Neuropsychiatric complications after liver transplantation

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Objective
The aim of this retrospective study was to evaluate the incidence of neuropsychiatric complications (NPCs) after living donor liver transplantation.
Methods
Between May 2001 and April 2005, 110 recipients were admitted to the ICU after liver transplantation (LT) and were evaluated by full general, psychiatric, and neurological examinations, electroencephalography, and brain computed tomography and/or MRI. Diagnosis of psychiatric disorders was made according to the *Diagnostic and Statistical Manual of Mental Disorders*, *4th ed*., Text Revision criteria, and the presence or absence of paradoxical psychiatric syndrome (PPS) was evaluated on the basis of the diagnostic criteria for PPS. Patients were observed after LT for 1 year.
Results
Of the patients who underwent transplantation, 50.9% developed NPCs and these patients' stay in the ICU was much longer than that of all admitted patients. Neurological complications were observed in 32.7% of patients and psychiatric disorders in 43.6%, of which 62.5% developed PPS. The survival rate after LT of patients with NPCs was similar to that of patients without NPCs. The incidence of neuropsychiatric symptoms was found to be similar between patients treated with cyclosporine and those treated with tacrolimus. Finally, no correlation was observed between the primary cause of liver disease and the NPCs reported.
Conclusion
There was a high incidence of NPCs after LT, prolonging the patients' stay in intensive care significantly. Careful preoperative and postoperative neuropsychiatric evaluations are important for early diagnosis of NPCs.

Keywords:
liver transplantation, neuropsychiatric complications, paradoxical psychiatric syndrome

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Introduction

There are several obvious reasons for conducting a comprehensive neuropsychiatric evaluation of patients after successful liver transplantation (LT). Psychometric tests can detect the presence of cerebral dysfunction in the absence of overt clinical signs of encephalopathy (Surman *et al.*, 2009). Moreover, these tests are known to be more sensitive indicators of central nervous system (CNS) pathologic conditions compared with an electroencephalogram (Tarter *et al.*, 1984). Certain neuropsychological indexes are predictors of social and vocational adjustment and can thus be used to either counsel or direct rehabilitation efforts after transplantation (Diller and Gordon, 1981; DiMartini *et al.*, 2008).

Behavioral, psychiatric, and emotional disturbances are common in prospective transplant patients with advanced liver disease, many of whom have hepatic encephalopathy. Because these latter disturbances can negatively influence the individual's capacity to function behaviorally, as well as their social environment, the assessment of neuropsychiatric status after successful LT is of utmost importance in evaluating the holistic outcome of hepatic transplantation (Dobbels *et al.*, 2009; Maldonado, 2009; Cherkassky, 2011).

Psychiatrists play an essential role in the pretransplant evaluation and continuous care of liver transplant patients. The prevalence of mental disorders among postliver transplant patients has ranged from 30 to 70%, depending on the study sites, the time of investigation after transplantation, and the diagnostic criteria used (Goetzmann *et al.*, 2007; Noma *et al.*, 2008; López-Navas *et al.*, 2010). Although most of these disorders will remit by the time the patient is discharged from the hospital, acute treatment is imperative for the relief of painful experiences from patients and the family members involved (Chiu *et al.*, 2009; Nien-Mu *et al.*, 2009; Telles-Correia *et al.*, 2009a).

In living related organ transplantation to patients with kidney or liver failure, recipients are prone to having guilt feelings about their donors. The incidence of living related organ transplantation has been increasing worldwide (Telles-Correia *et al.*, 2009b; Szeifert *et al.*, 2010;

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Corruble *et al.*, 2011). Recent psychiatric studies have demonstrated that recipients and donors who undergo living related organ transplantation sometimes exhibit 'paradoxical psychiatric syndrome (PPS)' despite successful transplantation without major complications (Fukunishi *et al.*, 2002a).

Recipients who undergo child-to-parent living related LT may be more likely to have guilt feelings compared with the experience of a child who receives an organ donation from a parent (Fukunishi *et al.*, 2001).

The occurrence of PPS was significantly related to recipients' guilt feelings toward living donors, but these were strongly superseded by the recipients' desire to escape from approaching death just before living related transplantation. These results suggest that pretransplant psychological assessment is useful for predicting post-transplant occurrence of psychiatric disorders. In each instance, psychiatric complications occurred following transplantation, despite an otherwise favorable surgical course for both donor and recipient (Dew *et al.*, 2007; Gangeri *et al.*, 2007; Yang *et al.*, 2011).

