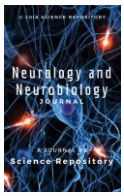

Available online at www.sciencerepository.org

Science Repository

Research Article

Neurological Complications after Liver Transplantation According to Immunosuppressive Therapy

Laura Tortolero*, Javier Nuño, Patricia Luengo, Luis Gajate, Adolfo Buenadicha, Ana Serrano, Fernando Liaño, Roberto Peromingo and Pedro López Hervás

Liver Surgery Department, Ramón y Cajal Hospital, Madrid, Spain

ARTICLE INFO

Article history:
Received: 19 May, 2020
Accepted: 3 June, 2020
Published: 16 July, 2020

Keywords:
Neurological complication
liver transplantation
immunosuppressive therapy
basiliximab
anticalcineurinics
neurotoxicity

ABSTRACT

Background: Neurological complications (NC) after liver transplantation (LT) are frequent, appearing in up to 60% of patients. Etiology is often related to immunosuppressant neurotoxicity and opportunistic infections. The use of basiliximab allows for less toxic immunosuppressive therapies. The aim of this study was to evaluate the neurological complications present during the first 30 days after LT and to evaluate its relationship with renal function, immunosuppressive therapy, and mortality.

Methods: A total of 231 recipients were included in the retrospective, longitudinal, and nonrandomized study under 2 different immunosuppression protocols (with -group B- or without basiliximab -group A-).

Results: NC were present in 14.3% of patients (n: 33), the average age of these patients was 55.4 years. The incidence of NC was significantly higher in group A than in group B (19.5% vs. 9.3% p <0.05), with no differences in the incidence of infection or rejection between both groups. The incidence of acute renal failure, the need for renal replacement therapy, the days of admission to the ICU, the days of hospital admission, as well as mortality during admission and one year after LT were higher among patients with NC. However, when analyzing patients with a neurological complication, patients in group A had a higher incidence of complications than in group B.

Conclusion: The use of immunosuppressive therapies that apply lower doses of anticalcineurinics and with a later onset, classically called nephroprotective as used in group B, could also be neuroprotective, reducing the appearance of neurological complications and, therefore, morbidity. These findings most be verified in studies with a larger number of patients and randomized.

Introduction

Post-transplant neurological complications (NC) have a multiple etiology, and clinically range from mild to life-threatening symptoms. Most common complications include seizures and encephalopathy, and occurrence of central pontine myelinolysis is relatively specific for liver transplant recipients [1]. Its incidence is not well established, given the wide variety of pathologies they cover. Etiology is often related to immunosuppressant neurotoxicity and opportunistic infections. Despite improvements in immunosuppressive therapy, prophylaxis against opportunistic germs, approximately 13% to 60% of liver transplant (LT) recipients have been described as suffering from neurological disorders [2-5]. The delayed use and at lower doses of the anticalcineurinic as an immunosuppressive strategy to minimize postoperative renal damage through immunosuppressive induction with anti-CD25 drugs, such as Basiliximab, may provide improvements in terms of reduction of neurological complications after LT.

The outcome of LT is usually not affected by neurologic complications, but additional morbidity may delay post-transplant recovery [2]. Knowledge of the potentially modifiable risk factors associated with NC

**Correspondence to: Laura Tortolero, Liver Surgery Department, Ramón y Cajal Hospital, Carretera de Colmenar Viejo Km 9, 100, Postal Code 28034, Madrid, Spain; Tel: 34656518646; E-mail: laura_tortolero@yahoo.com*

http://dx.doi.org/10.31487/j.NNB.2020.02.14

can have a high impact on the quality of life and survival of these patients.

The aim of this study was to evaluate the neurological complications present during the first 30 days after liver transplantation and to assess its relationship with immunosuppressive therapy, kidney function, and mortality.

