NÖRO PSİKİYATRİ ARŞİVİ

Research Article / Araştırma Makalesi

Arch Neuropsychiatr 2015; 52: 15-8 • DOI: 10.5152/npa.2015.7226

Evaluation of Early Postoperative Neurological Complications Following Living Donor Liver Transplantation

Canlı Vericili Karaciğer Nakli Sonrasında Erken Dönemde Gelişen Nörolojik Komplikasyonların Değerlendirilmesi

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ABSTRACT

Introduction: Liver transplantation is one of the best treatment options for end-stage liver disease. In Turkey, living donor liver transplantation (LDLT) is performed more frequently than cadaveric transplantation, because organ donation is unpopular in our country. Neurological complications contribute to poor postoperative outcomes after liver transplantation. In the present study, we aimed to evaluate the outcomes of LDLT patients in whom such complications developed early during postoperative follow-up in the intensive care unit.

Methods: Of 217 LDLTs performed between August 2011 and August 2012, neurology consultations were arranged for 29 patients (13.36%) because of development of new-onset neurological symptoms and/or findings in patients with neurologically uneventful preoperative histories. We retrospectively collected data on age, gender, primary disease, Model for End-Stage Liver Disease (MELD) score, and postoperative hospitalization duration of those who survived. The indications for neurological consultation and diagnoses were categorized into acute confusion/encephalopathy, epileptic seizures, leukoencephalopathy, and focal neurological deficits. The immunosuppressive treatment regimens prescribed were also considered. The outcomes of the 2 groups (with and without neurological complications) were compared.

Results: The mean patient age was 44.52±16.24 years, and males predominated (65.5%, n=19). Acute confusion/encephalopathy was the most frequent complication (62.1%, n=18), followed by epileptic seizures (27.6%, n=8), cerebrovascular disease (6.9%, n=2), and leukoencephalopathy (3.4%, n=1). Statistically significant between-group differences in age (44.5±16.2 vs. 34.33±20.98 years; p<0.001), and proportions of patients with a disease of viral etiology (55.17% vs. 35.63%, p<0.05), were evident. Mortality was significantly higher in the group with neurological complications (65.5% vs. 37.32%, p<0.05). The duration of postoperative hospitalization was also significantly longer in this group (29.80±15.04 vs. 10.00±5.47 days; p<0.05).

Conclusion: Mortality was significantly higher and the duration of postoperative hospitalization significantly longer in LDLT patients with new-onset neurological complications than in those without such complications.

Keywords: Liver transplantation, neurological complication, encephalopathy, immunosuppression.

ÖZET

Amaç: Karaciğer nakli, son dönem karaciğer yetmezliğinin tedavisinde en seçkin yöntemdir. Ülkemizde organ bağışı oranının ihtiyaçları karşılayacak düzeyin altında olması nedeniyle canlı vericili karaciğer nakli (CVKN) daha sık uygulanmaktadır. Karaciğer nakli sonrası postoperatif dönemde gelişen nörolojik komplikasyonlar kötü prognozda önemli bir yer tutmaktadır. Çalışmanın amacı, CVKN yapılan ve kliniğimize ait yoğun bakım ünitesinde izlenen hastalarda postoperatif erken dönemde gelişen nörolojik komplikasyonları değerlendirmektir.

Yöntem: Ağustos 2011–Ağustos 2012 arasında 217 CVKN yapılan hasta içinde preoperatif dönemde herhangi bir nörolojik yakınması olmayan fakat postoperatif erken dönemdeki izlemleri sırasında yeni gelişen nörolojik semptom ve/veya bulgular nedeniyle nöroloji bölümünden konsültasyonu istenen hastalar çalışmaya dahil edildi. 217 CVKN yapılan hastanın 29'unda (%13,36) nöroloji konsültasyonu istenmişti. Hastaların yaş, cinsiyet, primer hastalıkları, Model for End Stage Liver Disease (MELD) skoru, yaşayan hastaların hastanede kalış süreleri, kullanılan immunsupresif tedavilere ilişkin veriler retrospektif olarak incelendi. Konsültasyon endikasyonları ve tanıları akut konfüzyonel durum/ensefalopati, epileptik nöbet, serebrovasküler hastalık başlıkları altında sınıflandı. Nörolojik komplikasyon gelişen ve gelişmeyen hastalar iki grup halinde bu veriler yönünden karşılaştırıldı.

