patients at the time of ECIIN diagnosis and altered mental status was the main presentation in this subgroup of patients.

An EEG was performed in 21 (75%) patients and radiological imaging of the brain was performed in 23 (82.1%) patients (CT: 19 patients; CT and MRI: four patients). Two-thirds of patients (75%) had slow-wave activity and none had any seizure activity on EEG. Radiological studies were normal in 17/23 patients. Two patients had signs of posterior leukoencephalopathy syndrome on CT and MRI. Small vessel disease and volume loss were present in four patients. All patients with ECIIN underwent at least one EEG, CT, or MRI. The remaining 18% of cases that did not have imaging were evaluated by

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Table 1. Demographic, peri, and postoperative variables in all patients (n = 158).

Variable	ECIIN group (n = 28)	Control group (n = 130)	P-value
Recipient age (years), mean (SD)	57.4 (7.5)	52.8 (10.3)	0.025
Recipient gender (male), *n* (%)	18 (64.3)	88 (67.7)	0.73
Pre-LT MELD score, mean (SD)	16.3 (6.1)	14.9 (7.2)	0.34
Cause of transplantation			
Chronic viral hepatitis, *n* (%)	13 (61.9)	42 (56.8)	0.67
Alcoholic cirrhosis, *n* (%)	5 (23.8)	10 (13.5)	0.31
FAP, *n* (%)	0 (0)	4 (5.4)	0.57
Fulminant hepatic failure, *n* (%)	1 (4.8)	8 (10.8)	0.68
Others, *n* (%)	2 (9.5)	10 (13.5)	0.99
Retransplantation, *n* (%)	2 (7.1)	12 (9.2)	0.99
History of hepatic encephalopathy, *n* (%)	16 (57.1)	37 (28.5)	0.004
Active hepatic encephalopathy at LT, *n* (%)	2 (7.1)	10 (7.3)	0.92
Pre-LT hyponatremia, *n* (%)	7 (25)	14 (10.8)	0.044
Serum creatinine at LT (mg/dl), mean (SD)	1.06 (0.37)	1.00 (0.38)	0.46
Type of donor			
Cadaveric donor, *n* (%)	25 (89.2)	119 (91.5)	0.98
Nonbeating donor, *n* (%)	1 (3.6)	4 (3.1)	0.64
Living donor, *n* (%)	1 (3.6)	3 (2.3)	0.78
FAP recipient, *n* (%)	1 (3.6)	4 (3.1)	0.64
Cold ischemia time (h), mean (SD)	7.39 (2.33)	7.32 (2.26)	0.89
Surgical time (h), mean (SD)	6.97 (1.49)	6.73 (1.35)	0.42
Surgical time >7 h, *n* (%)	15 (53.6)	42 (32.3)	0.03
Post-LT hyponatremia, *n* (%)	8 (28.6)	14 (10.8)	0.014
Post-LT serum creatinine >1.5 mg/dl, *n* (%)	4 (14.3)	11 (8.5)	0.34
Post-LT hypomagnesemia, *n* (%)	10 (35.7)	65 (50)	0.17
Post-LT hypocholesterolemia, *n* (%)	21 (75)	93 (71.5)	0.71
Post-LT glucose (mg/dl), mean (SD)	125 (31)	122 (44)	0.86
Post-LT bilirubin (mg/dl), mean (SD)	3.91 (2.98)	4.18 (3.07)	0.84
Post-LT ALT (U/l), mean (SD)	389 (365)	276 (251)	0.41
Reoperation, *n* (%)	9 (32.1)	26 (20)	0.16

LT, liver transplantation; MELD, model for end-stage liver disease; FAP, familial amyloidotic polyneuropathy; h, hour.

the treating physicians and excluded on the basis of a detailed history and physical exam and spinal tap.

The CNI dose reduction was prescribed in 13 patients (46.4%) and in the remaining 15 patients (53.6%), CNI was initially stopped and switched after the resolution of the ECIIN. Patients with seizures received phenytoin. There were no cases of new onset seizures after the switch of CNI. Before and after the resolution of ECIIN, there were no confirmed cases of stroke, hemorrhage, CNS infection, or central pontine myelinolysis within 6 months after LT.

