Ochsner Journal 17:25–30, 2017

Post–Liver Transplant Delirium Increases Mortality and Length of Stay

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Background: Incidence of delirium after liver transplantation (LT) has been reported to occur in 10%-47% of patients and is associated with increased hospital and intensive care unit lengths of stay and poor outcomes.

Methods: Our primary objective was to evaluate the incidence and predisposing risk factors for developing delirium after LT. Our secondary objectives were to describe how delirium is managed in patients after LT, to examine the utilization of resources associated with delirium after LT, and to analyze the outcomes of patients who were treated for delirium after LT.

Results: In a population of 181 consecutive patients who received an LT, 38 (21.0%) developed delirium. In the multivariate analysis, delirium was associated with pretransplant use of antidepressants (odds ratio [OR] 3.34, 95% confidence interval [CI] 1.29-8.70) and pretransplant hospital admission for encephalopathy (OR 4.39, 95% CI 1.77-10.9). Patients with delirium spent more time on mechanical ventilation (2.0 vs 1.3 days, P=0.008) and had longer intensive care unit stays (4.6 vs 2.7 days, P=0.008), longer hospital stays (27.6 vs 11.2 days, P=0.003), and higher 6-month mortality (13.2% vs 1.4%, P=0.003) than patients who did not develop delirium.

Conclusion: The presence of delirium is common after LT and is associated with high morbidity and mortality within the first 6 months posttransplant. Pretransplant factors independently associated with developing delirium after LT include prior use of antidepressants and pretransplant hospital admission for encephalopathy. Efforts should be made to identify patients at risk for delirium, as protocol-based management may improve outcomes in a cost-effective manner.

Keywords: *Cognition disorders, delirium, liver transplantation, postoperative complications*

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INTRODUCTION

Delirium is a disturbance in cognition that includes altered attention, awareness, orientation, memory, and perception and develops during a short period of time.[1] The causes of delirium are highly variable, but delirium may result from medications, substance intoxication or withdrawal, or underlying medical conditions or it may be multifactorial.[1] Specifically in transplant patients, delirium may be caused by metabolic disturbances, infections, organ failure leading to hepatic or uremic encephalopathy, or neurotoxic side effects from immunosuppression medications such as calcineurin inhibitors or high-dose steroids. The incidence of delirium in general surgery patients has been reported to be as high as 53%, with the number increasing to 87% in patients admitted to the intensive care unit (ICU).[1,2] After liver transplantation (LT), the incidence of delirium has been reported to be as low as 10% in deceased-donor organ recipients and as high as 47% in living-donor organ recipients.[3-5]

While delirium in patients in the ICU has been well described, few studies focus on the risk factors and consequences of delirium specific to LT. These studies have reported that a history of alcohol abuse, preoperative hepatic encephalopathy, preoperative renal replacement therapy, intraoperative transfusion of packed red blood cells, need for mechanical ventilation, urgent LT, retransplantation, and high APACHE II (Acute Physiology and Chronic Health Evaluation) scores may contribute to the development of post-LT delirium.[4-8] The consequences of posttransplant delirium in patients in the ICU include increased length of ICU and hospital stay, increased mortality during transplant hospital admission, and increased rates of 1-year posttransplant mortality.[4,5]

The primary objective of this study was to evaluate the incidence and predisposing risk factors for developing delirium after LT. Our secondary objectives were to describe how delirium is managed in patients after LT, to examine the

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utilization of resources associated with delirium after LT, and to analyze the outcomes of patients who were treated for delirium after LT.

METHODS

In this single-center, retrospective, cohort study, we enrolled all patients aged ≥18 years who received an LT from October 1, 2012 to March 31, 2014. To identify patients with delirium, electronic medical records (EMRs) of LT recipients were searched for a diagnosis of delirium. In addition, we reviewed the EMRs of patients who were administered antipsychotics, benzodiazepines, or antidepressant medications for clinical notes that reflected mental changes or conditions consistent with delirium.

Immediately prior to the transplant, patients received induction therapy either with a steroid (methylprednisolone) protocol or thymoglobulin. Thymoglobulin induction was given to patients with hepatitis C and a Model for End-Stage Liver Disease (MELD) score <25 in an effort to minimize hepatitis C recurrence after LT. All patients were initiated on a tacrolimus-based maintenance immunosuppression regimen in combination with mycophenolate and a prednisone taper. Patients who underwent steroid induction (the methylprednisolone protocol) were targeted to be on tacrolimus monotherapy at 6 weeks. The thymoglobulin protocol is steroid free by postoperative day 2, and patients are targeted to be on tacrolimus monotherapy after 2 weeks.

