NEUROLOGICAL DISORDERS IN LIVER TRANSPLANTATION

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Background and purpose – Liver transplantation is the only curative treatment in patients with end-stage liver failure. It has been associated with neurological disorders more frequently than other solid organ transplantations. We aimed to detect neurological disorders in liver transplantation patients and determine those that affect mortality.
Methods – One hundred eighty-five patients, 105 with and 80 without neurological disorders, were included in this study. The follow-up was categorized into three periods: preoperative, early postoperative and late postoperative. We analyzed all medical records, including demographic, laboratory, radiological, and clinical data.
Results – Neurological disorders were observed in 52 (28.1%) patients in the preoperative period, in 45 (24.3%) in the early postoperative, and in 42 (22.7%) in the late postoperative period. Hepatic encephalopathy in the preoperative and altered mental state in the postoperative period were the most common neurological disorders. Both hepatic encephalopathy (37.5%) and altered mental state (57.7%) caused high mortality (p=0.019 and 0.001) and were determined as independent risk factors for mortality. Living donor transplantation caused less frequent mental deterioration (p=0.049). The mortality rate (53.8%) was high in patients with seizures (p=0.019). While mortality was 28.6% in Wilson's disease patients with neurological disorders, no death was observed in patients without neurological disorders.
Conclusion – We identified a wide variety of neurological disorders in liver transplantation patients. We also demonstrated that serious neurological disorders, including hepatic encephalopathy and seizures, are associated with

NEUROLÓGIAI KÓRKÉPEK MÁJÁTÜLTETETT BETEGEKBEN

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Háttér és cél – A májtranszplantáció a végstádiumú májelégtelenségben szenvedők egyetlen kuratív lehetősége. A májtranszplantáció a többi szervátültetéshez képest gyakrabban társul neurológiai betegségekkel. Vizsgálatunk célja az volt, hogy számba vegyük, milyen neurológiai rendellenességek jelentkeznek a májtranszplantáltak körében, és meghatározzuk, hogy ezek közül melyek befolyásolják a mortalitást.
Módszerek – Száznyolcvanöt beteget vontunk be a vizsgálatba, közülük 105-nek voltak neurológiai rendellenességei, míg 80-nak nem. Az utánkövetést három periódusba soroltuk: preoperatív, korai posztoperatív és késői posztoperatív szakaszba. Elemeztük az összes orvosi feljegyzést, beleértve a demográfiai, laboratóriumi, radiológiai és klinikai adatokat is.
Eredmények – Neurológiai rendellenességeket 52 betegnél (28,1%) figyeltünk meg a preoperatív periódusban, 45 betegnél (24,3%) a korai posztoperatív, és 42 betegnél (22,7%) a késői posztoperatív időszakban. A leggyakoribb neurológiai rendellenesség a preoperatív szakaszban a hepaticus encephalopathia, a posztoperatív szakaszban pedig a módosult mentális állapot volt. A hepaticus encephalopathia és a módosult mentális állapot egyaránt magas mortalitást okozott (37,5% és 57,7%; p = 0,019 és 0,001), és a halálozás független rizikófaktorának bizonyult. Az élő donoros transzplantáció ritkábban okozott mentális állapotromlást (p = 0,049). A halálozási arány magas volt (53,8%) a rohamokban szenvedő betegeknél (p = 0,019). Míg a neurológiai rendellenességben szenvedő Wilson-kóros betegeknél 28,6%-os volt a mortalitás, a neurológiai rendellenességekkel nem rendelkező betegek körében nem fordult elő haláleset.

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high morbidity and mortality. Therefore, in order to avoid poor outcomes, hepatic encephalopathy should be considered as a prioritization criterion for liver transplantation.

Keywords: *liver transplantation, neurological disorders, hepatic encephalopathy, altered mental status, Wilson's disease*

Következtetés – Számos neurológiai rendellenességet azonosítottunk a májtranszplantált betegek körében. Kimutattuk azt is, hogy a súlyos neurológiai rendellenességek, beleértve a hepaticus encephalopathiát és a görcsrohamokat, magas morbiditással és mortalitással járnak. Ezért a rossz kimenetel elkerülése érdekében a hepaticus encephalopathiát a májtranszplantáció elsőbbségi kritériumának kell tekinteni.