Risk factors associated with ECIIN

In the univariate analysis, the preoperative risk factors associated with the development of ECIIN were age of recipient, history of pre-LT HE, and pre-LT hyponatremia (Table 1). Surgical time >7 h was the only perioperative factor associated with ECIIN. Finally, post-LT hyponatremia was the only post-transplant variable associated with ECIIN (ECIIN group 28.6% vs. control group 10.8%; P = 0.014). The multivariate analysis included significant variables in univariate analysis as well as alcoholic etiology of liver disease, MELD score, post-LT serum creatinine >1.5 mg/dl, and post-LT hypomagnesemia and hypocholesterolemia. In the analysis, history of pre-LT HE, surgical time >7 h, and post-LT hyponatremia were independent predictors of ECIIN (Table 2).

Clinical events after ECIIN development

The main clinical events occurring within 3 months after LT in those that developed ECIIN are summarized in Table 3. Patients in the ECIIN group had a twofold incidence of acute graft rejection compared to the control group. Furthermore, the incidence of severe graft rejection with a need of steroid bolus therapy was more frequent in this group. The mean time of acute graft rejection diagnosis was similar in both groups (ECIIN group: 17.1 days vs. control group: 16.5 days, P = 0.91).

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Table 2. Risk factors associated with early calcineurin inhibitor-induced neurotoxicity (ECIIN) in the logistic regression analysis.

Variable	Crude OR (CI 95%)	Adjusted OR (CI 95%)	*P*-value
History of pre-LT HE	3.59 (1.52–8.49)	3.16 (1.29–7.75)	0.012
Post-LT hyponatremia	3.22 (1.18–9.29)	3.34 (1.38–9.85)	0.028
Surgical time >7 h	2.73 (1.06–7.05)	2.62 (1.07–6.41)	0.035

LT, liver transplantation; HE, hepatic encephalopathy.

Table 3. Clinical evolution within 90 days after liver transplantation (LT) according to early calcineurin inhibitor-induced neurotoxicity (ECIIN) development.

Variable	ECIIN group (n = 28)	Control group (n = 130)	*P*-value
Acute graft rejection, *n* (%)	13 (46.4)	29 (22.3)	0.009
Steroid bolus therapy*, *n* (%)	7 (25)	15 (11.5)	0.062
Bacterial infections, *n* (%)	15 (53.6)	30 (23.1)	0.001
CMV viral syndrome, *n* (%)	4 (14.3)	2 (1.5)	0.009
CMV end-organ disease, *n* (%)	4 (14.8)	9 (6.9)	0.24
Fungal infection, *n* (%)	5 (17.8)	2 (1.5)	0.002
Invasive aspergillosis, *n* (%)	2 (7.1)	2 (1.5)	0.14
ICU stay (days), mean (SD)	9.4 (16.4)	6.5 (9.2)	0.19
Hospital stay (days), mean (SD)	35.3 (27.78)	20.2 (12.1)	0.009
Death, *n* (%)	2 (7.1)	3 (2.3)	0.21

*Acute graft rejection with need of steroid bolus therapy (3 doses of methylprednisolone, 1 g/day). CMV, cytomegalovirus; ICU, intensive care unit; ECIIN, early calcineurin inhibitor-induced neurotoxicity.

The rate of bacterial infections was significantly higher in the ECIIN group (Table 3). This group had a higher incidence of Staphylococcal (10 episodes/28 patients vs. 10 episodes/130 patients, $P = 0.0001$) and catheter-related infections (9 episodes/28 patients vs. 8 episodes/130 patients, $P = 0.0002$) compared to those of the control group. The isolation of other bacteria as well as the location of other infections were similar in both groups. There was no difference in CMV serology mismatch (D+/R−) between both groups (ECIIN group 7.1% vs. control group 11.5%, $P = 0.49$). Although the incidence of CMV viral syndrome was higher in patients with ECIIN, time between LT and CMV viral syndrome and the incidence of end-organ disease because of CMV were similar in both groups (Table 3). Nonetheless, CMV viral syndrome was more common in patients with acute rejection and ECIIN compared to control patients with acute rejection (30.8% vs. 0%, $P = 0.035$). Patients with ECIIN had a higher frequency of postoperative fungal infections compared to that in the control group (Table 3). In the ECIIN group *Candida* spp. (respiratory tract infection, two episodes) and *Candida tropicalis* (urinary tract infection, one episode) were isolated in three patients. The incidence of invasive aspergillosis within 3 months after LT was similar in both groups. Finally, the probability of remaining free of clinical complications (acute graft rejection or infections) within 90 days after LT was lower in patients that developed ECIIN (log rank $P = 0.001$) (Fig. 1).