Patients and Methods

Two hundred sixty-five consecutive adult liver transplantation were performed at the Ramón y Cajal Hospital, from August 2007 to December 2014. Two hundred thirty-one recipients were included in the retrospective, longitudinal and nonrandomized study. We therefore excluded: suffer from chronic kidney disease with baseline serum creatinine ≥3 mg/dL, or requirement for renal replacement therapy (RRT); no patient who underwent a simultaneous liver and kidney transplant was included; re-transplanted patients (during de first ten days following the LT) and deceased patients the first ten days after LT. Two immunosuppression groups were established:

i. Group A: Methylprednisolone (5mg/kg IV) was administered intraoperatively followed by 20mg/day IV administration post-transplantation during 3 weeks and gradually tapered to oral prednisone. Oral tacrolimus (0,10-0,15mg/kg/day) was started within 24 hours postoperatively.
ii. Group B: Methylprednisolone (same doses than A group), basiliximab (Novartis Pharma AG, Basle, Switzerland) 20mg was administered 6 hours after portal vein reperfusion. Tacrolimus administration was delayed until third day after surgery (0,10mg/kg/day), and mycophenolate mofetil (CellCept, Roche, Humacao, Puerto Rico) was administered postoperatively with a starting dose of 1000mg each 12 hours.

Neurological complications were recorded during the first 30 days after LT. When a patient presented more than one complication, only the most serious was recorded. All deaths were collected during the first year posttransplant. To determine the risk factors related to renal insufficiency and mortality, preoperative, intraoperative, and postoperative variables were evaluated. Among these, central nervous system complications.

Clinical and biological data were retrospectively gathered from a database. The following parameters were analysed: donor and recipient demographics data, underlying liver disease, Child-Pugh and Model for End Stage Liver Disease (MELD) scores, cold ischemia time, the development of intraoperative reperfusion syndrome, portocaval shunt, requirements for vasopressors and posttransplant transfusions, posttransplant liver and renal function (estimated by KDIGO system), RRT, postoperative complication (arterial, biliary), central nervous system complications, the lengths of admission to the intensive care unit and to the hospital [6]. Renal insufficiency was assessed the first ten days after LT and Mortality at the time of discharge and during the first year after transplantation.

Statistical Analyses

Statistical comparisons between patients alive in the first year with those who do not were undertaken. Pearson´s, Chi-cuadrado or Fisher´s exact test were used for categorical data. Student´s t-test or Mann-Whitney U test were used for quantitative data. Normality assessed with the Kolmogorov-Smirnov test. A multivariate analysis of estimated logistic regression was carried out. Differences were considered to be statistically significant when p was <0.05. Analyses were undertaken using the statistical package SPSS 18 (SPSS Inc, Chicago, IL, USA).

Results

231 patients, 179 men and 52 women, aged between 27 and 68 years, were transplanted, the mean age being 53.3 ± 8.7 years. 41.6% had hepatic encephalopathy (n: 96) at the time of transplantation and 12.1% had hepatorenal syndrome. According to the immunosuppressive regimen used, already described, group A consisted of 113 patients and group B 118, without significant differences in the preoperative variables between both treatment groups, as well as, in the appearance of post-transplant infection (38.9% vs. 29.7%) and in the incidence of acute rejection, being significantly lower in group B (37.2% vs. 17.9% p 0.001).

The overall incidence of acute renal failure was 59.8% (138 patients), present in 70.8% of patients in group A and in 49.2% in group B, this difference showed statistical significance. Requiring renal replacement therapy 17.3% of the general population. The overall stay in days in the intensive care unit was 6.6 ± 8.7 and the days of hospital admission were 28.6 ±28.1. The overall annual survival was 85.2% (197 patients), with mortality during admission being 6.5% and at one year 14.3%.

Table 1: Characteristics of patients in the global study population compared to patients with neurological complications.

Characteristics of patients	Global population (n: 231)	Patients with NC (n: 33)
Age (years)	53,3	55,4
Male sex (%)	77,8	72,8
Indication for LT due to tumor (%)	45,9	42,2
History of hepatic encephalopathy (%)	41,6	75,8
History of hepatorenal syndrome (%)	12,1	18,1
Acute kidney failure after LT (%)	59,8	81,8
Need for RRT (%)	17,3	48,5
Days of admission to the ICU	6,6 +/- 8,7	14,8
Hospital discharge (days)	28,6 +/- 28,1	48
Mortality during admission (%)	6,5	9
Mortality one year after LT (%)	14,3	21,2

ICU: Intensive Care Unit; LT: Liver Transplantation; NC: Neurological Complication; RRT: Renal Replacement Therapy.