Neurological complications that are responsible for significant mortality and morbidity after LT have been reported in 8.3 to 47% of cases in various series (Haghighi *et al.*, 2005; Stracciari *et al.*, 2011; Yilmaz *et al.*, 2011), and these complications include encephalopathies, CNS infection, cerebrovascular diseases, drug toxicities, and other less commonly occurring syndromes (Rowley *et al.*, 1990; Saner *et al.*, 2010; Vizzini *et al.*, 2011). However, these previously reported neuropsychiatric complications (NPCs) and others have not been described, nor have they been reported in Egypt yet. The aim of this study was to evaluate the incidence of NPCs after living donor liver transplantation (LDLT) and the impact of immunosuppression on NPCs.

Patients and methods

A total of 110 patients who received LT were observed at the ICU from May 2001 to April 2005. All patients (100%) received LDLT. The primary diagnostic findings of the liver in all patients are summarized in Table 1. These patients are the first 110 patients to undergo LDLT in Egypt.

All operations were performed using standard techniques, and postoperative care was similar for all patients. The warm and cold ischemia time was recorded. All patients received immunosuppressive therapy based on corticosteroids, mycophenolatmofetile (19/12; Cell-Cept, Roche Laboratories Inc., New Jersey, USA), cyclosporine (CSA, 5 mg/kg/12 h orally; Sandimmune, Novartis Pharmaceuticals Corporation, East Hanover, New Jersey, USA), or tacrolimus (TAC, 0.05 mg/kg/12 h orally; Prograf Astellas Pharma US, Inc.; Deerfield, IL, USA, Fujisawa). Daily doses and trough levels of CSA or TAC were measured. The length of stay in the ICU for all patients was recorded.

The laboratory data for systemic infection were recorded and the function of the liver and kidney was measured daily. The observation time for all patients after LT was 1 year. After providing informed consent all recipients were assessed by two psychiatric and neurological consultants. Diagnosis of psychiatric disorders was made on the basis of the *Diagnostic and Statistical Manual of Mental Disorders, 4th ed.*, Text Revision (DSM-IV-TR) criteria (American Psychiatric Association, 2000). The presence or absence of PPS was evaluated on the basis of diagnostic criteria for PPS (Table 2). When all four elements existed, psychiatric symptoms were judged as PPS (Fukunishi *et al.*, 2002a). Diagnoses of neurological complications (NCs) were made by neurological examinations including examination of symptoms, cerebral computed tomography, and/or brain MRI.

Table 1 The primary liver diagnosis

Diagnoses	Number of patients (%)
Hepatitis C	48 (43.6)
Hepatitis B	37 (33.6)
Primary biliary cirrhosis	5 (4.5)
Autoimmune	8 (7.3)
Acute liver failure	7 (6.4)
Wilson disease	2 (1.8)
Alcoholic cirrhosis	3 (2.8)
Total	110 (100)

Results

Incidence of neuropsychiatric complications following liver transplantation

The total number of patients was 110 (74 men and 36 women), with a mean age of 54 ± 13.73 years. NPCs occurred in 56 patients (38 men and 18 women, with a mean age of 52 ± 13.1 years), resulting in an incidence of 50.9% of all LT patients (56/110). Neuropsychiatric symptoms occurred on postoperative day 6.7 ± 7.4 (range: postoperative day 1–30). Neurological complications occurred in 36/110 (32.7%) patients (Table 3), whereas psychiatric disorders occurred in 48/110 (43.6%) patients, of whom 15 (31.3%) suffered from major depression, 13 (27.1%) from depressive disorder not otherwise specified, nine (18.7%) from adjustment disorder, six (12.4%) from brief psychotic disorder, two (4.2%) from post traumatic stress disorder, and the remaining three (6.3%) patients suffered from substance-related disorder (Table 4). Among 48 recipients who met the diagnosis of psychiatric disorders based on the DSM-IV-TR criteria, 30 met the diagnostic criteria for PPS. The PPS diagnosis was seen in 62.5% (30 of 48 recipients with psychiatric disorders) and 27.3% (30 of 110 recipients) of patients.