Data Collection

We collected patient characteristics including sex, age, body mass index (BMI), medical history, previous hospital admission history, home medications, reason for transplant, MELD score at time of transplant, details of transplant surgery, and postoperative hospital course from the EMRs. Pertinent details of transplant surgery included cold ischemic time, type of donor, number of units of packed red blood cells infused during surgery, induction immunosuppression used, post-LT peak of alanine aminotransferase (ALT) and aspartate aminotransferase (AST), change in serum sodium within 48 hours of transplant (delta sodium), and type of transplant (liver alone vs liver/kidney). Postoperative information collected included ICU length of stay, hospital length of stay, days on mechanical ventilation, maintenance immunosuppression, laboratory results at the time of delirium onset, medications used to treat delirium, tests ordered to work up altered mental status, microbiology results at the time of delirium onset, and disposition.

Statistical Analysis

Data were analyzed using SAS v.9.3 (SAS Institute Inc.). For bivariate analysis, chi-square analysis was used for categorical variables, and continuous variables were analyzed with either a *t* test or a Wilcoxon rank sum test, selected based on an assessment of normality via the Shapiro-Wilk test. Logistic regression was utilized for multivariate analysis, with a stepwise selection protocol implemented to select for the most appropriate variables associated with the outcome. We considered *P* values <0.05 statistically significant.

RESULTS

Study Population

Throughout the 18-month study period, 181 consecutive patients underwent deceased-donor LT (Table 1). Of 181 patients, 38 (21.0%) developed delirium after a mean of 6.9 days (interquartile range, 4-8 days). No significant differences were observed between patients who developed delirium vs those who did not regarding age, sex, BMI, or indication for transplantation. Patients who developed delirium were more likely to have a previous hospital admission for hepatic encephalopathy (36.8% vs 16.8%, *P*=0.010), a history of depression (52.6% vs 32.2%, *P*=0.022), or a history of antidepressant therapy just prior to surgery (44.7% vs 21.0%, *P*=0.004).

Risk Factors for Delirium

In the univariate analysis, MELD scores were significantly higher in the delirium group compared to the nondelirium group (25.0 vs 19.2, *P*=0.003), as was the number of units of packed red blood cells infused during surgery (7.9 units vs 3.5 units, *P*<0.001). Mean 24-hour change in serum sodium (delta sodium) was significantly higher in the delirium group (9.6 mEq/L vs 7.4 mEq/L, *P*=0.002). A significantly higher number of patients in the delirium group were admitted to the hospital at the time of transplant offer compared to the nondelirium group (55.3% vs 23.1%, *P*<0.001).

After multivariate analysis, factors associated with an increased odds ratio (OR) for developing delirium included pretransplant use of antidepressants (OR 3.34, 95% confidence interval [CI] 1.29-8.70) and pretransplant hospital admission for encephalopathy (OR 4.39, 95% CI 1.77-10.9).

Management of Delirium

Table 2 lists patient characteristics at the time of delirium onset. The mean tacrolimus level at the time of delirium onset was 6.2 ng/mL, with 3 (7.9%) patients having a supratherapeutic level >12 ng/mL. Of patients with delirium, 18.4% had a documented infection at the time of onset, all of whom were administered antibiotics at the time. Of 31 patients who did not have a documented infection, 22 (71.0%) were administered antibiotics empirically at the time of delirium onset.

Table 3 delineates the management of delirium. The 2 most common pharmacologic agents used to treat patients were olanzapine and quetiapine, both of which were used in >50% of the cohort of patients with delirium. With the potential adverse effect of neurotoxicity, tacrolimus was held in 18.4% of patients with delirium and was switched to either cyclosporine or sirolimus in another 18.4%. As expected, significantly more patients in the delirium group underwent neurologic evaluation compared to the nondelirium group, and more patients in the delirium group required head computed tomography (CT) scans (65.8% vs 5.6%, *P*<0.001), head magnetic resonance imaging (MRI) studies (31.6% vs 0.7%, *P*<0.001), and neurologic and/or psychiatric consult service requests (76.3% vs 6.9%, *P*<0.001) compared to the nondelirium group. In only 4 (10.5%) of the 38 patients in the delirium group did the extensive neurologic testing (head CT scans, MRI, electroencephalogram [EEG], or lumbar puncture) reveal abnormal results: 1 patient showed evidence of status epilepticus on EEG, 1