Bulgular: Yaş ortalaması 44,52±16,24 olan hastalarda erkek cinsiyet baskın idi (%65,5, n=19). Sıklık sırasına göre akut konfüzyonel durum/ensefalopati (%65,5, n=19), epileptik nöbet (%27,6, n=8), ve serebrovasküler hastalık (%6,9, n=2) gelişmişti. Nörolojik komplikasyon gelişmeyen hastalarla kıyaslandığında, erken dönemde nörolojik komplikasyon gelişen hastalarda yaş ortalaması (44,5±16,2'ye karşılık 34,33±20,98), etiyolojide viral nedenlerin oranı (%55,17'ye karşılık %35,63), postoperatif hastanede kalış süresi (10±5,47 gün'e karşılık 29,80±15,04 gün) ve mortalite oranı (%65,5'e karşılık %37,32) anlamlı derecede yüksekti.

Sonuç: CVKN hastalarında erken dönemde gelişen nörolojik komplikasyonlar postoperatif hastanede kalış süresini uzatmakta ve sağ kalıma olumsuz etki göstermektedir.

Anahtar kelimeler: Karaciğer nakli, nörolojik komplikasyon, ensefalopati, immunsupresyon

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Received/Geliş Tarihi: 26.04.2013 **Accepted/Kabul Tarihi:** 19.01.2014

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INTRODUCTION

Orthotopic liver transplantation (OLT) is the only current definitive treatment for those with end-stage liver disease (1). However, liver transplantation is also indicated for those with acute liver failure, selected metabolic derangements with or without associated liver failure, and hepatocellular carcinoma (or, very rarely, other tumors) (1). Significant progress in OLT surgical techniques and postoperative management of OLT has been made over the last 2 decades, and new immunosuppressive regimens have been developed. The survival of OLT recipients has improved (1,2).

Acute graft rejection, ischemic hepatic injury, difficulties in psychological adjustment, technical problems with vascular or biliary anastomotic sites, renal failure, recurrent liver disease, and complications of immunosuppressive treatment can all occur after liver transplantation (1,2,3,4). In addition, neurological complications including encephalopathy, seizures, infections, cerebrovascular disease, difficulties associated with the use of immunosuppressive agents, and neoplasms have been reported to occur in 9.7%-46% of patients who undergo OLT (2,4,5). Both neurological and other complications are associated with poor outcomes, independent of the Model for End-Stage Liver Disease (MELD) score (3,4) used to assess the severity of liver disease. This scoring system is also used to prioritize allocation of liver transplants. MELD uses serum bilirubin and creatinine levels and the international normalized ratio (INR) of prothrombin time to predict survival. Higher MELD scores are associated with poorer outcomes (6). Cadaveric organ donation is unpopular in Turkey and thus living donor liver transplantation (LDLT) is performed more frequently.

The aim of the present study was to evaluate the incidence of early postoperative neurological complications developing during postoperative intensive care unit (ICU) follow-up of LDLT patients.

METHODS

Study Design

We retrospectively reviewed the medical records of 217 patients who underwent LDLT in our institution between August 2011 and August 2012. We identified all patients who received neurology consultations because of the development of new-onset neurological symptoms and/or signs during postoperative follow-up in the ICU. We excluded all patients with histories of any preoperative neurological disorder.

Evaluation of the Study Population

Age, gender, primary disease, MELD score, and postoperative duration of hospitalization were recorded. The immunosuppressive regimens employed were also examined.