Neurological complications occurred in 14.3% of patients (n: 33), the average age was 55.4 years with a range of 38-68 years. The most frequent indication for liver transplantation was tumor in 42.2%, as happened when the entire study population was analysed. Furthermore, 75.8% of them had hepatic encephalopathy and 18.1% hepatorenal syndrome (Table 1).

The NC consisted of a wide group of pathologies such as: low level of consciousness, confusion, encephalopathy, seizures, tremor, dysarthria, myoclonus, transient hemiparesis, polyneuropathy of the critically ill patient, agitation, right parietal stroke and left frontal, Cerebellar and basal ganglia haemorrhage, behavioural abnormality, central pontine myelinolysis and subdural hematoma. Some patients had more than one neurological complication concomitantly. They are presented in (Table 2), according to treatment groups.

Table 2: Central Nervous System Complications.

Presentation	Group A	Group B
Low level of consciousness	7	1
Confusional syndrome	3	2
Encephalopathy	1	3
Seizures	3	0
Tremor	0	2
Dysarthria	1	1
Myoclonus	1	0
Transient hemiparesis	1	0
Critical patient polyneuropathy	1	0
Agitation	0	1
Right parietal stroke, left frontal	1	0
Cerebellar and basal ganglia haemorrhage	1	0
Behavioural abnormality	1	0
Central pontine myelinolysis	1	0
Subdural hematoma	0	1
Total	22 (19,5%)	11 (9,3%)

On the other hand, posttransplant acute renal failure had an incidence of 81.8% among this group of patients, with the need for renal replacement therapy in 48.5% of them. The average of his ICU stay was 14.8 days with a range of 3-59 days and his hospital stay was 48 days (range 16-167 days). Regarding hospital mortality, it was 9% and one year after liver transplantation, 21.2%, in both cases higher than the global study population (Table 1). Next, we present an analysis of neurological complications in relation to:

i. Preoperative kidney function: Among the patients who did not present pre-transplant acute renal failure, there were significant differences in the appearance of NC of group A with respect to group B (group A 18.3% vs. group B 8% p<0.05). However, when analysing patients with acute kidney failure before liver transplantation, there were no significant differences by treatment group (group A 21.3% vs. group B 17.2% p >0.05).

ii. Immunosuppressive treatment: The incidence of NC by treatment groups was significantly higher in group A than in group B (19.5% vs. 9.3% p <0.05) as can be seen in detail in (Table 3). Some of the NC were dose-dependent on tacrolimus and, as previously stated, were more frequently present in patients in group A.

iii. Analysis as a risk factor in postoperative kidney function: NC was a risk factor in the univariate analysis for the development of post-transplant acute renal failure (OR: 3.5, 95% CI 1.4-8.9, p 0.005), but it was not significant in the multivariate analysis (Table 4).

iv. Survival and mortality: Among the patients with a survival greater than 1 year, there were no significant differences in the appearance of NC between treatment groups (14.9% vs. 8.7% p>0.05). Nor was there when analysing the patients who died during the first year after transplantation according to treatment groups (42.1% vs. 13.3% p>0.05).

v. Analysis as a risk factor for mortality one year after transplant: NC was found to be a significant risk factor for mortality in the univariate analysis but not in the multivariate analysis (OR: 3.2, CI: 1.3-7.4, p 0.014) (Table 4).

Table 3: Central Nervous System Complications according to treatment groups.

Factors	Group A N (%)	Group B N (%)	*p*
Patients without preoperative renal failure	15(18.3)	8 (8)	*<0.05*
Patients with preoperative renal failure	17(21.3)	10(17.2)	n.s
Immunosuppressive therapy	22(19.5)	11(9.3)	*<0.05*
Patients alive 1 year after LT	14(14.9)	9(8.7)	n.s
Patients dead 1 year after LT	8(42.1)	2(13.3)	n.s

CI: Confidence Interval; LT: Liver Transplantation; OR: Odds Ratio; n.s: nonsignificant.

