Neurologic complications in adult living donor liver transplant patients: an underestimated factor?

Fuat Hakan Saner · Julia Gensicke · Steven W. M. Olde Damink · Goran Pavlaković · Juergen Treckmann · Marc Dammann · Gernot M. Kaiser · Georgios C. Sotiropoulos · Arnold Radtke · Susanne Koeppen · Susanne Beckebaum · Vito Cicinnati · Silvio Nadalin · Massimo Malagó · Andreas Paul · Christoph E. Broelsch

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Abstract Liver transplantation is the only curative treatment in patients with end-stage liver disease. Neurological complications (NC) are increasingly reported to occur in patients after cadaveric liver transplantation. This retrospective cohort study aims to evaluate the incidence and causes of NC in living donor liver transplant (LDLT) patients in our transplant center. Between August 1998 and December 2005, 121 adult LDLT patients were recruited into our study. 17% of patients experienced NC, and it occurred significantly more frequently in patients with alcoholic cirrhosis (42%) and autoimmune hepatitis (43%) as compared with patients with hepatitis B or C (9/10%, \( P = 0.013 \)). The most common NC was encephalopathy (47.6%) followed by seizures (9.5%). The choice of immunosuppression by calcineurin inhibitor (Tacrolimus or Cyclosporin A) showed no significant difference in the incidence of NC (19 vs. 17%). The occurrence of NC did not influence the clinical outcome, since mortality rate, median ICU stay and length of hospital stay were similar between the two groups. Most patients who survived showed a nearly complete recovery of their NC. NCs occur in approximately 1 in 6 patients after LDLT and seem to be predominantly transient in nature, without major impact on clinical outcome.

Keywords Encephalopathy · Liver transplantation · Neurological complication · Immunosuppression · Living donor

Abbreviations
NC Neurologic complication
TAC Tacrolimus
CSA Cyclosporine A
AST Aspartate transaminase
ALT Alanine transaminase
ESLD End-stage liver disease
LDLT Living donor liver transplantation

Introduction

Liver transplantation (LT) has been performed since 1963 [29]. At that time all patients died from uncontrolled bleeding or acute rejection. The first successful liver transplantation was performed in 1967 [28]. Since that time
survival rates of patients undergoing LT have improved markedly, mostly due to improved peri-operative care, operative techniques and improved immune suppressive therapy [7, 23]. Improved long-term survival after LT has led to increasing awareness of the occurrence of neurological complications (NC) in recent years [15, 24, 27]. NCs in patients following LT are reported to occur in up to 75% of cases [1, 8, 9, 13, 21, 22]. The main diagnoses of NC are encephalopathy, seizure, immunosuppressant related neurotoxicity, and peripheral nerve damage [1, 31, 32]. Due to organ shortage, the first clinical LDLT program was started by Broelsch [4, 5] at the University of Chicago in 1989 and has become an alternative approach for adult and pediatric liver transplantation in many centers throughout the world [17]. We conducted this retrospective cohort study to evaluate the incidence of NCs in LDLT patients in our center.

Patients and methods

The study was conducted in accordance with the Declaration of Helsinki. Adult living donor liver transplant recipients transplanted at the Department of General-, Visceral- and Transplant Surgery, University Duisburg-Essen, Germany between October 1998 and December 2005 were included in the analysis. Exclusion criteria were pediatric patients (age <18 years) and incomplete patient records. Our policy towards the selection of patients appropriate for LDLT has been described elsewhere [17, 33].