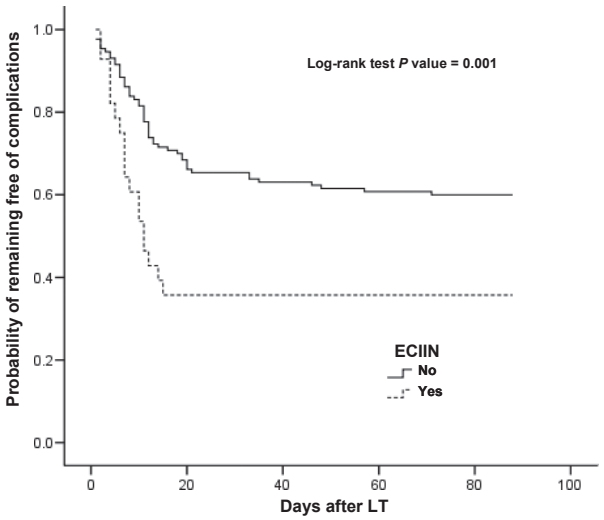

Figure 1 Kaplan–Meier plot showing the 3 months probability of remaining free of complications after liver transplantation (LT) in patients with and without early calcineurin inhibitor-induced neurotoxicity (ECIIN).

Patients in the ECIIN group had a longer hospital stay (median of 15 days longer) than the control group (Table 3). There was no difference in mortality within 90 days after LT between both groups. Septic shock was the cause of all deaths within 90 days after LT.

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Discussion

Neurotoxicity related to CNI use remains a common problem after LT. Previous studies identified several risk factors for CNI neurotoxicity which include age, MELD score, high levels of CNI, ALT, bilirubin, creatinine, glucose, hypocholesterolemia, and/or hypomagnesemia [7,8,10,11]. In addition, one study identified the presence of the polymorphism in the multidrug resistant ABCB1 gene as a risk factor for tacrolimus-induced neurotoxicity [18]. That said, there is a lack of information that specifically identifies pre, peri, and post liver transplant risk factors for ECIIN. The results of this study demonstrate a high frequency (18%) of moderate and severe neurotoxicity related to CNI use within 4 weeks after LT. Novel significant associations between post-LT hyponatremia and prolonged surgical time and the development of ECIIN are described. Furthermore, the present findings confirm previous data regarding the relation between pre-LT HE and neurotoxicity [10,11] and show that the development of ECIIN is associated with early postoperative complications and a prolonged hospital stay.

Several studies previously demonstrated that pre-LT HE is a significant predictor of neurological complications after LT [19–22]. However, there is little evidence showing an association between pre-LT HE and CNI neurotoxicity [10,23]. One study found a relationship between pre-LT HE and mild manifestations of neurotoxicity but failed to show an association with moderate or severe neurological events [10]. Our findings indicate that there is a significant association between pre-LT HE and the development of ECIIN and that pre-LT HE increases the risk of ECIIN by threefold. These findings indicate that patients with HE, which are known to have functional and morphological neurological changes, are at risk of developing neurotoxicity likely because of alterations in astrocyte function, disruption of the blood–brain barrier, and neurotransmitter clearance, but this needs further investigation [19]. In contrast with previous studies, other preoperative factors such as age, etiology of liver disease (i.e. alcohol-related liver disease), and high MELD score were not found to be independent predictors of ECIIN [11,19,23–25].

Hyponatremia is a risk factor for the development of HE in patients with advanced cirrhosis [26]. In addition, patients that undergo LT with hyponatremia develop more neurological complications, renal failure, and bacterial infections during the first 30 days after transplant and an increased 3-month mortality with respect to patients without hyponatremia [13,20]. An important finding of this study is that persistent hyponatremia during the first week after LT clearly increased the risk of ECIIN. Of note, this effect was independent of the presence of renal insufficiency after LT. Interestingly, patients in whom pre-LT hyponatremia was resolved early after LT showed a similar rate of ECIIN than in patients without pre-LT hyponatremia (20% vs. 15.3%). To our knowledge, the association of post-LT hyponatremia and ECIIN has not been previously reported. This indicates that the correction of perioperative hyponatremia might prevent the development and complications associated with ECIIN. Furthermore, new treatments for hyponatremia in cirrhosis with V2 receptor antagonists such as tolvaptan may improve serum sodium levels in listed patients and improve the outcome of patients that undergo LT with low serum sodium levels.