Kulcsszavak: *májtranszplantáció, neurológiai rendellenességek, hepaticus encephalopathia, módosult mentális állapot, Wilson-kór*

Liver transplantation (LT) has become a life-saving treatment for patients with end-stage liver disease, acute liver failure (ALF), and well-selected hepatocellular carcinoma (HCC). Although enormous advances have been made since the first successful LT in 1967, problems related to postoperative complications, the patient's survival time, graft failure, and organ allocation have not been completely eliminated[1–3].

In the pretransplant period, LT candidates may develop a wide variety of neurological disorders (ND) depending on the degree of liver failure and underlying etiological causes. LT, which is a major surgical procedure, is itself also the cause of serious NDs such as mental deterioration and seizure[4, 5]. In the posttransplant period, potent immunosuppressants lead to NDs through an increased risk of opportunistic infections and direct neurotoxic effects. When all these are taken together, 30-40% of LT patients experience neurological problems during their follow-up. This rate is much higher than the frequency of NDs in other solid organ transplantations[3, 4].

Several studies have shown that neurological problems increase poor outcomes after transplantation[6, 7]. Today, prioritization in organ allocation in LT is based solely on Model for End-stage Liver Disease (MELD) score, with the exception of HCC cases[8]. Even serious NDs are not considered as an indication for LT. Some authors suggest that hepatic encephalopathy (HE) patients should be prioritized in the LT list, and that such an approach prevents poor outcomes after transplantation[9]. However, other researchers claim that the existence of NDs in LT patients has no effect on mortality[10, 11]. Therefore, whether NDs affect the prognosis of LT patients remains a controversial issue.

We aimed firstly to detect NDs in the preoperative, early, and late postoperative periods in LT patients, secondly to determine which NDs affect mortality, and thirdly to investigate whether HE affects the NDs observed in the early and late postoperative periods.

Methods

This study was conducted in Ankara City Hospital. Patients who had undergone LT and received follow-up care in the liver transplantation unit were retrospectively evaluated, and 185 patients were included in the study. Patients who did not come regularly for post-transplant follow-up were excluded from the study. All patients with adequate and regular medical records were included in our study. We analyzed all written and electronic medical records, including demographic data, medical history, hospital admissions, preoperative and postoperative follow-up, clinical course, laboratory data, and radiographic studies. We recorded patients' pre-transplantation information, including age, sex, height, weight, medical comorbidities, liver failure etiology, presence of HE, ascites, and esophageal varices, MELD score, donor type, transplant urgency, and transplant time. The parameters recorded in the postoperative period were laboratory values, immunosuppressive agents and their serum concentrations, and the last transplantation unit visit or date of death.

The follow-up of the patients was categorized into three periods, including preoperative (the time before transplantation), early postoperative (the first 30 days after transplantation), and late postoperative (the time from 30 days after transplantation to the last visit or death).

Patients who developed neurological findings in any of these periods were put in the group with ND (105 patients) and the others in the group without

Table 1. *Neurological disorders according to follow-up periods in patients with liver transplantation*

	Preoperative	Postoperative Early	Postoperative Late
All neurological disorders	*52 (28.10%)*	*45 (24.32%)*	*42 (22.70%)*
HE/AMS	48 (25.94%)	26 (14.05%)	10 (5.40%)
Cerebrovascular event	-	3 (1.62%)	2 (1.08%)
Seizure	2 (1.08%)	9 (4.86%)	3 (1.62%)
PRES	-	1 (0.54%)	1 (0.54%)
Central pontine myelinolysis	-	1 (0.54%)	-
Wernicke encephalopathy	-	1 (0.54%)	-
ALS-like disorder	-	-	2 (1.08%)
Headache	2 (1.08%)	1 (0.54%)	16 (8.64%)
Peripheral neuronal damage	4 (2.16%)	14 (7.56%)	16 (8.64%)
Compression neuropathy	-	*6*	1
Toxic-metabolic	*4*	*7*	*15*
Guillain-Barre syndrome	-	*1*	-
Tremor	2 (1.08%)	6 (3.24%)	7 (3.78%)

HE: hepatic encephalopathy, AMS: altered mental state, PRES: posterior reversible encephalopathy syndrome, ALS: amyotrophic lateral sclerosis

ND (80 patients). We defined any change in consciousness or transient delirium as an altered mental state (AMS). The immunosuppression regimen of our liver transplantation unit included calcineurin inhibitor, mycophenolate mofetil, inhibitors of the mammalian target of rapamycin, and steroids. Immunosuppressive drug doses were adjusted according to each patient's medical condition and the associated side effects.

This retrospective study was approved by the local ethical committee (Ankara City Hospital Ethics Committee, E1-20-993).