Table 4: Factors related to Central Nervous System Complications: Univariate Analysis.

Factors	Present n/N	Absent n/N	P	OR	CI 95%
Renal insufficiency	27/33	111/198	0.005	3.5	1.4-8.9
Mortality one year after LT	10/33	24/198	<0.05	3.2	1.3-7.4

CI: Confidence Interval; LT: Liver Transplantation; n: patient with or without the factor; N: total patients with or without Central Nervous System Complication; OR: odds ratio.

Discussion

The incidence of neurological complications occurs in 13-60% of liver allograft recipients [2-5]. We reported in the present study that the occurrence rate of neurological complications after LT was 14,3% (33/231), including low level of consciousness, confusion, encephalopathy, seizures, tremor, dysarthria, myoclonus, transient hemiparesis, polyneuropathy of the critically ill patient, agitation, right parietal stroke and left frontal, Cerebellar and basal ganglia haemorrhage, behavioural abnormality, central pontine myelinolysis (CPM) and subdural hematoma. The results were similar with the report by Li *et al*. showing that the occurrence rate of NC after LT was 12,2% (54/474) [4]. Central pontine myelinolysis has been reported to have an unfavourable prognosis, which is the main cause of early death in patients [7]. In our case, there was only one case of CMP with a 10-year survival after liver transplantation, although with neurological sequelae (cerebellar ataxia and polyneuropathy). It is interesting to note that patients transplanted from a living donor liver have a lower incidence of neurological complications than patients transplanted with a cadaver donor (20.4% vs. 26.7%, respectively). This cannot be verified in our study because the LT was always carried out from a cadaver donor [8].

Some studies suggest that neurological complications may be related to the high rate of preoperative hepatic encephalopathy associated with an unfavourable clinical condition (malnutrition, pre-transplant kidney dysfunction, hyponatremia, coagulopathy, etc.) [9, 10]. In our study, the antecedents of hepatic encephalopathy and hepatorenal syndrome before

LT were more frequent in the group of patients who developed a neurological complication than in the general study population (41.6% vs 75.8% and 12.1% vs 18.1%, respectively).

As well as the development of acute renal failure, the need for renal replacement therapy were more frequent in this group of patients. Also, the average number of days of admission to the ICU and the hospital, mortality during admission and one year after transplantation were also higher (Table 1). One of the possible explanations for these findings, is that the patients who developed a neurological complication, were in a serious condition and their appearance was a consequence and not a cause of that severity.

The patients were divided according to the immunosuppressive treatment into two groups (group A: higher doses of anticalcineurinic vs group B: delayed introduction and at lower doses of the anticalcineurinic associated with basiliximab), there were no significant differences in the preoperative variables between both groups. However, when we compared the appearance of NC according to the treatment group, these were more frequent in group A than in group B (19.5% vs. 9.3% p <0.05). As well as the appearance of complications among patients with NC were greater in group A than in group B, some significantly (Table 3).

Among the significant results, the higher incidence of neurological complication in patients with normal pre-transplant kidney function compared to those with renal dysfunction may be due to the fact that, among these patients, anticalcineurinic treatment was at a lower dose, even in patients belonging to group A (without basiliximab). As happened according to the immunosuppressive treatment. One of the causes described in the appearance of neurological complications is the use of anticalcineurinics, with neurotoxicity being a frequent side effect of anticalcineurinics [11]. Immunosuppression in the transplant patient is in a delicate balance between toxicity and rejection. In this sense, small doses can be ineffective in avoiding rejection and high doses can be harmful by producing toxic effects. In both cases, the viability of the graft and the life of the patient are compromised. In our study, there were no significant differences in the appearance of postoperative infections between both groups and with a significantly lower incidence of acute rejection in group B.

The mechanism by which the anticalcineurinic affects the central nervous system seems to be related to disorders of natremia control in the immediate postoperative period, due to a poorly understood metabolic mechanism. It presents as a generalized motor disorder that almost always affects the language area, in the form of motor aphasia, and may even leave motor and language sequelae. Withdrawal or decrease of anticalcineurinic improves the clinical picture. On the other hand, tremor due to calcineurin inhibitors is frequent, especially with tacrolimus, but it is not serious and usually reverses with time and dose reduction [12, 13].