Table 2 Diagnostic criteria for paradoxical psychiatric syndrome

Prominent conflicts associated with transplantation (e.g. guilt regarding the donor's welfare)
Situational reaction such as depression, anxiety, conversion, somatization, adjustment disorder, and/or psychosis
The reaction occurs as a late complication after liver transplantation (within the first year of transplant)
Favorable medical status of the donor and recipient, without tissue rejection or other medical complications

Table 3 The types of neurological complications following liver transplantation

Complications	*N*=36	Percentage (32.7)
Encephalopathy	25	(69.4) 22.7
Seizures	8	(22.2) 7.3
Ischaemic stroke	3	(8.3) 2.7
CNS infection	3	(8.3) 2.7
Intracerebral hemorrhage	1	(2.8) 0.9
Ataxia	6	(16.7) 5.5
Dysphasia	1	(2.8) 0.9
Headache	5	(13.9) 4.5
Tremor	7	(19.4) 6.4
Posterior leucoencephalopathy syndrome (PLE)	2	(5.6) 1.8
Central pontine myelinolysis	2	(5.6) 1.8
Peripheral neuropathy	6	(16.7) 5.5
Brachial plexus injury	4	(11.1) 3.6

CNS, central nervous system.

Table 4 The psychiatric disorder (DSM-IV-TR criteria) following liver transplantation

Psychiatric disorder	*N*48	Percentage (43.6)
Major depression	15	(31.3) 13.6
Adjustment disorder	9	(18.7) 8.2
Depressive disorder NOS	13	(27.1) 11.8
Brief psychotic disorder	6	(12.4) 5.5
PTSD	2	(4.2) 1.8
Substance-related disorder	3	(6.3) 2.7

DSM-IV-TR, *Diagnostic and statistical manual of mental disorders*, *4th ed.*, text revision; NOS, not otherwise specified; PTSD, post traumatic stress disorder.

PPS was diagnosed in 77.1% (27/35) of recipients who received a donor liver from one of their children, in 8% (2/25) of patients who received a graft from brothers or sisters, in 6.7% (1/15) of those who received spousal donation, and in none who received a graft from the father (0/21) or from an unrelated donor (0/14).

The length of stay in the ICU for patients with NPCs was 18.2 ± 17.2 days. This was significantly longer compared with that for the total number of patients (7.9 ± 9.8 days) ($P<0.05$).

EEG changes revealed generalized slowing down in 25/110 patients (22.7%) and 15 of 36 (41.7%) had NCs; focal changes (focal slowing down or focal spike and wave) were observed in 10/110 patients (9.1%) and only in six of the 36 patients having NCs (16.7%).

Neuroradiological results revealed positive findings in 13/110 patients (11.8%), nine of whom had NCs (69.2%) (9/13), two had central pontine myelinolysis, and two had posterior leucoencephalopathy syndrome. Intracranial hge was detected in one patient and cerebral infarctions in three, in cases in which patients had more than one NC.

Influence of neuropsychiatric complications on the survival rate after liver transplantation

The survival rate (SVR) after LT of patients with NPCs was lower [76.8% (43/56)] than that of patients without NPCs [81.5% (44/54)], but no significant difference was recorded ($P>0.05$) (Table 5).

Table 5 Influence of neuropsychiatric complications on survival rate after liver transplantation

Groups	Number	SVR
Patients with NPC	56	43 (76.8%)
Patients without NPC	54	44 (81.5%)
Total	110	87 (79.1%)

NPC, neuropsychiatric complication; SVR, survival rate.

Table 6 Effect of cyclosporine and tacrolimus on neuropsychiatric complications

Treatment	All patients	Patients with NPCs	Incidence	Onset (POD)
TAC	83	42	50.6%	7.3 ± 8.1
CSA	27	14	51.9%	5.1 ± 4.6
Total	110	56	50.9%	6.7 ± 7.3

CSA, cyclosporine; NPCs, neuropsychiatric complications; POD, postoperative day; TAC, tacrolimus.

Table 7 Effect of primary diagnoses on neuropsychiatric complications

	All patients	Patients with NPCs post-LT	Incidence of NPCs (%)
Hepatitis C	48	27	56.3
Hepatitis B	37	19	51.4
Primary biliary cirrhosis	5	2	40
Autoimmune	8	4	50
Acute liver failure	7	3	42.9
Wilson's disease	2	0	0.00
Alcoholic cirrhosis	3	1	33.3
Total	110	56	50.9

LT, liver transplantation; NPCs, neuropsychiatric complications.