All statistical analyses were done using IBM SPSS statistic 22.0 (Chicago, IL, USA). Data were expressed as mean±SD. Continuous variables were compared using the Mann-Whitney U test. Categorical variables were compared using the Chi-Square test. Binary logistic regression analysis was performed to detect independent factors associated with mortality. A p-value < 0.05 was considered statistically significant.

Results

ND was observed in 52 (28.1%) patients in the preoperative period, in 45 (24.3%) in the early postoperative period, and in 42 (22.7%) in the late postoperative period **(Table 1)**. HE was the most common ND in the preoperative period. While the most common ND in the early postoperative period was AMS, it was severe headache and peripheral neuronal damage in the late postoperative period **(Table 1)**. All other NDs detected in LT patients according to their follow-up periods are presented in **Table 1**. Age, gender, donor type, body mass index, and MELD score were similar in both groups with and without ND (p=0.977, p=0.986, p=0.544, p=0.831, and p=0.068, respectively). There was no significant difference between the two groups in terms of etiological causes, comorbid diseases, HCC, cirrhosis complications and acute kidney injury **(Table 2)**. The mortality rate in the group with ND was higher than without (p=0.043) **(Table 2)**. All laboratory data are presented in **Table 2**.

Patients with HE in the preoperative period had a higher MELD score and mortality rate than those without HE (p=0.001 and p=0.019) **(Table 3)**. HE was determined as an independent risk factor for mortality (p=0.040) (Odds ratio=2.485, %95 confidence interval; 1.043-5.921). While HE in the preoperative period caused more frequent AMS and seizure in the early postoperative period (p=0.001 and p=0.016), it did not affect the late postoperative period **(Table 3)**.

Patients with AMS in the early postoperative period had a higher mortality rate than those without AMS (57.7% vs 19.5%, p=0.001). AMS was determined as an independent risk factor for mortality in the early postoperative period **(Table 4)**. In the early postoperative period, while AMS and tremor were observed more frequently in patients with deceased donors than those with living donors (p=0.049 and p=0.047), there was no difference between the two groups in terms of other NDs **(Table 5)**. NDs in patients with deceased or living donors were similar in the late postoperative periods **(Table 5)**. Seizure emerged more frequently in

Table 2. *Comparison of demographic, laboratory, and clinical data of the group with ND and without ND*

	Group without ND n=80	Group with ND n=105	p
Age	47.31±10.85	47.16±11.53	0.977
Gender female / Male	26 (32.5%) / 54 (67.5%)	34 (32.4%) / 71(67.6%)	0.986
Donor type living / Deceased	47 (58.8%) / 33 (41.2%)	57 (54.3%) / 48 (45.7%)	0.544
Mortality	14 (17.5%)	32 (30.5%)	*0.043*
MELD	22.07±4.70	24.62±8.48	0.090
BMI	26.37±4.44	26.42±4.74	0.831
Etiology			
Hepatitis B virus	34 (42.5%)	48(45.7%)	
Hepatitis B virus + Delta	*8*	*8*	
Hepatitis C virus	8 (10.0%)	10 (9.5%)	
Alcoholic	4 (5.0%)	6 (5.7%)	
Autoimmune diseases	9 (11.3%)	6 (5.7%)	
Wilson disease	5 (6.3%)	7 (6.7%)	0.395
Toxic hepatitis	2 (2.5%)	10 (9.5%)	
Cryptogenic	9 (11.3%)	8 (7.6%)	
NASH	-	3 (2.9%)	
Liver malignancy	2 (2.5%)	2 (1.9%)	
Miscellaneous	7 (8.8%)	5 (4.8%)	
HCC	32 (40%)	28 (26.9%)	0.061
Complications of cirrhosis			
Ascites	39 (48.8%)	48 (45.7%)	0.682
Variceal bleeding	9 (11.3%)	12 (11.4%)	0.970
Acute kidney injury	-	5 (4.8%)	0.071
Comorbidities			
Cardiovascular diseases	5 (6.3%)	3 (2.9%)	0.261
Hypertension	22 (27.5%)	20 (19.0%)	0.174
Diabetes mellitus	24 (30.0%)	28 (26.7%)	0.625
Chronic pulmonary disease	7 (8.8%)	7 (6.7%)	0.596
Chronic renal failure	1 (1.3%)	4 (3.8%)	0.288
Laboratory tests			
Alanine aminotransferase U/L	173.14±301.74	528.94±1159.87	0.190
Aspartate aminotransferase U/L	167.39±367.31	555.38±1216.52	*0.043*
Albumin g/L	3.44±0.79	3.33±0.66	0.383
Total bilirubin mg/dL	3.34±3.22	7.08±8.58	*0.019*
Creatinine mg/dL	0.81±0.24	1.07±0.62	*0.005*
Sodium mmol/L	138.28±5.82	138.45±7.17	0.736
Platelets 109/L	98.90±67.26	125.25±96.42	0.177
Hemoglobin g/dL	11.94±2.54	11.32±2.47	0.078
INR	1.66±0.50	2.17±1.26	*0.019*
Tacrolimus mg/mL	8.85±3.07	9.22±3.90	0.495

