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Incidence, Etiology, and Outcomes of Altered Mental Status in the Perioperative Setting of Liver Transplantation

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Abstract

Background: We examined neurologic consultations for altered mental status in perioperative liver transplant patients to determine the overall incidence, to assess the presumed etiology and the data reviewed to determine that etiology, and to assess outcomes. **Methods:** Retrospective chart review conducted for all 728 adult patients receiving orthotopic liver transplantation (OLT) between January 01, 2010, to June 30, 2014, with identification of 218 receiving neurology consults between 30 days pre-OLT and 90 days post-OLT, with review of all records necessary to determine initial findings and follow-up examination. **Results:** Seventy-three consults for 69 patients were identified, with 27 felt to be altered since a procedure, 20 with sudden-onset altered mentation, and 26 with gradual or waxing–waning course. A single underlying etiology was identified in only 19 cases, with multiple factors involved in all others, with metabolic, toxic, infectious, and structural etiologies most often implicated. There was no statistically significant difference in outcome for those with altered mental status consults versus the total OLT population, though the sudden-onset presentation group did show significantly increased mortality rates. **Conclusions:** This systematic study illustrates the variety of potential causes of altered mentation within the perioperative setting of liver transplantation. Workup including neuroimaging (preferably magnetic resonance imaging), infectious cultures, and expanded metabolic laboratory tests should be undertaken.

Keywords

hepatic encephalopathy, brain diseases, metabolic, outcomes, techniques

Introduction

Neurologic complications of orthotopic liver transplantation (OLT) are well described, with estimated incidences ranging between around 15% and 45%.[1-9] These complications range from transient encephalopathies associated with toxic, metabolic, and/or infectious etiologies to permanent neurologic injury caused by ischemic stroke, intracranial hemorrhage, or osmotic myelinolysis.[3,8] However, upon initial presentation, it may be difficult to determine the underlying cause of a neurologic abnormality, particularly perioperatively, given a high incidence of pretransplant hepatic encephalopathy, and postoperatively associated with medication and/or metabolic shifts associated with improved function of the transplanted liver.[2,8,10,11]

Altered mental status is among the most common reasons prompting neurologic consultation from liver transplantation specialists. As these cases may require urgent action, initial recommendations for workup are often provided via telephone prior to a full examination. In other cases, consultation may occur after initial workup ordered by the liver transplantation team indicates abnormal imaging or electroencephalographic findings. In order to refine our workup for such cases and expand knowledge in the literature on this important topic, we conducted a systematic, retrospective review of all cases where altered mental status led to the request for neurologic consultation at one of the highest volume liver transplant programs in the country.

Methods

A retrospective chart review was conducted on all patients who received OLT at a single center between January 2010

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and June 2014, including a total of 728 adult patients. This review was approved by the institutional review board of University of California. A waiver of informed consent was granted. A total of 218 of these patients were evaluated by one or more of our institutional neuroscience services (general neurology, stroke neurology, neurosurgery, or neurocritical care) within a period between 30 days prior to and 90 days following OLT. Retrospective chart review was performed to identify the reasons for consultation and to obtain relevant examination findings, laboratory test values, and imaging results. The presumed etiology of altered mental status was taken from the assessments of the consulting neuroscience service.

We reviewed all consultations in which altered mentation was felt to be either the direct reason for consultation or associated with the reason for consultation. This included consults for imaging abnormalities, when the imaging was obtained by the primary team to evaluate altered mental status, and consults where altered mentation occurred along with another neurologic issue, such as involuntary movements or a new focal deficit. An exception was made to exclude patients whose altered mentation occurred solely within the context of a seizure-like episode, if mental status returned to baseline following resolution of the seizure, and wearing off of benzodiazepine agents used to terminate the seizure activity. Those patients who were noted to have altered mental status preceding an episode concerning for seizure, and/or persisting well after such an episode, were included in the study.

Where possible, follow-up notes were obtained to determine whether any chronic neurologic sequelae were noted. This was limited in several cases where the patient obtained long-term follow-up outside of our institution, either due to moving outside our region or where insurance coverage restricted the patient's ability to follow at our institution. The goal was to obtain follow-up from at least 1 year after transplantation, with the most thorough report of neurologic function used. Comparison of 1-year mortality rates versus that of the total OLT population was conducted using the χ^2 test.

