ORIGINAL ARTICLE

NEUROPSYCHIATRIC COMPLICATIONS IN LIVER TRANSPLANT PATIENTS IN A TERTIARY HOSPITAL IN SINGAPORE

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Abstract

Objective: **The aims of the study were to investigate the percentage, types and presentations of neuropsychiatric complications in liver transplant patients in the Singapore General Hospital and discuss relevant diagnostic and therapeutic issues.** ***Methods*****: Case notes and electronic medical records were accessed in order to identify patient characteristics and outcomes, and documentation of the various teams involved.** ***Results:*** **The percentage of liver transplant patients who developed neuropsychiatric complications was 15.6% (10 out of 64 patients). This ties in with figures in the literature but was likely to have been higher.** ***Conclusion*****: Neuropsychiatric complications post-liver transplantation can manifest in a multitude of ways and at various time-points which makes detection and management challenging. Given the impact these have on patient and transplant outcome, it is important to have vigilance, timely intervention, and close collaboration between disciplines.** ***ASEAN Journal of Psychiatry, Vol. 16 (1): January – June 2015: XX XX.***

Keywords: Liver Transplantation, Neuropsychiatry, Consultation-Liaison Psychiatry, Delirium

Introduction

The prevalence of neuropsychiatric complications in liver transplant patients ranges from 8.3% to 64.5% [1-5]. Such complications include delirium, brief psychotic disorder, major depression, mania, adjustment disorder, anxiety, post-traumatic stress disorder, seizures, cerebrovascular disorders, insomnia, migraine, vertigo, movement disorders and peripheral neuropathy [1-3]. This study investigates the percentage, types and presentations of neuropsychiatric complications noted in liver transplant patients for whom psychiatric referrals were made since the inaugural liver transplant at the Singapore General Hospital. Diagnostic and therapeutic issues are then raised. It is hoped that this highlights the importance of monitoring for a range of symptomatology in order to optimise post-transplant outcomes.

Methods

A total of 64 patients underwent liver transplantation at the Singapore General Hospital between 15th February 2006 and 7th March 2013 inclusive. As part of the pre-transplantation assessment, all patients were interviewed by consultant psychiatrists with an interest in transplantation psychiatry, and any new psychiatric diagnosis which was made according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) or past psychiatric history obtained from records was detailed in the assessment form. Post-transplantation, 10 patients

required psychiatric referral. Details of the liaison consultations and DSM-IV diagnoses made by the attending trained psychiatrists were documented in case notes.

For this case series, case notes and electronic medical records of the 64 patients were studied in order to identify patient characteristics and outcomes. Ethical approval was obtained from the Centralised Institutional Review Board. No consent was obtained as it was a retrospective study accessing patient records with no patient contact. There are no identifying patient details in this paper, such as names or specific individual socio-demographic profiles, and hence it is not possible for anyone to identify the patients and lead to any breach of confidentiality.

Results

Ten of the 64 patients (15.6%) had psychiatric referrals either in the immediate post-operative period or during subsequent follow-up with the transplant team. Tables 1–4 detail characteristics and outcomes of the 64 patients.

Table 1. Social demographics of transplant recipients

	All Recipients (n=64)		**With neuropsychiatric complications** (n=10)	**Without neuropsychiatric complications** (n=54)
Age at liver transplant (years)				
	Mean	55.0	57.6	54.5
	Range	26 – 71	42 – 71	26 – 68
Sex				
	Male	43	5	38
	Female	21	5	16
Race				
	Chinese	54	7	47
	Malay	3	1	2
	Indian	3	2	1
	Others *	4	0	4
Marital status				
	Married	53	8	45
	Single	4	1	3
	Divorced	3	0	3
	Widowed	1	0	1
	Unknown	3	1	2
Occupational status pre-transplant				
	Employed	31	1	30
	Non-employed	4	2	2
	Retired	16	3	13
	Homemaker	7	3	4
	Unknown	6	1	5
Donor				
	Living	15	3	12
	Deceased	49	7	42