All operations were performed using standard surgical techniques and a standardized anesthesia protocol was applied to all patients. Patients were treated postoperatively in a single intensive care unit applying standardized care consisting of triple immune suppression [corticosteroids, mycophenolate mofetil (MMF) and tacrolimus (TAC) or cyclosporine A (CSA)], antimicrobial prophylaxis and selective digestive decontamination [26]. Daily trough levels of the calcineurin inhibitors (CNIs) (TAC or CSA) were measured for adjusting the daily dose. Rejection episodes of the graft were treated with 500 mg prednisolone three times daily intravenously. Renal replacement therapy (CVVHD) was initiated if creatinine exceeded 2.5 mg/dL, if blood urea nitrogen exceeded 100 mg/dL or if patients had impaired oxygenation due to volume overload. Blood samples were collected 1 day before liver transplantation and then every morning after liver transplantation until the patient was discharged from the ICU. Laboratory routine work-up was performed daily and included at least total bilirubin, aspartate transaminase (AST), alanine transaminase (ALT), creatinine, c-reactive protein (CRP), hemoglobin, leukocytes, platelets and international normalized ratio (INR). The follow-up was 1 year for all patients.

Definition

Diagnoses of NCs were assessed by neurologic examination, cerebral computed tomography (cCT) or cerebral magnetic resonance tomography (cMRT). A central nervous system complication was considered to occur when there was clinical and/or radiologic evidence of central nervous system damage which was not associated with a poor graft function, sepsis or other diseases that could be associated with central nervous system signs. Delirium, stupor and coma with regular cCT or cMRT images were grouped under the term encephalopathy.

Clinical examinations were performed by the ICU and transplantation staff. The clinical diagnoses were confirmed by neurologists.

Statistical analyses

Categorical variables were analyzed by the Chi-squared test with Yates correction. Continuous variables were analyzed by the one-way analysis of variance and t test, when normal distribution was given. Non-normally distributed continuous variables were analyzed by the Kruskal–Wallis one-way analysis of variance on ranks. The Mann–Whitney Rank Sum test was performed when the equal variance test failed; P < 0.05 was considered significant. Data are presented as mean ± SD.

Results

 Patients

From October 1998 to December 2005, 167 living donor transplantations were performed at the surgical department of the University of Essen; of these 34 were transplantations in pediatric patients that were not enrolled into the study. Twelve of the 133 adult LDLT patients had incomplete records, so were also excluded from the study. Complete medical records of the remaining 121 adult patients were retrospectively reviewed. The primary liver diagnoses are listed in Table 1.

Incidence of neurological complications

After LDLT, 17% of patients (10 men, 11 women, age 48 ± 14) experienced NCs. The most common complication was encephalopathy, including somnolence, mental alteration and confabulation, which occurred in ten
patients. Two patients experienced seizures, another two developed peripheral polyneuropathy. The trough levels of CSA or TAC at the time of NC onset were in the therapeutic range (for TAC 8–15 ng/ml, for CSA 200–250 ng/ml). Miscellaneous complications occurred in seven patients [posterior leucencephalopthy (1), ischemic stroke (1), intracerebral bleeding (1), heparin-induced thrombocytopenia related ischemia (2), subarachnoidal hemorrhage (1), and pontine myelinolysis (1), see Table 2]. The patient with the ischemic stroke suffered from post transplant diabetes, whereas the patient with the intracerebral hemorrhage suffered from hypertension.

The occurrence of NC could not be explained by differences in MELD score, ICU- hospital stay or cold- and warm ischemia time between the groups (see Table 3). 52% of patients that experienced NC (11/21 patients) already showed pretransplant signs of advanced encephalopathy, as opposed to 15% (15/100 patients) in the group without NC (P < 0.001).

In both patient groups the clinical course of the transplanted liver graft was normal and did not differ significantly (see Table 4). We recorded a significant decline of AST on admission compared with 1 week following transplantation within each group. Bilirubin remained nearly the same 1 week after transplantation as compared with the value on admission to the ICU. Renal function, expressed as serum creatinine concentrations, did not alter during the first week following transplantation in either group (see Tables 4, 5).

Most NCs (90%) were encountered in the first month after LT. In the majority of cases, encephalopathy (80%) and seizure (60%) presented in the first 2 weeks. Only one patient experienced NC after hospital discharge.

Effect of the primary diagnosis on NC

Viral hepatitis and alcoholic cirrhosis were the main causes of pre-operative liver decompensation (see Table 1). 42% of the alcoholic group and 43% of the autoimmune group showed the highest rate of NCs. The incidence of NC in these groups was significantly higher as compared to patients with hepatitis B or hepatitis C (9.4%, P = 0.006 and P = 0.04, respectively).