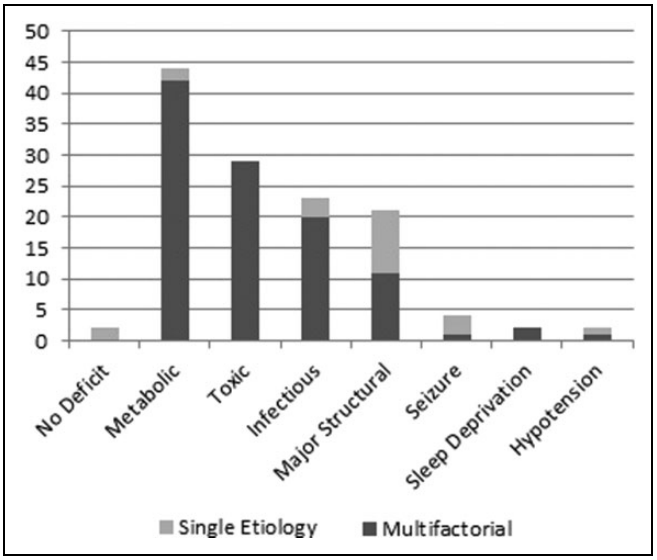

Figure 1. Identified etiologies of altered mental status. In a minority of cases (19 of 73), a single etiology was identified, with the remainder thought to be associated with more than 1 factor. In two cases, examination was normal without observed neurologic deficits, and the mental status changes were felt to have resolved prior to the consultation.

Results

Incidence

Seventy-three consultations were performed for 69 patients within the time window (age range = 20-78 years). This represents 33.5% of all neurologic consults in this group and 9.5% of the overall cohort of patients receiving liver transplantation. Of these, cognitive changes were the sole reason for consultation in 43 (58.9%) cases and were accompanied by other issues prompting neurologic evaluation (focal neurologic changes, neuroimaging abnormalities, involuntary movements, or episodes concerning for seizure) in the remaining 30 (41.1%). The presentation of altered mental status was broken down into 3 subgroups. The most common presentation was of altered mentation that had persisted since a procedure (typically the OLT itself), noted in 27 (37.0%) cases. Abrupt mental status changes from a previously normal baseline were seen in 20 (27.4%) cases. The third group had less well-defined start points of mental status changes, sometimes described as a gradual decline in mentation, or as waxing/waning mentation, and comprised the remaining 26 (35.6%) cases. In 2 cases, neurologic examination did not find any evidence of altered mental status. In one of these cases, abrupt onset of tremulousness and confusion had been noted by the primary team but resolved prior to examination. In the second, possible altered mental status over the previous night appeared to have resolved by the morning the consult took place. In the remaining 71 cases, some degree of impairment was noted, ranging from relatively mild impairments in attention and memory to complete unresponsiveness.

Etiology

Potential causes were broken into one of 7 categories, with multiple factors identified in a majority of cases. The most commonly implicated category was metabolic derangement, seen in 60% of the sample. Involvement of toxic, infectious, and structural abnormalities was noted in around 30% of cases each. A full breakdown is shown in Figure 1. A single, specified cause of altered mental status was not typical, found in only 19 (26.0%) cases in this sample. Ten of these were associated with new structural brain abnormalities (5 intracranial hemorrhages, 4 large ischemic lesions, and 1 osmotic myelinolysis), with the remainder including 3 seizures, 3 infectious processes (1 case of herpes encephalitis, 1 disseminated

Aspergillus, and 1 sepsis secondary to pneumonia), 2 cases of metabolic acidosis secondary to acute hypercapnia, and 1 episode of hypotension caused by an intra-abdominal bleed.

Neuroimaging was performed in 67 of the 73 cases, including 27 where the desired imaging study had already been performed at the time of the consultation and 40 where the study was performed following the recommendations of the initial consultation. In 30 of these cases, neuroimaging revealed acute findings, including 21 cases where the finding was presumed to be a major (or primary) contributor to the patient's altered mental status. This group includes 7 central pontine and/or extra-pontine myelinolysis, 5 intracranial hemorrhages, 5 ischemic strokes, 1 case where both ischemic and hemorrhagic strokes were noted simultaneously, 2 cerebral infectious processes, and 1 case of severe cerebral edema secondary to hyperammonemia. For the remaining 9 cases where new imaging findings were not definitely associated with the cause of altered mentation, 5 were diffusion-positive small ischemic strokes, 2 were small bleeds, and 2 involved new T2/fluid attenuation-inversion recovery hyperintensities of unclear etiology. In all 9, another potential etiology of altered mentation was identified.

Electroencephalogram (EEG) was obtained in 43 cases, including 2 cases where the EEG was obtained prior to neurologic consultation. In 2 cases, initial findings on routine EEG led to transition to a long-term continuous EEG indicating nonconvulsive status epilepticus (NCSE); a third case showed near-continuous bilateral periodic lateralizing epileptiform discharges and was treated as NCSE. Additionally, another case of NCSE was identified in a patient postoperatively, after a pretransplant initial EEG showed diffuse slowing and triphasic waves. In 5 other cases, focal electrographic abnormalities (slowing and/or epileptiform discharges) were identified. Diffuse slowing was noted in almost all of the remainder, as only 5 EEGs obtained were read as normal.