A prolonged surgical period and development of ECIIN have two possible explanations. First, longer periods of surgery lead to a higher exposure to anesthetics, sedatives, and analgesics which may trigger to neurological toxicity of CNI. In addition, there is a higher degree of cytokine release that may contribute to cerebral dysfunction, placing these patients at a higher risk of ECIIN [27]. Second, previous data from other studies indicate that prolonged surgical time is associated with several postoperative complications [28]. In this specific analysis, the underlying reason for this extended surgical time was not fully explored. Furthermore, it may be possible that prolonged surgical time could be a surrogate as these extended procedures are associated with a high rate of transfusion requirements that in turn may impact on 1-year survival rate of LT recipients [29]. Other studies have not demonstrated an association between the duration of the operative procedure and neurological complications after LT [10,21,22,30].

The cohort of patients with ECIIN in this study had a higher incidence of early postoperative complications and a prolonged hospital stay. Patients with ECIIN presented a twofold incidence of acute graft rejection and a higher proportion of severe graft rejection compared to controls. This higher incidence of acute graft rejection in patients with neurotoxicity because of CNI was reported by other investigators [10,31]. Bacterial, viral, and fungal infections within 90 days after LT were also more frequent in patients with ECIIN. This association of ECIIN and a higher rate of infections within 3 months of LT have not been previously reported. In addition, we found a relationship between ECIIN, acute graft rejection, and CMV viral syndrome which could be explained by the modification of immunosuppression in those with ECIIN. Patients with ECIIN presented a longer hospital stay than controls (35 vs. 20 days) which confirms results from previous studies in patients with early neurological complications after LT [32].

There are some limitations in the current study. First, this is a retrospective analysis of patients in one

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high volume center which does not represent the true frequency of unwanted effects in clinical practice. Second, the adequate collection data was the subject of an appropriate recognition and documentation of events by the transplant and intensive care specialists. Although patients were closely followed, subtle neurological changes that might have required modifications of CNI therapy could have gone unnoticed.

In conclusion, a history of pretransplant HE, the presence of hyponatremia within the first week after LT, and a long operative time are predictive factors for ECIIN development. The findings of this study indicate that early management of patients after LT mandates a strict control of serum sodium levels and prevention of hyponatremia particularly in those patients with previous episodes of HE and a prolonged surgical operation. Likewise changes of immunosuppression after ECIIN should be judiciously implemented, particularly in patients with altered mental status, to avoid abrupt modifications of immunosuppression that may lead to acute graft rejection and infections. ECIIN is associated with important clinical complications in the early period of LT such as acute graft rejection and infections, and a longer hospital stay. Further studies are needed to confirm these results and identify LT recipients at risk for CNI neurotoxicity.

Authorship

DB: designed study, collected and analyzed data, analyzed results, and wrote the paper. JP: collected and analyzed data. AC: analyzed data, wrote the paper, and edited the paper. MN: designed study, analyzed data, wrote the paper, and edited the paper.

Funding

Part of the research reported in this article was funded by the ''Emili Letang'' grant from the Hospital Clínic of Barcelona.