*2 Burmese; 1 Eurasian; 1 Sikh

Table 2. Diagnoses of transplant recipients

	All Recipients (n=64)		**With neuropsychiatric complications** (n=10)	**Without neuropsychiatric complications** (n=54)
Liver disease aetiology with				
	Autoimmune cholangiopathy	3	2	1
	Primary biliary cirrhosis	7	2	5
	Hepatitis C	6	1	5
	Hepatitis B	29	4	25
	Alcohol	5	0	5
	Cryptogenic	5	1	4
	Drug	4	0	4
	Primary sclerosing cholangitis	1	0	1
	Familial amyloidotic polyneuropathy	2	0	2
	Citrullinaemia	1	0	1
	Non-alcoholic steatohepatitis	1	0	1
	Hepatocellular carcinoma	31	2	29
MELD * score †				
	Mean Range	16.8 6 – 43	19.7 8 – 35	16.1 6 – 43

*Model for End-stage Liver Disease
†At point of evaluation for liver transplantation. For patients with hepatocellular carcinoma (HCC), the unadjusted score was used (all cases with HCC had an adjusted MELD score of 15).

Table 3. Past history of transplant recipients

		All recipients (n=64)	**With neuropsychiatric complications** (n=10)	**Without neuropsychiatric complications** (n=54)
Past psychiatric history		7	2 *	5 †
Past suicide attempt		1	1	0
Cigarette use	Current smoker	3	0	3
	Ex-smoker	16	4	12
	Non-smoker	36	4	32
	Unknown	9	2	7
Alcohol use	History of whom were formally diagnosed with alcohol use disorder	23	4	19
		1	0	1
	None	30	3	27
	Unknown	11	3	8
Illicit drug use		0	0	0
Prednisolone use pre-transplant	Yes	4	1	3
	No	51	9	42
	Unknown	9	0	9
Other immunosuppressant use pre-transplant	Yes	2	1	1
	No	53	9	44
	Unknown	9	0	9

*Diagnoses were: psychotic depression; adjustment disorder of depressive subtype.
†Diagnoses were: depression; adjustment disorder of depressive subtype; adjustment disorder of anxious subtype; depression; alcohol dependence.

Table 4. Outcomes of transplant recipients

	All Recipients (n=64)		**With neuropsychiatric complications** (n=10)	**Without neuropsychiatric complications** (n=54)
Length of hospitalisation (days) *	Mean Range	19 5 – 81	24 10 – 47	18 5 – 81
Attend follow-up		64	10	54
Alcohol use relapse		1	0	1
Suicide attempt		1	1	0
Occupational status post-transplant	Employed Non-employed Retired Homemaker Unknown	26 6 16 7 9	2 1 3 3 1	24 5 13 4 8
Evidence of graft rejection †		7	2	5
Deceased during post-operative hospitalisation		5	1	4
Deceased between after post-operative hospitalisation and present		8	0	8
Total deceased at present		13	1	12

*Data from those (5) who passed away during that hospitalisation was omitted.
†All were successfully treated and resolved.

The 10 patients who developed neuropsychiatric complications are as follows:

1. Mdm H, a 58-year-old Chinese lady with autoimmune cholangiopathy, underwent cadaveric liver transplantation. Post-operatively she developed mild acute tubular necrosis and tacrolimus was started on Day 5 when her renal function improved. By Day 8 she was noted to be hypomanic and agitated, and experienced bad nightmares. A degree of peripheral neuropathy was also present. This lady had no past history of psychiatric illness and as tacrolimus-induced neurotoxicity was suspected, she was held off the immunosuppressant. Haloperidol was administered for three days to control her acute confusion. Cyclosporin A was started after the neurotoxic effects of tacrolimus wore off, its dose being adjusted according to its plasma levels, and Mdm H's liver function test results. The behavioural issues resolved within the hospitalisation and no psychiatric follow-up was required. Interestingly, Mdm H also manifested opiate sensitivity between days 1 and 3, when she appeared 'dazed' and 'staring' while on low doses of opiates. These were corrected when opiates were stopped.