The indications for neurology consultation and diagnoses were reviewed. Patients with preoperative histories of neurological disorders, those with predisposing neurological factors treated via fluid/electrolyte replacement, those with modifications or termination of immunosuppressive treatment, or those undergoing treatment for infection were excluded. In other words, we confined our analysis to patients with new-onset postoperative neurological symptoms. If a neurological condition was not fully diagnosed, that patient was excluded from the study.

Neurological complications were categorized into 3 groups: acute confusion/encephalopathy, epileptic seizures, and cerebrovascular disease. Patients were divided into 2 groups on the basis of the presence or absence of such complications. Those with complications were placed in Group 1 and those without complications were in Group 2. The 2 groups were compared in terms of the MELD score, duration of postoperative hospitalization, and mortality rate.

Statistical Analysis

Statistical analysis was performed using PASW Statistics version 18.0 (PASW Statistics, Chicago, IL, USA). Data are presented as means± standard deviations (SDs). Between-group differences in continuous variables were compared using the t-test and the independent samples Mann-Whitney U-test. Fisher's exact chi-square test was used to compare differences in categorical variables. An alpha level of ≤0.05 was considered to reflect statistical significance.

RESULTS

A total of 217 LDLT patients were included in the present study. Neurology consultations were scheduled for 29 (13.36%) patients because of the development of new-onset neurological symptoms.

Demographic and Clinical Characteristics

The mean age of all patients was 44.52±16.24 years, and males predominated (65.5%, n=19). Of the primary diseases, HBV was the most common (44.8%, n=13), followed by cryptogenic cirrhosis (10.3%, n=3) and HCV (10.3%, n=3).

Acute confusion/encephalopathy was the most frequent neurological complication (65.5%, n=19), followed by epileptic seizures (27.6%, n=8) and cerebrovascular disease (6.9%, n=2).

Of the patients with seizures, 50% (n=4) had a history of FK506 treatment. In 2 patients, there were strong signals on T2 and FLAIR imaging in the bilateral basal ganglia; however, in both patients, diffusion had normalized in the basal ganglia. In 1 patient, there were isolated T2 changes in the basal ganglia and deep gray matter, with no associated diffusion restriction. The mean number of seizures was 1.75±1.63. All these patients had multiple seizures (range: 2-6). A single patient had 1 seizure episode (status epilepticus) without any radiological deficits and benefited from anti-epileptic treatment. No patient with seizures had other neurological symptoms or deficits.

Ischemic stroke was another major presentation in patients. One patient had a cerebral infarct in the right frontoparietal region (right middle cerebral artery). Another patient had a brain stem infarct (basilar artery infarct). The mean time taken to complete diagnosis of a neurological complication was 15.21±13.37 days.

The basic demographic data and the clinical characteristics of the groups are shown in Table 1. We conducted between-group comparisons of mean ages, proportions of patients with a disease of viral etiology, MELD scores, durations of postoperative hospitalization, and mortality rates. Statistically significant between-group differences were observed in terms of both age (44.5±16.2 vs. 34.33±20.98 years; p<0.001) and proportion of patients with a disease of viral etiology (55.17% vs. 35.63%; p<0.05). The MELD score of Group 1 was 22.52±10.97 and that of Group 2

Table 1. Basic demographic and clinical characteristics of the groups

Characteristic	Group 1 (%)	Group 2 (%)
Age	44.5±16.2	34.33±20.98
Male	19 (65.5)	117 (62.23)
Female	10 (34.5)	71 (37.76)
HBV	13 (44.8)	55 (29.25)
Cryptogenic cirrhosis	3 (10.3)	33 (17.55)
HCV	3 (10.3)	12 (6.38)