Patients with autoimmune hepatitis received significantly more immunosuppressive drugs preoperatively, such as prednisone or azathioprine, as compared with patients suffering from PBC or PSB [4/7 (57%) vs. 2/17 (12%), P = 0.02].

| Underlying disease       | Number of patients (%) |
|--------------------------|------------------------|
| Hepatitis C              | 43 (36)                |
| Hepatitis B              | 21 (17)                |
| Alcoholic cirrhosis      | 14 (12)                |
| PBC/PSC                  | 17 (14)                |
| Autoimmune hepatitis     | 7 (6)                  |
| Cryptogenic              | 9 (7)                  |
| Miscellaneous            | 10 (8)                 |
| Total                    | 121 (100)              |

Miscellaneous: Cholangiocellular carcinoma (2), Klatskin tumor (1), M. Wilson (1), Neuroendocrine tumor (2), acute intermittent porphyria (1), sarcoma of the liver (1), hemangiosarcoma of the liver (1), α1 antitrypsine deficiency (1)

| Table 3 Perioperative patients’ data | Patients with NC | Patients without NC |
|--------------------------------------|------------------|---------------------|
| MELD score                           | 18 ± 2           | 16 ± 1              |
| Ventilation time in h                | 106 ± 34         | 99 ± 25             |
| ICU stay in days                     | 12 ± 4           | 11 ± 2              |
| Hospital stay in days                | 37 ± 6           | 58 ± 27             |
| WIT (min)                            | 43 ± 9           | 42 ± 4              |
| CIT (min)                            | 224 ± 28         | 225 ± 13            |
| GBWR                                 | 1.05 ± 0.2       | 1.1 ± 0.25          |
| 1 Year survival (%)                  | 74               | 70                  |

All data are given as mean ± SD

WIT warm ischemia time, CIT cold ischemia time, GBWR graft body weight ratio

| Table 2 Type of neurological complication | Complication     | Number | Incidence (%) |
|------------------------------------------|------------------|--------|---------------|
| Encephalopathy                           | 10               | 48     |
| Seizure                                  | 2                | 10     |
| Peripheral polyneuropathy                | 2                | 10     |
| Miscellaneousa                           | 7                | 33     |
| Total                                    | 21               |        |

*a Miscellaneous diagnoses see text
Influence of neurologic complications on outcome after LDLT

The occurrence of NC in patients after LDLT did not influence the main clinical outcome parameters median ICU stay, length of hospital stay or one year survival (see Table 3). The long term neurological function did not differ between the groups.

Effect of the calcineurin inhibitor on neurological complications

CSA was the predominantly used immunosuppressant in our cohort (78 of all patients), whereas 43 patients were treated with TAC. NCs occurred in 19% of TAC treated patients, and in 17% of the CSA-group ($P = 0.9$).

Discussion

The present study shows that NCs occur frequently after LDLT. The reported incidence of NC after cadaveric liver transplantation ranges from 10 to 75% [8, 9, 13, 21, 22]. In the present study the rate of NCs was 17%. The main clinical outcome parameters median ICU stay, hospital stay and one year survival rate did not differ between patients with and without NC. The MELD score and graft function were comparable in patients with and without NCs. Patients with alcoholic and autoimmune related cirrhosis showed a significant higher rate of NCs as compared with other diagnoses. Development of NC after LDLT was related to pre-transplant deterioration in neurological function, but was not influenced by type of immunosuppressant used.

The incidence of NC in 17% of patients observed in our study is comparable with other reports. Kim et al. [15] reported an incidence of 15.4% of NC in their LDLT patients. The incidence of NC in LT patients with a deceased donor was recorded to be 25% in the group of Mueller [20]. The highest incidence of NCs in LT patients with a deceased donor was mentioned by Ghaus et al. [13] with an incidence of 75%. The reason for the higher incidence of NC in the Ghaus study [13] may be the smaller number of evaluated patients (21 vs. 45 patients), whereas the Mueller study [20] recruited 130 patients. Moreover, Ghaus [13] et al. also included peripheral neurologic disorders such as tremor, which may be responsible for this high incidence of 75% in their study.