Table 1. Baseline Characteristics

Characteristic	Delirium Group (n=38)	Nondelirium Group (n=143)	*P* Value
Mean age, years	58.33	57.20	0.477
Male sex, n (%)	26 (68.4)	95 (66.4)	0.817
Mean body mass index, kg/m^2	26.8	28.5	0.118
Medical history, n (%)			
ESRD on HD	3 (7.9)	8 (5.6)	0.608
Bipolar disorder	2 (5.3)	1 (0.7)	0.0853
Depression	20 (52.6)	46 (32.2)	0.022
Home antidepressant	17 (44.7)	30 (21.0)	0.004
Home antipyschotic	3 (7.9)	3 (2.1)	0.109
Home benzodiazapine	4 (10.5)	13 (9.1)	0.790
Past hospital admission for encephalopathy	14 (36.8)	24 (16.8)	0.010
Reason for transplant, n (%)			
Hepatitis B	0 (0)	3 (2.1)	0.232
Hepatitis C	15 (39.5)	73 (51.0)	0.203
ETOH	10 (26.3)	24 (16.8)	0.195
Autoimmune disorder	0 (0)	7 (4.9)	0.066
NASH	5 (13.2)	27 (18.9)	0.398
PBC/PSC	1 (2.6)	5 (3.5)	0.787
Fulminant hepatic failure	1 (2.6)	4 (2.8)	0.956
Other	6 (15.8)	22 (15.4)	0.93
Transplant details			
Admitted at time of transplant offer, n (%)	21 (55.3)	33 (23.1)	<0.001
Mean MELD score	25.0	19.2	0.003
Mean intraoperative packed red blood cells, units	7.9	3.5	<0.001
Mean cold ischemic time, min	343.6	311.3	0.176
DBD, n (%)	32 (84.2)	128 (89.5)	0.432
DCD, n (%)	6 (15.8)	15 (10.5)	0.382
Liver alone, n (%)	32 (84.2)	126 (88.1)	0.521
Liver/kidney, n (%)	6 (15.8)	17 (11.9)	0.530
Previous transplant, n (%)	4 (10.5)	7 (4.9)	0.226
Mean AST peak, ng/dL	1,762.9	1,821.4	0.887
Mean ALT peak, ng/dL	1,039.0	868.8	0.466
Mean 24-h delta sodium, mEq/L	9.6	7.4	0.002
Steroid induction, n (%)	32 (84.2)	102 (71.3)	0.107
Thymoglobulin induction, n (%)	6 (15.8)	41 (28.7)	0.093

ALT, alanine aminotransferase; AST, aspartate aminotransferase; DBD, donation after brain death; DCD, donation after cardiac death; ESRD, end-stage renal disease; ETOH, ethyl alcohol; HD, hemodialysis; MELD, Model for End-Stage Liver Disease; NASH, nonalcoholic steatohepatitis; PBC/PSC, primary biliary cirrhosis/primary sclerosing cholangitis.

patient had evidence of a focal parenchymal hemorrhage on CT of the head, and 2 patients had an abnormal MRI study (one had a small hemorrhagic lesion in the parasagittal occipital lobe and another had nonspecific metabolic changes).

Outcomes

Patients with delirium spent more time on mechanical ventilation (2.0 vs 1.3 days, *P*=0.008) and had longer mean ICU lengths of stay (4.6 vs 2.7 days, *P*=0.008), longer mean hospital lengths of stay (27.6 vs 11.2 days, *P*=0.003), and higher 6-month mortality (13.2% vs 1.4%, *P*=0.003) than patients who did not develop delirium (Table 4). We found no difference in 6-month biopsy-proven rejection, with occurrences of 13.2% in the delirium group and 13.3% in the nondelirium group (*P*=0.983).

The reasons for death of the 5 patients who were defined as having delirium during the study period included sepsis (4 patients) and retroperitoneal bleed (1 patient). The mean

Table 2. Characteristics at Delirium Onset

Variable	Delirium Group (n=38)
Mean postoperative day of onset (interquartile range)	6.9 (4-8)
Mean serum creatinine, mg/dL	1.7
Mean total bilirubin, mg/dL	4.09
Mean sodium, mEq/L	133.4
Mean blood urea nitrogen, mg/dL	46.97
Documented infection within 48 h, n (%)	7 (18.4)
Mean tacrolimus level (ng/mL)	6.2

time of death from transplant was 90 days (range, 18-152 days).

DISCUSSION

The incidence of delirium after LT has been reported to be 10%-47% of patients, which correlates with our incidence of 21%.[4,5,9] Although the presence of delirium after LT seems multifactorial, some potential contributing factors that could elicit acute mental status changes after LT have been identified. History of alcohol abuse has been shown to be an independent risk factor for developing delirium in the ICU,[7] but we found that no single etiology for LT was significantly associated with developing delirium postoperatively as previous studies reported.[9] Neurotoxicity from calcineurin inhibitors has been reported to be associated with mental changes including delirium.[10-12] Although only 3 patients in our delirium cohort had a supratherapeutic level of tacrolimus, neurotoxicity from tacrolimus can occur even at therapeutic levels, leading to immunosuppression changes and the potential risk of rejection.[13]

Infection may also cause mental status changes and delirium. All patients were intensively evaluated for potential severe infection. Of interest, 71.0% of patients who had delirium but did not have a documented infection at the time of the delirium onset were administered antibiotics empirically. The development of delirium may lead to unnecessary antibiotics, one of the leading causes of the development of antimicrobial resistance.[14] Severe hyponatremia and rapid correction of hyponatremia (>12 mmol/L/24h) have also been associated with mental changes after LT, including delirium.[15] In our study, hyponatremia was associated with delirium in the univariate analysis but did not reach statistical significance in the multivariate analysis. Of interest, the presence of pretransplant depression appears to be a significant risk factor that could be managed ahead of time and certainly deserves attention.