2. Mdm S, a 59-year-old Chinese lady with primary biliary cirrhosis, underwent cadaveric liver transplantation. On Day 4 post-operation she was found staring blankly at the ceiling. Mutism was noted. She was disoriented and a resting tremor was present. EEG did not reveal an epileptic focus and MRI of the brain was unremarkable. Blood cultures were negative. There was no past psychiatric history. Tacrolimus was stopped and cyclosporin A commenced. On Day 5 Mdm S was able to recognise people and verbalise. She described "vivid images of myself in the train and trying to stop the train or it will explode" and kept asking the nurses which train station she was in. On Day 6 she was more alert and oriented and no longer experienced the visual hallucinations. She returned to her normal mental state before discharge. Tacrolimus-induced neurotoxicity was likely.

3. Mdm T, a 54-year-old Chinese lady with autoimmune cholangiopathy, underwent living donor liver transplantation. On her third post-operative day she was observed to be staring at newspapers and chanting. She was oriented to time, place and person and answered questions calmly and rationally. Organic work-up was unremarkable. MRI of the brain was consistent with chronic hepatic encephalopathy and no infarct was seen. MRA did not reveal abnormality. EEG showed diffuse encephalopathy but no epileptiform discharge. Past psychiatric history was negative. Tacrolimus toxicity was suspected and on tailing Mdm T off tacrolimus her symptoms resolved.

4. Mr A, a 71-year-old Chinese man with hepatitis B with hepatocellular carcinoma, underwent cadaveric liver transplantation. He had no past psychiatric history. On Day 2, he was noted to be anxious and hyperventilating. On Day 4 he was acutely confused, with prominent echolalia and disorientation. No organic cause was detected and tacrolimus toxicity was surmised. Cefepime was stopped as well, in view of possible drug-induced psychosis. However the confusion persisted and Mr A was aggressive, including spitting at others, thus requiring physical restraints. Further work-up returned negative and Neurology's impression was metabolic encephalopathy. A Psychiatry referral was also made. The impression was delirium with multiple causes – drug-induced, acute renal impairment, hepatic encephalopathy, constipation. Haloperidol was started for management of aggression. On Day 7 and Day 11 respectively, Mr A repeatedly verbalised "sex" and "thank you". On Day 12 he remained confused and agitated and was noted to have extrapyramidal signs. Haloperidol was discontinued and olanzapine instituted. A sudden and dramatic improvement in mental status occurred the next day, whereby Mr A was alert and oriented to time, place and person. The impression was that of prolonged tacrolimus toxicity secondary to delayed clearance from poor renal function. Psychiatry prescribed olanzapine 2.5mg ON for two weeks following discharge and at outpatient follow-up, Mr A remained well.

5. Mdm R, a 59-year-old Indian lady with primary biliary cirrhosis, underwent living donor liver transplantation. She had no past psychiatric history. On Day 4, she was unable to obey commands and her eyes deviated to the right. Organic work-up was negative. Neurology's impression was septic or metabolic encephalopathy. Following an Infectious Diseases (ID) referral, IV acyclovir 300mg 12-hourly was started. On Day 6, Mdm R was screaming in pain but no localising signs were found. ID reviewed again and their impression was septic encephalopathy or intra-abdominal sepsis. A 2gm dose of IV meropenem was given followed by 1gm BD, as well as IV vancomycin 1gm daily. CTAP, EEG and MRI brain were unremarkable. On Day 8, her mental state improved but on Day 9, she developed seizures which were aborted with IV midazolam and PO levetiracetam. CT brain was unremarkable and EEG showed diffuse encephalopathy. CTAP showed stable fluid collection around the graft. Mdm R was started on PO levetiracetam,

PO voriconazole, IV linezolid, IV levofloxacin, and IV metronidazole. On Day 14, her mental status and alertness improved. On Day 21, she was referred to Psychiatry for what seemed to be hallucinations and delusions. Psychiatry's impression was an organic psychosis. MRI brain revealed new areas of T2W hyperintensity in the right parietal cortex, right frontobasal region, right insula and left medial temporal region which, though did not show restricted diffusion or enhancement, were in the typical location for herpes encephalitis. Mdm R was kept on IV acyclovir and completed 21 days before being converted to PO prophylactic dosing. On Day 31, she became confused and disoriented, likely secondary to sepsis or congestive cardiac failure, but improved over the week and was oriented and conversant on discharge. The overall impression for Mdm R's altered mental status was viral encephalopathy. She was prescribed levetiracetam till her follow-up with Neurology three months later.