Effect of cyclosporine and tacrolimus on neuropsychiatric complications

NPCs occurred in 50.6% of TAC-treated patients and in 51.9% of CSA-treated patients. There was no significant difference between these two groups ($P>0.05$). Neuropsychiatric symptoms were similar between these two groups but seemed to develop earlier in CAS-treated patients than in patients who received TAC ($P>0.05$) (Table 6).

Effect of primary diagnoses on neuropsychiatric complications

Hepatitis C and hepatitis B were the most common causes of liver failure (Table 2). However, no correlation between primary diagnosis and incidence of NPCs was found ($P>0.05$) (Table 7).

Discussion

NPCs are commonly seen after LT. Use of immunosuppressive drugs, incidence of cerebral hemorrhage, and systemic infection were causative factors. With the exception of cerebral hemorrhage and cerebral infarct most of them carry a good prognosis. Most complications occur early following LT, and a variety of etiologies exists. Effective treatment specific for different etiologies can

help to improve the prognosis of such patients (Borg *et al.*, 2008; Maldonado *et al.*, 2008; Saner *et al.*, 2009).

In our current study, NPCs occurred in 56 patients, resulting in an incidence of 50.9% of all LT patients (56/110). The reported incidence of NCPs was variable for different studies. Yinghong *et al.* (2003), in their retrospective study, found an incidence rate of 35.0%, which was much lower than that of our study as the researchers assessed the recipients in the first week after LT, whereas in our study recipients were assessed for 1 year. Another reason for the variation is that the authors did not evaluate psychiatric disorders that are responsible for a large proportion of NPCs. However, our prevalence (50.9%) is within the range reported by Gangeri *et al.* (2007), who found that an overall 49/94 patients (52%) reported various postoperative neuropsychiatric symptoms.

Psychiatric disorders occurred in 43.6% (48/110) of our patients; this proportion was much lower than those in the studies by Fukunishi *et al.* (2002a, 2002b), in which psychiatric disorders occurred in 58.5% (31/53) and 61.0% (25/41), respectively. Such higher incidence might be because those researchers added Delirium to psychiatric disorders (17 and 17.2%, respectively), whereas in our study it was added to NC. Incidence of other psychiatric disorders (major depression, adjustment disorder, brief psychotic disorder, post traumatic stress disorder, and substance-related disorder) was nearly similar to our findings.

PPS was diagnosed in 62.5% of our recipients (30 of 48 recipients with psychiatric disorders). This was higher than the 51.6% (16/32) found by Fukunishi *et al.* (2002a). This difference might be because of the higher proportion of recipients who received a donor liver from one of their children in our study, 77.1% (27/35), whereas for the other study the proportion was 72.2 (13/18). This category of recipients (parent) had the higher rate of feelings of guilt after surgery (the core symptom of PPS). Before LT, recipients' desire to escape from approaching death supersedes their conflicted feelings related to the prospect of living organ donation. After LT, the fear of death subsides and concern for the donor (his child) becomes more pronounced. Other categories (brothers/sisters and spousal donation) experience less guilt with much lower incidence of PPS (Fukunishi *et al.*, 2001, 2002a).

In contrast, Fukunishi *et al.* (2001) found that 12 (80%) of 15 adult recipients exhibited PPS. This higher percentage compared with that of our study might be because all their patients were in the category of recipients with adult child-to-parent donors. Another important variable is the small number of patients (15) compared with our study (110).

Neurological complications occurred frequently following LT. These complications are associated with significant mortality and morbidity and may lead to longer stay in the hospital (Pujol *et al.*, 1994; Campagna *et al.*, 2010). We found that major NCs affected 32.7% of all LT patients. The reported incidence of NC was variable for different centers. Mueller *et al.* (1994) reported a rate of 21% for NCs following LT, whereas a 9.42% rate was reported by Vogt *et al.* (1988). However, our prevalence (32.7%) is within the range reported in other medical centers (8.3 to 47%) (Busuttil *et al.*, 1987; Rowley *et al.* 1990; Menegaux *et al.*, 1994) and much higher than that reported by Haghighi *et al.* (2005).

A diffuse encephalopathy is considered the most common complication after LT (69.4% in this study). Adams *et al.* (1987) reported an encephalopathy rate of 76% in his series. Similar results were presented by Moreno *et al.* (1993), who reported an encephalopathy rate of 73%. The underlying mechanisms are unknown. However, in a large prospective study the authors diagnosed a diffuse encephalopathy (anoxic, septic, or metabolic) as the most common complication occurring in 56.5% of NCs in LT patients (Pujol *et al.*, 1994). Postmortem studies show diffuse anoxic–ischemic changes as the most common neuropathological findings (Ferreiro *et al.*, 1992; Martínez, 1998).