Of the 44 cases where metabolic derangement was associated, the most commonly noted findings indicate hepatic and/or renal impairment. Of the 44 cases, 28 had a total bilirubin level 2 times greater than the upper limit of normal, and 9 of them had values above 10 mg/dL. Transaminitis with an aspartate aminotransferase greater than twice the upper limit of normal was seen in 14 patients, 2 of whom had values above 1000 U/L (range: 11-3395 U/L). Uremia was also common, with Blood Urea Nitrogen levels greater than twice the upper limit of normal were seen in 22 of the 44 cases, often in the context of ongoing need for dialysis (overall range: 5-134 mg/dL). Ammonia levels were checked within 24 hours of consultation in only 28 cases, with 7 patients showing values above the upper limit of normal of 90 μg/dL (range: 24-387 μg/dL).

It is routine practice to obtain vitamin B_{12}, HIV, and rapid plasma reagin (RPR) on inpatients with altered mental status in our institution. In 39 of the 73 cases studied, vitamin B_{12} was obtained within 90 days of consultation, with all values at or above goal (range: 750-4000 pg/mL). Rapid plasma reagin within 1 year of consultation was obtained in 60 of 73 patients, all of whom were nonreactive. HIV within 1 year of consultation was obtained in 62 of 73 patients, with 1 positive initial test later felt to be false positive after Western blot and the remainder negative. Thiamine was obtained within 90 days of consultation in only 16 cases overall, 5 of which were below our lower limit of normal of 70 nmol/L (range: 13-379 nmol/L). Only 1 of these 5 required a transplant for alcohol-associated liver disease.

Of the 23 cases where infection was considered as a potential etiology for altered mentation, only 10 met 2 or more systemic inflammatory response syndrome criteria at the time of initial consultation. However, 19 of the 23 had some evidence of positive culture found on infectious workup. Respiratory sources were seen in 8 of these cases, urinary sources in 5, intra-abdominal sources in 3, bacteremia in 2, and cerebrospinal fluid (CSF) only in 1. Of the 50 cases where infectious etiologies were not included in the initial differential, 35 did not have any positive cultures, but subsequent workup did find respiratory infectious sources in 10, bacteremia in 5, positive urine cultures in 2, and intra-abdominal infection in 1. Lumbar puncture was requested in 10 cases and obtained in 7; only one of these showed increased White Blood Cell count in the CSF (the case of Herpes Simplex Encephalitis).

Outcomes

The overall 1-, 3-, and 5-year survival of all 728 patients receiving OLT during this period were 79%, 65%, and 45%, respectively. Of the 69 patients receiving consults for altered mental status, overall 1 year survival was 72.5%. This difference did not reach statistical significance when evaluated using χ^2 testing ($P = .208$). Of the 19 patients who did not survive to 1 year, 15 (78.9%) died before they could be discharged to outpatient follow-up, between 4 and 124 days after transplantation. Three of these deaths were associated with large intracranial hemorrhages, all of which presented as acute, severe alterations in consciousness, eventually progressing to brain death. One patient had persistent electrographic abnormalities in association with diffuse cortical and brain stem injury from prolonged cerebral edema, leading to withdrawal of care after it was felt she was unlikely to wake up again. Seven other cases had altered mentation in association with infectious complications, with sepsis associated with the final cause of death. In the remaining 4, an event occurring after initial neurologic consultation without a definite association was presumed to be the proximate cause of death.

Of the remaining patients discharged to outpatient follow-up, records were reviewed to identify the most thorough available record of the neurologic examination, at 1 year or more post OLT. Mean timing of follow-up was 358 days post OLT (range: 97-959 days). Amongst this group, 34 were felt to have no persistent neurologic deficit on follow-up. The remaining 16 had abnormal findings on follow-up neurologic examination, including 7 with impaired mental status, 6 with diffuse

Table 1. Outcomes at 1 Year by Presentation.

Presentation	No Neurological Deficit	Alive w/Neurological Deficit	Dead	Total
Persistent since surgery	14	8	5	27
Gradual/waxing–waning	16	4	6	26
Sudden	7	5	8[a]	20

[a]Statistically significant ($P < .05$) difference in mortality rate versus total population of orthotopic liver transplantation (OLT) patients (N = 728) on χ^2.

Table 2. Outcomes at 1 Year by Associated Etiology.

Associated Etiologies	No Neurological Deficit	Alive w/Neurological Deficit	Dead	Total
No deficit	1	1	0	2
Metabolic	25	7	12	44
Toxic	19	3	6	28
Infectious	12	4	7	23
Major structural	4	9	8	21
Seizure	1	2	1	4
Sleep deprivation	2	0	0	2
Hypotension	1	1	0	2

Table 3. Outcomes at 1 Year by Study Findings.