To our knowledge, this is the first study that describes the management of delirium after LT. The Society of Critical Care Medicine clinical practice guideline on pain, agitation, and delirium reports that haloperidol does not decrease the duration of delirium in the ICU, but atypical antipsychotics may decrease the duration of ICU delirium.[2] While quetiapine and olanzapine were the most commonly used medications in our study, no single drug was associated with a shorter hospital length of stay.

One consistency in the literature regarding delirium after LT is the effect on outcomes. Our findings corroborate data showing that developing delirium after LT is associated

Table 3. Management of Delirium

Treatment	Delirium Group (n=38)	Nondelirium Group (n=143)	*P* Value
Antipsychotic, n (%)			
Haloperidol	7 (18.4)	N/A	
Olanzapine	22 (57.9)	N/A	
Quetiapine	22 (57.9)	N/A	
Risperidone	4 (10.5)	N/A	
Immunosuppression modification, n (%)			
Tacrolimus held for a minimum of 24 hours	7 (18.4)	N/A	
Tacrolimus switched to cyclosporine	4 (10.5)	N/A	
Tacrolimus switched to sirolimus	3 (7.9)	N/A	
Diagnostic studies, n (%)			
Electroencephalogram	4 (10.5)	N/A	
Head magnetic resonance imaging	12 (31.6)	1 (0.7)	<0.001
Head computed tomography	25 (65.8)	8 (5.6)	<0.001
Lumbar puncture	2 (5.3)	N/A	
Other, n (%)			
Neurologic/psychiatric consult	29 (76.3)	10 (6.9)	<0.001
Antibiotics initiated without documented infection	22/31 (71.0)	N/A	

N/A, not applicable.

Table 4. Patient Outcomes

Outcome	Delirium Group (n=38)	Nondelirium Group (n=143)	*P* Value
Mean intensive care unit length of stay, days	4.6	2.7	0.008
Mean hospital length of stay, days	27.6	11.2	0.003
Mean time on mechanical ventilation, days	2.0	1.3	0.008
Retransplant in 6 months, n (%)	0 (0)	1 (0.7)	0.491
Discharged to rehabilitation/skilled nursing facility, n (%)	2 (5.3)	8 (5.6)	0.724
6-month mortality, n (%)	5 (13.2)	2 (1.4)	0.003
Rejection, n (%)	5 (13.2)	19 (13.3)	0.983

with longer ICU length of stay, longer hospital length of stay, longer time on mechanical dependence, and a higher rate of mortality. Delirium is more frequently seen in sicker patients, so establishing whether delirium is the cause, or a manifestation, of a patient's critical condition is impossible. In addition, our study looked at the utilization of resources involved in managing patients with delirium and found that these patients require significantly more imaging studies, more consults to neurology and psychiatry services, and more invasive procedures such as lumbar punctures. Given the costs of extended ICU and hospital lengths of stay in addition to more diagnostic studies and procedures, developing delirium clearly poses an economic burden.

Identifying risk factors for developing delirium is only useful if we are able to improve the incidence of delirium in high-risk patients. A recent study suggests that using delirium prevention strategies may decrease delirium prevalence as well as ICU length of stay.[16] While these strategies are more labor intensive than usual care, implementing them in patients at higher risk for developing delirium may still prove cost-effective.

This study has several limitations. Because this study is retrospective, our ability to confirm potential confounding factors is limited. For example, hepatic encephalopathy previous to LT could be confused with depression because low level of activity, poor appetite, and sleep disturbance are common symptoms of both conditions.[17] In addition, delirium itself is associated with multiple comorbidities, so its association with high morbidity and mortality may indicate that delirium affects a sicker subset of patients. The retrospective design of our study made evaluating delirium resolution difficult. Thus, we cannot report whether certain antipsychotics were more effective than others.

CONCLUSION

The presence of delirium is common after LT and is associated with high morbidity and mortality within the first 6 months posttransplant. Pretransplant factors independently associated with developing delirium after LT include prior use of antidepressants and pretransplant hospital admission for encephalopathy. Efforts should be made to identify patients at risk for delirium as protocol-based management may improve outcomes in a cost-effective manner.

ACKNOWLEDGMENTS

The authors have no financial or proprietary interest in the subject matter of this article.

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