ND: neurological disorder, MELD: Model for End-stage Liver Disease, BMI: body mass index, NASH: nonalcoholic steatohepatitis, HCC: hepatocellular carcinoma, INR: international normalized ratio

the early postoperative period (4.86%) than in the preoperative (1.08%) and late postoperative periods (1.62%) **(Table 1)**. The mortality rate (7/13, 53.8%) was high in patients who developed seizures (p=0.019).

In our study group, there were 12 Wilson's disease patients (30.41±8.90 years old). NDs were detected in seven patients during follow-up. In the preoperative period, encephalopathy was observed in four patients, and three of them developed AMS in the early postoperative period. Two of the seven Wilson's disease patients with neurological involvement (28.6%) died. One of the patients with Wilson's disease who died had developed AMS nine months before transplantation, and the other developed AMS and seizure attack six months before. None of the Wilson's disease patients without neurological involvement in the preoperative period died.

Table 3. *Comparison of demographic and clinical data of the groups with HE and without HE in the preoperative period*

	Group without HE n=137	Group with HE n=48	p
Age	47.90±11.00	45.29±11.71	0.188
Gender Female / Male	41 (29.9%) / 96 (70.1%)	19 (39.6%) / 29 (60.4%)	0.219
MELD	21.93±5.75	27.87±8.82	*0.001*
Mortality	28 (20.4%)	18 (37.5%)	*0.019*
Neurological disorders in the early postoperative period			
Altered mental state	12 (8.8%)	14 (29.2%)	*0.001*
Neuropathy	11 (8.0%)	3 (6.3%)	0.688
Seizure	3 (2.2%)	5 (10.4%)	*0.016*
Focal involvement	2 (1.5%)	1 (2.1%)	0.769
Tremor	4 (2.9%)	2 (4.2%)	0.675
Headache	-	1 (2.1%)	0.090
Neurological disorders in the late postoperative period			
Altered mental state	6 (4.4%)	4 (8.3%)	0.297
Neuropathy	10 (7.3%)	5 (10.4%)	0.496
Seizure	3 (2.2%)	-	0.301
Focal involvement	2 (1.5%)	-	0.400
Tremor	5 (3.6%)	2 (4.2%)	0.872
Headache	13 (9.5 %)	3 (6.3%)	0.492

HE: hepatic encephalopathy, MELD: Model for End-stage Liver Disease

Table 4. *Independent factors associated with mortality in the early postoperative period*

	Mortality		
	p	Exp(B)	95% CI
Age	0.206	1.024	0.987 - 1.062
Donor type	0.996	0.988	0.472 - 2.107
MELD score	0.580	1.017	0.957 - 1.081
Hepatocellular carcinoma	0.987	0.993	0.429 - 2.298
Acute liver failure	0.755	1.226	0.340 - 4.417
Seizure	0.094	4.170	0.783 - 22.220
Altered mental state	*0.004*	4.190	1.562 - 11.243

MELD: Model for End-stage Liver Disease

Discussion

We detected that more than half of the patients with LT developed ND during follow-up. Mental deterioration was the most common neurological disorder in both preoperative and postoperative periods. HE and early postoperative AMS were associated with high mortality rates. Living donor LT was linked with a lower frequency of AMS. We found that seizure attacks resulted in increased mortality. There was an increase in the development of peripheral nerve damage in the postoperative period.