Diffuse encephalopathy is considered to be the main NC in patients after liver transplantation [19]. Encephalopathy was also the main NC in the present study, with an incidence rate of 48%. The cause of post-transplant encephalopathy in patients with a primary functioning graft remains unclear. Post mortem results of an anecdotal study indicate anoxic–ischemic changes as the main neuropathological findings, which could be the cause of encephalopathy [10].

The second most common cause of NC in LT patients is seizures. The reported incidence is up to 20% [16, 22]. In our study the incidence of seizures was 10% and confirmed previous data from our group, which indicates an incidence of 11.6% [22]. In the recent 10 years the rates of seizures seems to have declined. One center reported a reduction in the incidence of seizures in patients following LT from 42% [34] to 0% [31] at two different time periods. The reasons for this reduction could be improved postoperative intensive care, improvement in accurate diagnosis and treatment of metabolic disorders, and improved immunosuppressive drugs with fewer side effects.

In the present study, one patient developed central pontine myelinolysis (CPM). CPM was first described in 1959 [2] and first reported after a liver transplantation in 1978 [30]. CPM presents symmetrical demyelinating lesions at the center of the pons. Despite being first described in alcoholics and malnourished patients, several reports describe its occurrence in patients after liver transplantation, with incidence rates ranging between 1.2 and 10% [3, 6]. Due to study design, the incidence of CPM in autopsy studies is significantly higher as compared with clinical studies.

The etiology and pathogenesis of CPM remains unclear, though rapid correction of hyponatremia seems to be a main factor which triggers this syndrome with signs of dysarthria, paraparesis or quadriaparesis [36]. The patient in our report died due to lack of causative treatment. However, in some selected cases a combination of plasmapheresis and immunoglobulins could be considered as a rescue treatment [25].
Furthermore, one patient developed posterior leukoencephalopathy (PLE), which was first described in 1996 [14]. This illness was recognized as a reversible syndrome of headache, visual abnormalities and hemipareses induced by severe hypertension. After successful treatment of hypertension all patients recovered. However, our group published a case of a LDLT patient, who developed a TAC related PLE 3 months after transplantation. On admission she was comatose and remained unconscious until she died [12].

It has been documented that the incidence of NC is higher in patients receiving liver grafts from deceased donors for alcoholic and primary biliary cirrhosis [16]. In contrast to our data, Kim et al. [15] did not find a relationship between NCs and primary liver diagnosis in LDLT patients. Our data indicate a significant higher rate of NC in patients who received a transplant for alcoholic liver disease and autoimmune hepatitis.

In our study the survival rate of patients with or without NC did not differ significantly. In a prospective clinical trial, Pujol et al. [21] showed a significant higher mortality rate for liver transplant patients with NC as compared to those without (55 vs. 17%), whereas Wijdecks et al. [35] indicate no impact of NC on mortality.

The relationship between immunosuppressive therapy and the development of NC has been well established for calcineurin inhibitors [20]. McDiarmid [18] reported a higher incidence of NC in TAC based immunosuppression regime as compared with CSA. The incidence of major NCs such as coma, seizures, and encephalopathy occurred only in the TAC group. This observation is supported by the study of Mueller [20], who showed a significantly higher incidence of NC in patients treated with TAC as compared with CS. However, both authors initially used the intravenous formulation of TAC, which is recognized as inducing more neurologic complications than TAC administered via the oral route. Freise [11] and Lewis [16] did not find higher rates of NC in patients treated with TAC as compared with CSA. These data are supported by the present study.

In conclusion, the present report emphasises the frequent development of NCs following liver transplant patients. A careful recognition, diagnosis of central nervous system lesions and prompt treatment is necessary.

**Conflict of interest statement** The authors have no financial or other potential conflicts of interest.

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