References

1. Moore KA, Jones R, Burrows GD. Quality of life and cognitive function of liver transplant patients: a prospective study. *Liver Transpl* 2000; **6**: 633.
2. Mazariegos GV, Molmenti EP, Kramer DJ. Early complications after orthotopic liver transplantation. *Surg Clin N Am* 1999; **79**: 109.
3. Lodi R, Tonon C, Stracciari A, *et al.* Diffusion MRI shows increased water apparent diffusion coefficient in the brain of cirrhotics. *Neurology* 2004; **62**: 762.
4. Lewis MB, Howdle PD. Neurological complications of liver transplantation in adults. *Neurology* 2003; **61**: 1174.
5. Senzolo M, Ferronato C, Burra P. Neurologic complications after solid organ transplantation. *Transpl Int* 2009; **22**: 269.
6. Bronster DJ, Emre S, Boccagni P, Sheiner PA, Schwartz ME, Miller CM. Central nervous system complications in liver transplant recipients—incidence, timing, and long-term follow-up. *Clin Transplant* 2000; **14**: 1.
7. Gijtenbeek JM, van den Bent MJ, Vecht CJ. Cyclosporine neurotoxicity: a review. *J Neurol* 1999; **246**: 339.
8. Bechstein WO. Neurotoxicity of calcineurin inhibitors: impact and clinical management. *Transpl Int* 2000; **13**: 313.
9. Wijdicks EF. Neurotoxicity of immunosuppressive drugs. *Liver Transpl* 2001; **7**: 937.
10. Mueller AR, Platz KP, Bechstein WO, *et al.* Neurotoxicity after orthotopic liver transplantation. A comparison between cyclosporine and FK506. *Transplantation* 1994; **58**: 155.
11. DiMartini A, Fontes P, Dew MA, Lotrich FE, de Vera M. Age, model for end-stage liver disease score, and organ functioning predict posttransplant tacrolimus neurotoxicity. *Liver Transpl* 2008; **14**: 815.
12. Ginès P, Berl T, Bernardi M, *et al.* Hyponatremia in cirrhosis: from pathogenesis to treatment. *Hepatology* 1998; **28**: 851.
13. Londoño MC, Guevara M, Rimola A, *et al.* Hyponatremia impairs early posttransplantation outcome in patients with cirrhosis undergoing liver transplantation. *Gastroenterology* 2006; **130**: 1135.
14. Levey AS, Coresh J, Balk E, *et al.* National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Ann Intern Med* 2003; **139**: 137.
15. Ormonde DG, de Boer WB, Kierath A, *et al.* Banff schema for grading liver allograft rejection: utility in the clinical practice. *Liver Transpl Surg* 1999; **5**: 261.
16. Ljungman P, Griffiths P, Paya C. Definitions of cytomegalovirus infection and disease in transplant recipients. *Clin Infect Dis* 2002; **34**: 1094.
17. Ascioglu S, Rex JH, de Pauw B, *et al.* Defining opportunistic invasive fungal infections in immunocompromised patients with cancer and hematopoietic stem cell transplants: an international consensus. *Clin Infect Dis* 2002; **34**: 7.
18. Yamauchi A, Ieiri I, Kataoka Y, *et al.* Neurotoxicity induced by tacrolimus after liver transplantation: relation to genetic polymorphisms of the ABCB1 (MDR1) gene. *Transplantation* 2002; **74**: 571.
19. Dhar R, Young GB, Marotta P. Perioperative neurological complications after liver transplantation are best predicted by pre-transplant hepatic encephalopathy. *Neurocrit Care* 2008; **8**: 253.
20. Hackworth WA, Heuman DM, Sanyal AJ, *et al.* Effect of hyponatraemia on outcomes following orthotopic liver transplantation. *Liver Int* 2009; **29**: 1071.

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21. Pujol A, Graus F, Rimola A, *et al.* Predictive factors of in-hospital CNS complications following liver transplantation. *Neurology* 1994; **44**: 1226.
22. Saner FH, Gensicke J, Olde Damink SW, *et al.* Neurologic complications in adult living donor liver transplant patients: an underestimated factor? *J Neurol* 2010; **257**: 253.
23. Kanwal F, Chen D, Ting L, *et al.* A model to predict the development of mental status changes of unclear cause after liver transplantation. *Liver Transpl* 2003; **9**: 1312.
24. Saner FH, Sotiropoulos GC, Gu Y, *et al.* Severe neurological events following liver transplantation. *Arch Med Res* 2007; **38**: 75.
25. Buis IC, Wiesner RH, Krom RA, Kremers WK, Wijdicks EF. Acute confusional state following liver transplantation for alcoholic liver disease. *Neurology* 2002; **59**: 601.
26. Guevara M, Baccaro ME, Torre A, *et al.* Hyponatremia is a risk factor of hepatic encephalopathy in patients with cirrhosis: a prospective study with time-dependent analysis. *Am J Gastroenterol* 2009; **104**: 1382.
27. Hei Z, Chi X, Cheng N, Luo G, Li S. Upregulation of TLR2/4 expression in mononuclear cells in postoperative systemic inflammatory response syndrome after liver transplantation. *Mediators Inflamm* 2010; **2010**: 519589.
28. Tenza E, Bernardo CG, Escudero D, *et al.* Liver transplantation complications in the intensive care unit and at 6 months. *Transplant Proc* 2009; **41**: 1050.
29. Massicotte L, Sassine MP, Lenis S, Seal RF, Roy A. Survival rate changes with transfusion of blood products during liver transplantation. *Can J Anaesth* 2005; **52**: 148.
30. Ghaus N, Bohlega S, Rezeig M. Neurological complications in liver transplantation. *J Neurol* 2001; **248**: 1042.
31. Emre S, Genyk Y, Schluger LK, *et al.* Treatment of tacrolimus-related adverse effects by conversion to cyclosporine in liver transplant recipients. *Transpl Int* 2000; **13**: 73.
32. Lewis MB, Howdle PD. Neurologic complications of liver transplantation in adults. *Neurology* 2003; **61**: 1174.

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