HE is one of the most common neurological complications of cirrhosis[9, 12]. The presence of HE in the pretransplantation period has been associated with perioperative complications occurring after LT[4]. Dhar et al. suggested that preoperative HE is a strong predictor of postoperative morbidity[7]. Consistent with this, in our study, we showed that one-third of patients with preoperative HE developed AMS in the early posttransplantation period. We also found a mortality rate of up to 40% in these patients. HE alone is not generally accepted as an indication for LT unless there is a significant increase in the MELD score[2, 9, 12]. Considering the serious negative impact of severe HE on postoperative outcomes, some authors have stated that overt HE should be considered as a high priority criterion

Table 5. *Comparison of demographic and clinical data of the deceased donor group and the living donor group*

	Donor Type		
	Deceased donor n=81	Living donor n=104	p
Age	48.81±11.15	45.99±11.16	0.073
Gender Female / Male	26 (32.1%) / 55 (67.9%)	34 (32.7%) / 70 (67.3%)	0.932
MELD	23.34±5.57	23.62±8.23	0.965
Mortality	22 (27.2%)	24 (23.1%)	0.524
Hepatic encephalopathy	22 (27.2%)	26 (25.0%)	0.739
Neurological disorders in the early postoperative period			
Altered mental state	16 (19.8%)	10 (9.6%)	*0.049*
Neuropathy	6 (7.4%)	8 (7.7%)	0.942
Seizure	4 (4.9%)	4 (3.8%)	0.717
Focal involvement	-	3 (2.9%)	0.123
Tremor	5 (6.2%)	1 (1.0%)	*0.047*
Headache	1 (1.2%)	-	0.256
Neurological disorders in the late postoperative period			
Altered mental state	4 (4.9%)	6 (5.8%)	0.804
Neuropathy	5 (6.2%)	10 (9.6%)	0.395
Seizure	1 (1.2%)	2 (1.9%)	0.713
Focal involvement	2 (2.5%)	-	0.107
Tremor	4 (4.9%)	3 (2.9%)	0.468
Headache	7 (8.6%)	9 (8.7%)	0.998

MELD: Model for End-stage Liver Disease

for LT[9]. Our results support the prioritization of HE patients, as suggested by those authors.

Seizure is another important complication seen in patients with LT. Incidence of seizure has been reported as 5-10% in LT patients. The most common causes of seizure attacks in LT patients are immunosuppressive drug toxicity, infections, metabolic disorders, hypoxia, and cerebrovascular events[3, 4, 13]. Seizure attacks increase the risk of mortality. The underlying cause of seizures is the main factor that determines the prognosis. Seizures caused by immunosuppressant toxicity have a good prognosis, whereas those caused by cerebrovascular events and sepsis have a poor prognosis[14]. We demonstrated that the seizure frequency was 7.02%, and the mortality rate in these patients was 53.8%.

The question regarding whether the use of living or deceased donors in LT affects the type or frequency of neurological complications has remained a curious topic. Although a handful of well-designed studies in the literature have evaluated living and deceased donor transplantations in terms of neurological complications, they have not compared the findings in detail[11, 15]. Although we found a lower frequency of mental deterioration and tremors in the early postoperative period in living donor LT, the frequency of neurological complications in the late postoperative period was similar in living and deceased donor LT. In our study, the mortality rate was slightly lower in living donor LT patients, but was not significant. Using living donors in risky patients may cause a decrease in severe neurological complications in the postoperative period.

The LT decision is based on the severity of liver disease in Wilson's disease patients unresponsive to medical therapy. Neurological involvement alone is not an indication for LT. Even if neurological complaints improve after LT, the presence of advanced neurological symptoms before LT continues to be a poor prognostic factor in survival[9, 16]. While no deaths were observed after LT in our patients without neurological complaints, the mortality rate was 28.6% in those with neurological involvement. Considering that the mean age of Wilson's disease patients in our cohort is about two decades younger than other patients, we may see how dramatically the mortality rate has risen. Therefore, prioritizing Wilson's disease patients on the LT list before their neurological conditions become severe would positively affect their prognosis[9].

Although not life-threatening, neuropathies are neurological complications seen after LT that sig-

nificantly reduce the quality of life. They are associated with prolonged immobile positioning, stretching during operation, metabolic disturbances, immunosuppressive agents, and extended intensive care unit stay[17]. We detected peripheral neuronal damage in approximately 15% of patients in the postoperative period.

Our study's major contribution is its detailed comparison of neurological complications in living and deceased donor LT according to the type of complication and the time of their appearance.

The limitation of our study was that we only assessed overt HE, because evaluation tests for minimal HE were not performed regularly. Therefore, we could not evaluate minimal HE's effect on neurological complications and mortality.

Conclusion

Preoperative HE is a predictor of increased mortality and serious neurological disorders in the early postoperative period. Therefore, taking into account the presence of neurological disorders in the prioritization of the LT list would be effective in reducing postoperative morbidity and mortality. Living donor LT in risky patients may contribute to the success of transplantation.

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The authors report no conflict of interest.

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