Findings	No Neurological Deficit	Alive w/Neurological Sequelae	Dead	Total
New imaging findings	9	10	9	28
No new imaging	25	9	7	41
Nonconvulsive status epilepticus	0	2	2	4
Focal EEG findings	1	2	2	5
Nonfocal EEG findings	17	8	7	32

Abbreviation: EEG, electroencephalogram.

weakness, 4 with focal weakness, 3 with tremor, 2 with peripheral sensory loss, and 1 with intranuclear ophthalmoplegia.

Although the overall consult population did not show significant difference in 1-year mortality versus the overall OLT population, the mortality rate within certain subgroups did reach statistical significance. Of the 20 patients with sudden-onset alteration of mental status, 9 died within the first year ($P = .04$), including all 4 patients who died within a week of initial mental status change. For the 28 patients with new structural abnormalities found on neuroimaging, we did not find a statistically significant difference ($P = .16$), though this trended closer toward significance for the 21 patients whose neuroimaging findings were thought to be likely etiologies of their mental status changes ($P = .06$). Too few patients found to be in NCSE were noted to reach statistical significance, but 2 died within the first year and the other 2 had persistent deficits. Further subgroup breakdowns by presentation (Table 1), by etiology (Table 2), and by study results (Table 3) are included.

Discussion

Our systematic study illustrates the myriad ways that altered mentation can present in the perioperative setting and the variety of underlying causes. On a case-by-case basis, from the history of altered mentation and initial examination alone, it does not appear to be possible to distinguish transient toxic–metabolic encephalopathies without apparent long-term neurologic sequelae from more severe insults such as ischemic stroke, intracranial hemorrhage, or osmotic myelinolysis. Although patients with sudden-onset presentation were more often associated with death, and those with causative structural findings had higher association with both mortality and permanent neurologic deficit, several patients from both groups were apparently normal at followup. The high incidence of structural lesions associated with altered mentation in this group indicates the necessity of obtaining neurologic imaging. Given the incidence of osmotic myelinolysis, which is rarely apparent on computed tomography imaging, in particular, magnetic resonance imaging (MRI) of the brain appears to be a necessary study for a proper workup in this setting. Additionally, although only a few cases of NCSE were identified, the potential consequences of leaving it untreated seem to favor a low threshold for obtaining routine EEGs, particularly when a patient remains altered in the absence of a more readily identifiable explanation.

In those cases without apparent structural changes, it was frequently difficult to isolate a single root cause, as there were frequently multiple metabolic abnormalities, and a high incidence of concurrent infection. However, our data suggest that a more traditional toxic–metabolic workup in these cases may be limited in identifying the specific derangements associated with liver transplant patients. Vitamin B_{12}, RPR, and HIV were obtained in a majority of the patients in our sample, without a single instance of an abnormal value to which the patient's altered mentation could be attributed. Thiamine was obtained much less often, but we identified multiple patients with low serum levels, which may have contributed to their mental status. The results of our study suggest that a proper workup for these cases should begin with neuroimaging (preferably MRI), infectious workup, and an expanded metabolic workup to include thiamine and ammonia, in addition to a basic metabolic panel and liver function testing. It is noted, however, that in the pretransplant population, significant derangements in liver function testing are to be anticipated, and uremia in the setting of hepatorenal syndrome is also frequently seen. In the immediate postoperative setting, these values may remain abnormal for several days as they begin to normalize following transplantation.

Our study has several limitations. A proper cause of altered mental status was not always readily identifiable, even with retrospective review of associated laboratories and procedures, given the number of potential causes. Although it is known that certain medications—most commonly the calcineurin inhibitors, though steroids and sedatives have also been implicated—may impair mentation, definite attribution is difficult, given altered pharmacokinetics associated with liver and kidney dysfunction and because normal serum levels of tacrolimus and cyclosporine may still be associated with neurologic findings.[9] Additionally, although many patients in this series had positive infectious workups, it is not readily identifiable whether infection was contributory to mental status in every case. Although our goal was to obtain follow-up on every patient, this was imperfect. In several cases, insurance restriction or geographic relocation meant patients received follow-up outside of our system. In almost all cases, the neurologic examination indicated on follow-up examinations was limited to cursory identification of orientation and gross sensorimotor abnormalities. Thus, it is possible that more subtle sequelae may be present in a larger number of these patients. Additionally, some of the neurologic findings at follow-up may have developed independently of the etiology causing perioperative neurologic consultation (eg, peripheral nerve injury from medication or prolonged immobility), though accurate determination of causality is extremely difficult.

This study appears to be the first to consider cases of altered mental status at the moment of initial consultation, encompassing patients identified in other studies in groups ranging from confusion to encephalopathy to seizures, myelinolysis, and neurovascular pathologies. Awareness of the full range of potential etiologies may streamline the initial workup process. Additionally, the follow-up on the patients in this series may help offer better prognostic value during the initial consultation period.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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