6. Mdm L, a 63-year-old Indian lady with cryptogenic liver cirrhosis, underwent cadaveric liver transplantation. She had no past psychiatric history. On Day 6, she was found restless and attempting to climb out of bed. She was talking to herself and disoriented to time, place and person but still able to obey commands. Hypomagnesaemia was corrected. Tacrolimus was not started and imipenem was withdrawn. Neurology's impression was encephalitis of septic or metabolic aetiology. IV acyclovir was started to cover HSV encephalitis. MRI brain and EEG were unremarkable. Septic work-up was negative. From Day 11, a gradual improvement in mental state was noted and on Day 14, Mdm L was alert, oriented, and sitting out of bed. Occasional confusion at night was noted however, and Psychiatry referral was made on Day 23. The previous night's confusion was an isolated episode and involved Mdm L talking about her husband visiting her and Mdm L requesting nurses for bananas. There was no aggression. Since the episodes resolved spontaneously and Mdm L was well in the day, the impression was residual encephalopathy or delirium. Monitoring of behaviour was advised and tranquillisers were not recommended. She was discharged well.

7. Mr N, a 42-year-old Malay man with Hepatitis C liver cirrhosis, underwent cadaveric liver transplantation. He had no past psychiatric history. Two and a half years post-transplant, he was referred to a psychiatrist for a one-year history of low mood, anhedonia, insomnia, loss of appetite, decreased libido and worthlessness. These were predated by his failed business and the death of his mother. An earlier referral to Psychiatry had been made by the liver transplant team but he had hoped to resolve matters himself. A diagnosis of major depressive disorder was made and escitalopram 5mg ON and hydroxyzine 10mg ON prescribed. A referral to Psychology was also made. Three weeks later, Mr N reported improvements in mood and sleep. He defaulted appointments for nine months before re-presenting with recurrence of the same depressive symptoms. The same medications were restarted. Mr N defaulted follow-ups with Psychiatry since.

8. Mr W, a 50-year-old Chinese man with subfulminant liver failure from an acute flare of hepatitis B, underwent cadaveric liver transplantation. He had a psychiatric history of psychotic depression with previous drug overdose but was assessed to be stable pre-transplant. Post-operatively no psychiatric issues were encountered. Subsequently the main issue faced was non-compliance to medications, primarily due to command auditory hallucinations. Poor finances, in the form of gambling debts, and non-employment status were further stressors. His relapses resulted in several psychiatric admissions, one of which involved a suicide attempt. Compliance with Psychiatry outpatient follow-ups was also an issue. Each time on admission, the presenting complaint would be low mood associated with anhedonia, insomnia, poor appetite, poor concentration, worsening auditory hallucinations, and

passive suicidal thoughts. Psychosocial strategies were taught to Mr W to help reinforce goals, improve compliance and manage certain symptoms, and his psychotropics were titrated.

9. Mr T, a 53-year-old Chinese man with hepatitis B and alcoholic liver cirrhosis, underwent cadaveric liver transplantation. Two months prior to transplantation he was diagnosed with adjustment disorder, depressive subtype, which was resolving. The post-operative hospitalisation was unremarkable. Nine days following discharge, he was referred for a Psychiatry outpatient consult for altered behaviour since the second day at home. His wife reported memory decline and poor sleep. He was delusional that a female bus passenger had sexually assaulted him. On three occasions. he emerged from the bathroom naked claiming he had dressed up and only mimicked so when instructed. Aggression or mood symptoms were absent and hallucinations denied. Haloperidol 0.5mg BD was prescribed for two weeks and a Neurology outpatient consult was attended on the same day. Neurological examination, labs and brain MRI were unremarkable. Mr L was no longer confused at Psychiatry follow-up two weeks later and he was discharged. This was a case of undetermined diagnosis.

10. Mr Y, a 67-year-old Chinese man with hepatitis B with hepatocellular carcinoma, underwent living donor liver transplantation. He had no past psychiatric history. Post-operatively, he was admitted to the surgical intensive care unit (SICU) for ventilatory support and on discharge to the ward a Psychiatry referral was made as he had verbalised suicidal ideations. Unfortunately, extreme drowsiness made assessment difficult and no diagnosis was made. Mr Y was re-admitted to the SICU and passed away a week later from septic shock.