Table 2. Statistical analysis of the groups

Parameter	Group 1 (new-onset neurological complications) (n=29)	Group 2 (without new-onset neurological complications) (n=188)	p
MELD score (min–max)	22.5±10.97 (7-40)	22.6±10.97 (7-48)	0.36
Postoperative hospitalization (days) (min-max)	29.8±15.04 (3-147)	10.0±5.47 (3-128)	<0.001
Mortality (n, %)	19, 65.5%	10, 34.5%	<0.001
MELD: Model for End-Stage Liver Disease			

22.6±10.97; these scores did not significantly differ (p=0.36). The duration of postoperative hospitalization in Group 1 was 29.80±15.04 days, significantly higher than that in Group 2 (10.00±5.47 days; p<0.05). The overall mortality rate was 37.3% (81/217 patients). The mortality rate in Group 1 was 65.5% (19/29 patients) and that in Group 2 34.5% (10/29). The mortality rate was significantly higher in Group 1 (p<0.05). These findings are summarized in Table 2.

Immunosuppressive Treatment

Treatment with methylprednisolone commenced (in the ICU) at a dose of 100 mg/day and was tapered with reference to graft functional status. On postoperative day 3, tacrolimus (2 mg/day) and cyclosporine (200 mg/day) were commenced if no contraindication was evident.

DISCUSSION

Neurological complications occur in 9.7%-42% of patients after liver transplantation (4). We found that the early postoperative neurological complication rate was 13.36%. Most such complications (75%) arose during the first postoperative month (2), and the mean time to diagnosis of the complications was 15.21±13.37 days.

Mean patient age and proportion of patients with a disease of viral etiology were significantly higher in those with early postoperative neurological complications. Previous studies have also indicated that older patients are more prone to the development of neurological complications (6,7).

Patients with histories of viral infection had a significantly higher postoperative incidence of new-onset neurological complications, in line with the findings of previous studies (7,8,9). However, further studies on possible correlations between disease etiology and development of neurological complications are required.

Acute confusion/encephalopathy was the most frequent complication observed (65.5%, n=19), followed by seizures and cerebrovascular disease. Lewis et al. (10) found that diffuse encephalopathy was the most frequent complication.

The second most common complication observed was seizures (27.6%; n=16). Lewis et al. (8) diagnosed seizures at a rate of 6%. In our present study, 50% (n=4) of patients with seizures had histories of FK506 (tacrolimus) treatment. In 3 patients, there were changes that were attributed to hypoxic-ischemic brain injury.

Liang et al. (2) studied neurological complications of liver transplantation and found that FK506 may contribute to the development of seizures. Bronster et al. (11) explored central nervous system complications of liver transplantation and found that 28.95% of seizures were associated with prescription of immunosuppressive drugs and that immunosuppressive treatment may contribute to the development of all observed neurological complications.

One of 2 patients with focal neurological deficits died. Our small number of patients rendered it difficult to compare mortality rates among patients with other neurological complications. Further studies with larger numbers of patients are essential.

In our study, cerebrovascular disease was observed in 2 patients. Both were diagnosed as cerebral infarction. Acute cerebrovascular disorders occur in 2%-6.5% of liver transplantation recipients, usually within 2 months following surgery (5).

Several risk factors have been described, some of which are directly associated with the primary disease (coagulation disturbances), and others are secondary to immunosuppressive therapy such as hypercholesterolemia, diabetes, and hypertension (5,7). Focal deficits may be obscured by diffuse encephalopathic findings. This may result in radiological underdiagnosis, and some patients with encephalopathy in our study may have a concomitant cerebrovascular disorder (12). Perioperative events, such as cerebral hypoperfusion and massive transfusion, may also favor cerebrovascular injury (5).

The duration of hospitalization was significantly longer in patients with neurological complications than in those without neurological complications. Lewis et al. (10) found that such complications developing after liver transplantation were associated with poor survival rates and longer hospital stays.

Neurological complications developing after liver transplantation are quite common and increase both mortality and the duration of hospital stay.

Conflict of Interest: The authors declared no conflict of interest.

Financial Disclosure: The authors declared that this study has received no financial support.

Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

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