In another order of ideal, the appearance of a neurological complication was an independent risk factor associated with the development of post-transplant acute renal failure and one-year mortality, increasing its risk by 3.5 and 3.2 times, respectively, in the univariate analysis, which cannot be confirmed in multivariate analysis. These findings coincide with some authors, although not unanimously [14, 15].

From our study, we deduced that the use of immunosuppressive therapies that apply lower doses of anticalcineurinics and with a later onset, classically called nephroprotective as used in group B, could also be neuroprotective, reducing the appearance of neurological complications and, therefore, morbidity. These findings should be verified in studies with a larger number of patients and randomized.

REFERENCES

1. Zivkovic S (2013) Neurologic complications after liver transplantation. *World J Hepatol* 5: 409-416. [Crossref]
2. Linden P, Zivkovic S (2008) Liver transplantation. In: Biller J, editor The Interface of Neurology and Internal Medicine. Philadlephia: *Lippincott Williams and Wilkins* 2008: 290-294.
3. Weiss N, Thabut D (2019) Neurological Complications Ocurring After Liver Transplantation: Role of Risk Factors, Hepatic Encephalopathy, and Acute (on Chronic) Brain Injury. *Liver Transpl* 25: 469-487. [Crossref]
4. Li C, Jin H, Yuan Q, Cai M, Li Z et al. (2017) Clinical analysis of neurological complications following liver transplantation. *Biomed Res* 28: 2471-2474.
5. Zivkovic SA, Abdel-Hamid H (2010) Neurologic manifestations of transplant complications. *Neurol Clin* 28: 235-251. [Crossref]
6. Scatton O, Meunier B, Cherqui D, Boillot O, Sauvanet A et al. (2001) Randomized trial of choledochocholedochostomy with or without a T tuve in orthotopic liver transplantation. *Ann Surg* 233: 432-437. [Crossref]
7. Ad-hoc working group of ERBP, Fliser D, Laville M, Covic A, Fougue D et al. (2012) European Renal Best Practice (ERBP) position statement on the Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guidelines on acute injury: part 1: definitions, conservative management ant contrast-induced nepropathy. *Nephrol Dial Transplant* 27: 4263-4272. [Crossref]
8. Saner F, Gu Y, Minouchehr S, Ilker K, Fruhauf N et al. (2006) Neurological complications after cadaveric and living donor liver transplantation. *J Neurol* 253: 612-617. [Crossref]
9. Fu K, DiNorcia J, Sher L, Velani S, Akhtar S et al. (2014) Predicitve factors of neurological complications and one-month mortality after liver transplantation. *Front Neurol* 5: 275. [Crossref]
10. Bronster D, Emre S, Boccagni P, Sheiner P, Schwartz M, Miller C (2000) Central nervous system complications in liver transplant recipients -incidence, timing, and long-term follow-up. *Clin Translpant* 14: 1-7.
11. Fraga E, Barrera P, de la Mata M (2007) Inmunosupresión en el trasplante hepático. *Gastroenterol Hepatol* 30: 70-77.
12. Gonzalez-Pinto I, Loinaz C, Gómez R, Jimenez C, Lumbreras C et al. (2006) Perspectivas Futuras en la Inmunosupresión del Trasplante Hepático. In: Vicente E and Loinaz C editores. El Trasplante Hepático en el Comienzo del Milenio. Sao Paulo: Atheneu Hispânica; 2006: 973-984.
13. Clemente G, Díaz A (2008) Complicaciones precoces tras el trasplante hepático. ¿Podemos llegar a predecirlas? *Rev Esp Enferm Dig (Madrid)* 100: 121-128.

14. Lewis M, Howle P (2003) Neurologic complications of liver transplantations in adults. *Neurology* 61: 1174-1178. [Crossref]

15. Fuat Hakan Saner, Georgious C Sotiropoulos, Yanli Gu, Andreas Paul, Arnold Radtke et al. (2007) Sever neurological events following liver transplantation. *Arch Med Res* 38: 75-79. [Crossref]