Of these 10 patients who manifested neuropsychiatric complications, 4 had a diagnosis of tacrolimus toxicity and 2 of encephalopathy (making a total of 6 of delirium), 2 of psychiatric sequelae and 2 of undetermined aetiology.

Discussion

Delirium

As in other studies [1-3, 5-8], the most common neuropsychiatric complication was delirium (6 out of 10 cases). Delirium can stem from a multitude of factors [1, 2], and identifying and treating it early is a common challenge [9]. It is important because disturbed behaviour can compromise patient and staff safety and delirium is a poor prognostic factor [4, 6, 7], being associated with an almost doubled risk of remaining in hospital, quadrupled risk of dying in hospital, and almost thrice the rate of death by one year [10]. In this study, mean hospitalisation duration was longer amongst those with neuropsychiatric complications than without (24 versus 18 days).

Encephalopathy

As much as a working postulate is made, the presentation of encephalopathy is very diverse and its precise cause is often multifactorial [11], involving a combination of aetiologies such as immunosuppressant toxicity, electrolyte or metabolic disturbance, infection, and organ failure. A willingness to review the patient and reconsider other hypotheses is needed.

Immunosuppressant

Immunosuppressant toxicity is recognised as a significant contributor to post-transplant neuropsychiatric complications [3, 4, 9, 12, 13] and recipients of liver transplants, as opposed to other organ transplants, are more susceptible [12]. Large centres found 25-40% of them manifesting some extent of cyclosporine or tacrolimus neurotoxicity [13]. In particular, tacrolimus toxicity might be more common than cyclosporine [1, 2], though some studies did not find this trend [2]. In our setting, tacrolimus was the immunosuppressant of choice and patients who were thought to have symptoms arising from tacrolimus toxicity were switched to cyclosporine, with symptom resolution. Symptoms of cyclosporine or tacrolimus neurotoxicity are wide-ranging and non-specific in nature [1, 2, 4, 13]. Possible factors in the pathogenesis of neurotoxicity include:

binding to neuroprotective intracellular proteins called immunophilins which are present throughout the central nervous system [2, 4]; endothelial dysfunction of the blood-brain barrier [1, 2, 4]; hypomagnesaemia [1, 4]; hypocholesterolaemia [1, 4]; hypoalbuminaemia [1]; hypertension [4]; pre-existing central nervous system damage [1]. Plasma drug levels poorly predict neurotoxicity which sometimes can only be surmised upon symptom resolution after drug discontinuation [2, 4].

Symptom onset
Of the 10 cases, 7 presented during hospitalisation post-operatively. These included all 6 cases of delirium and almost all presented in the first week. It is known that most neuropsychiatric complications occur early after surgery, usually within a month, and increases mortality risk [3, 4, 6, 7]. Mr Y's case highlights the possibility of depression developing in the immediate post-operative period.

One case of depression presented a year post-transplant (Mr N) and while it is difficult to ascertain the relative contributions of transplant-related biologic factors and psychosocial stressors, vigilance for late neuropsychiatric presentations remains important. The case of psychotic depression (Mr W) relapsed post-discharge. Lastly, a case of behavioural change post-discharge (Mr T) reveals yet another window in which psychiatric symptoms can manifest. Despite the lack of diagnosis, relevant investigations were made and haloperidol was sufficient to resolve symptoms. The importance of corroborative history from the family in identifying post-operative issues and of expedient management of oftentimes quick-evolving problems in this vulnerable patient group is exemplified here.

Relation between liver disease aetiology and neuropsychiatric complications
It is interesting that the patient with depression had hepatitis C liver cirrhosis. Higher incidences of depression are reported in patients transplanted for hepatitis C [1]. Hypotheses include side-effects of interferons [14], HCV recurrence [15], history of substance abuse, neuroendocrine changes, and direct HCV neuroinvasion [2].

Relation between liver disease severity and neuropsychiatric complications
In this case series, the mean Model for End-stage Liver Disease (MELD) score of patients who developed neuropsychiatric complications was higher than of non-cases (19.7 versus 16.1). A study investigating predictors of post-operative neurological complications found that the latter are best predicted by pre-transplant hepatic encephalopathy [8].