However, Haghighi *et al.* (2005) reported that the exact cause of this complication is difficult to ascertain in some cases. This was because of many confounding factors. Martinez *et al.* (1988) coined the term 'transplantation encephalopathy' to designate neurological disorders following graft dysfunction Martinez *et al.* (1988), which was the single most common cause of neurological complications. Cases that were attributed to electrolyte imbalance and uremic encephalopathy may have been because of a component of graft dysfunction. Ammonia, branched amino acids, mercaptans, manganese, short-chain fatty acids, and octopamine are substances implicated in cerebral dysfunction in liver failure (Victor and Ropper, 2000; Dejong *et al.*, 2007; Odeh, 2007).

The incidence of seizures following LT was reported as ranging from 0 to over 40% (Adams *et al.*, 1987; Vogt *et al.*, 1988; Estol *et al.*, 1989; Pujol *et al.*, 1994). In this study it was recorded to be 11.1%. The incidence of seizures after LT appears to be declining and the cause of this reduction seems to be the improvement in the management of multiple metabolic and toxic abnormalities causing seizures.

PLE consists of headache, visual disturbances, seizures, and a somnolent state, which can be caused by a variety of conditions and immunosuppressants (Hinchey *et al.*, 1996; Nakamura *et al.*, 1998). The accurate incidence of this condition is difficult to determine. Nevertheless, it has been reported to apply to about 5% of patients after LT (Adams *et al.*, 1987; De Groen *et al.*, 1987; Vogt *et al.*, 1988; Estol *et al.*, 1989; Stein *et al.*, 1992; Moreno *et al.*, 1993). In this study, we identified 5.6% of cases, which is in the same range as in earlier reports already described.

CNS infections have been reported in previous studies (Adams *et al.*, 1987; Lopez *et al.*, 1992; Pujol *et al.*, 1994) and occurred in about 5% of patients. In this study it has been reported in three of those patients with NCs (8.3%).

Cerebrovascular complications occur in about 4% of cases in different clinical series (Adams *et al.*, 1987; Moreno

et al., 1993; Pujol *et al.*, 1994). In our series, 2.8% of cases developed intracranial hge, and 8.3% experienced an ischemic stroke.

No correlation was observed between primary diagnosis and the incidence of NPC. Lewis and Howdle (2003) reported a higher rate of NC after LT for primary biliary cirrhosis and alcoholic cirrhosis. Ghaus *et al.* (2001) reported a very high incidence of NC following LT regardless of liver diagnosis (75%).

In this study the SVR between LT patients with NPCs and without NPCs was not significantly different. Similarly, Wijdicks *et al.* (1996) described no impact of NC on SVR after LT, which is in contrast to the study by Pujol *et al.* (1994), who reported that patients who had NCs had a significantly higher mortality rate than those without.

In the study by Haghighi *et al.* (2005), development of neurological complications was a predictor of fatal outcome, which in contrast to the study by Stein *et al.* (1992), which concluded that mortality at 1 and 2 years after transplantation was not related to neurological complications.

The application of CSA or TAC after LT has been reported to have a different effect on the incidence of NPCs. In this study, a similar incidence of neuropsychiatric symptoms was found between patients treated with CSA and TAC. The same observations were made by Lewis and Howdle (2003), Freise *et al.* (1991), Ardizzone *et al.* (2006), and Saner *et al.* (2006).

In contrast, Mueller *et al.* (1994) showed a higher incidence of NCs for TAC in comparison with CSA, and the most common complications were headache and tremor, a finding that was also reported by Ardizzone *et al.* (2006), Saner *et al.* (2006), and Padovan *et al.* (2000).

Conclusion

In conclusion, a high incidence of NPCs after LT was observed that led to these patients staying longer in the ICU. The major NPCs reported were encephalopathy, major depression, adjustment disorder, depressive disorder not otherwise specified, seizures, headache, and tremor. PPS has a high-incidence rate, especially when the donor is the child of the recipient. No correlation was found between primary liver disease and incidence of NPCs following LT, with no significant influence of NPCs on SVR. Thus, routine preoperative neuropsychiatric evaluation and careful postoperative examination are necessary for early diagnosis and recognition of NPCs after LT, and prompt treatment is essential for the recipients.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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