Psychosis
Mr W, with a history of psychotic depression, was deemed suitable for transplant because his psychiatric symptoms were stable pre-operatively. His relapses post-transplant point towards a need for tight psychiatric monitoring and input. If carefully selected and well-managed, such patients need not fare worse in terms of transplant outcome [16, 17]. Important considerations are compliance with medical and psychiatric follow-up, sufficient social (especially in-residence) support, and ability to form a working relationship with the transplant team, while risk factors for non-compliance post-transplantation include antisocial or borderline personality, history of assault, positive psychotic symptoms, dwelling alone, and family history of schizophrenia, with post-transplant non-compliance being found to be similar to that in general transplant populations [18].

Alcohol
Twenty-three of our 64 recipients had an alcohol history, one of whom was formally diagnosed with alcohol dependence. All of them complied with transplant protocol and quit alcohol. Post-transplant, one resumed drinking (not the person with previous alcohol dependence) but was noticed by his wife and managed to stay off alcohol with further advice from the team. This post-transplant recidivism rate of 4% compares favourably with that in the literature, which ranges from 8% to 60% depending on time-scale and extent of drinking [19-21]. Nevertheless, in both U.S. and European programmes, post-transplant alcohol use leading to premature death or graft failure is rare, with surgical outcomes and long-term survival of recipients with alcoholic liver disease, even the heaviest drinkers, equalling that of other aetiologies [20]. Also, family dedication to transplantation and medical factors were better outcome

predictors, including of alcohol resumption, than pre-transplant sobriety duration [21]. Furthermore, alcoholic cirrhosis per se was found not to be a risk factor for post-operative neurological complications. Instead, pre-existing or active hepatic encephalopathy or abnormal neurological examination pre-transplantation was found to be key [2, 7, 8]. Table 5 details outcomes of our patients with and without alcohol history.

Table 5. Outcomes of transplant recipients with and without alcohol history

	With alcohol history (n=23)	**Without alcohol history** (n=30)
Length of hospitalisation (days) *		
Mean	15	22
Range	9 – 31	5 – 81
With psychiatric referral	4 (17.4%)	3 (10.0%)
Deceased during post-operative hospitalisation	2 (8.70%)	2 (6.67%)
Deceased between after post-operative hospitalisation and present	0 (0%)	4 (13.3%)
Total deceased at present	2 (8.70%)	6 (20.0%)
Evidence of graft rejection †	1 (4.35%)	5 (16.7%)
Alcohol relapse	1 (4.35%)	NA

*Data from those (5) who passed away during that hospitalisation was omitted.
†All were successfully treated and resolved.

Stigma
Mr N's preferential follow-up with the transplant team but not the psychiatrist for his depression might be due to stigma associated with psychiatric consultation. Accordingly, better communication between the two disciplines would be ideal. It also shows how crucial psychological or psychiatric monitoring is at follow-ups – firstly, it aids the psychiatrist in monitoring the patient's symptoms, stressors and treatment response; secondly, it better identifies patients at risk of developing psychiatric conditions as in Mr N's case where depression developed a year post-transplant.

Psychiatric input is also valuable immediately post-transplant given commonly-occurring neuropsychiatric complications of diverse and fluctuating symptomatology and which respond well to psychotropics.

Limitations
Although the percentage of 15.6% in this population falls within literature figures, there is a potential selection bias and the actual percentage of patients who developed neuropsychiatric complications is likely higher as these were only cases with psychiatric presentation. Also, there was a reliance on access to records as well as their thoroughness of documentation and accuracy. Another

limitation is the inability to comment whether associations are statistically significant owing to small case number. Nevertheless the study is a local first and it is hoped that this will have bearing on the shaping of the transplantation landscape.

Conclusion

This study presents the percentage, types and presentations of neuropsychiatric complications in liver transplant patients in a tertiary hospital in Singapore. Such neuropsychiatric complications can manifest in a multitude of ways and at various time-points which makes detection and management challenging. Given the impact these have on patient and transplant outcome, it stresses the importance of vigilance, timely intervention and close collaboration between disciplines.

Conflict of interest: None

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