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ORIGINAL COMMUNICATION

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Neurological complications in liver transplantation

Abstract To define the incidence and type of neurological complications and associated factors, we reviewed 41 consecutive patients who had 45 procedures for liver transplantation. Encephalopathy occurred after 28 procedures (62 %) with immediate onset and no significant recovery before death or re-transplantation in 11 (24 %), slow recovery in eight (18 %) and delayed onset (1–50 days, average 11) in six (13 %). Intermittent confusion and agitation with full recovery followed three (6.6 %), and focal and generalized seizures followed five (11 %) procedures with multifocal myoclonus in two and status epilepticus in one; isolated focal seizures followed two and myoclonus or unclassified seizures, one each. All patients with seizures had encephalopathy. Three patients had neuropathy (2 generalised and 1 focal). Other complications included headache (2), tremors (2), fatigue (2), restlessness, nervousness, transient enuresis, intermittent dizziness, critical illness myopathy and detached retina. Brain imaging showed atrophy in three (6.6 %) instances, intracerebral hæmorrhage in two, multiple infarctions in one, and intracerebral and subarachnoid hæmorrhage with infarction in one. Cerebrospinal fluid analysis showed increased protein in three, hæmorrhage in one, and no abnormality in one patient. Of 12 patients (29 %) who died before discharge, five in the first and three in the second week post-transplantation, 11 (92 %) had encephalopathy post-operatively. Neurological complications after transplantation were associated with increased mortality. Post-operative hypomagnesæmia was associated with the development of nervous system complications. We did not identify any clear pre-operative predictors of development of post-operative neurological complications.

Key words CSF · Encephalopathy · Liver transplantation · Neurological complications · Seizures

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Introduction

Orthotopic liver transplantation (OLT) was first performed in 1963 [19]. Several advances, including improved patient selection, specialised transplantation centres and better immunosuppression, have had an impact on patient survival [20]; nonetheless, complications do still occur. Clinical series show that nervous system (NS) complications occur in 8 to 47 % of cases and include diffuse encephalopathy, cerebrovascular disorder [8], infection [13], immunosuppression-induced neurotoxicity [6], and peripheral nerve damage [11].

We present a series of patients who underwent OLT at King Faisal Specialist Hospital and Research Centre, a tertiary care facility in Saudi Arabia. We focus on the incidence and type of NS complications encountered after OLT until discharge, retransplantation or death, and analyse the associated factors.

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Materials and methods

Forty-five OLTs were performed on 41 consecutive patients (25 males, 16 females; mean age 37.8 years, range 7–69) between March 1994 and December 1996. The causes of liver failure are shown in Table 1. Five patients (12%) had a second transplant, four at this institution and one abroad. The donor livers were procured and transplanted using standard techniques [19, 20].

After surgery the patients were nursed in the Intensive Care Unit before transfer to the general ward. Details of the immunosuppression regimen are given in Table 2. The serum level of cyclosporine was measured daily and the dose adjusted accordingly. Other blood tests included complete blood count, prothrombin time, partial thromboplastin time, and magnesium, sodium, potassium, creatinine, urea, glucose, bilirubin, alkaline phosphatase, and aspartate and alanine aminotransferase concentration. Serum amylase, lactic acid and ammonia levels, arterial blood gas analysis, electrocardiography and chest radiography were performed in all patients whilst in the ICU. All patients were given intravenous ampicillin (1 g) and cefotaxime (1 g) at induction then 8-hourly for 48 hours, famotidine or ranitidine, multivitamin tablets and trimethoprim-sulphamethoxazole. After transplantation all patients were seen by the intensive care, hepatology and hepatic transplant surgery teams. Cerebrospinal fluid (CSF) examination, electro-encephalography, computed tomography (CT) and magnetic resonance imaging (MRI) of the brain, needle electromyography and nerve conduction studies were performed when clinically indicated and technically possible.

The clinical records of all the patients were reviewed. The pre-OLT variables collated were age, gender, type and duration of liver disease, previous episodes of hepatic encephalopathy or variceal bleed, seizures, stroke, and prior brain imaging. The operative variables were duration of surgery, use of veno-venous by-pass, episodes of arterial hypotension, immediate pre- and post-OLT serum sodium, magnesium and glucose levels.

Neurological complications were recorded as post-OLT if they were of new onset and not present before transplantation, and were analysed, distinguishing central (CNS) from peripheral NS involvement. Encephalopathy included delirium, stupor and coma. Cerebral vascular lesions were diagnosed by the clinical picture and ischæmic or hæmorrhagic insult on CT or MRI of the brain. Diagnosis of peripheral NS damage was based on electrophysiological data or clinical evidence of peripheral nerve involvement without CNS lesion on neuroimaging. Diagnosis of sepsis was considered if there were clinical and laboratory data on systemic infection. Multi-organ failure was diagnosed by abnormal function in more than one organ. Cyclosporine neurotoxicity was diagnosed by high plasma levels at the onset of neurological symptoms or signs. Primary graft failure was defined as dysfunction resulting from peri-operative difficulties. Rejection was diagnosed by laboratory indices and hepatic biopsy.

Table 1 Causes of Liver Failure Necessitating Orthotopic Liver Transplantation in 41 Patients

Disease	Number of Patients (%)
Hepatitis C	17 (41)
Cryptogenic	6 (14.6)
Wilson's disease	*3 (7.3)
Autoimmune hepatitis	2 (4.9)
Hepatitis C and hæmochromatosis	1
Hepatitis C and hepatic carcinoma	1
Hepatitis C and alcohol related disease	1
Hepatitis C and B	1
Miscellaneous:	
Drug-induced (acetaminophen & anti-depressants); fulminant hepatic failure; biliary atresia; familial intrahepatic cholestasis; chronic active hepatitis; cholestatic liver disease; congenital hepatic fibrosis; micronodular cirrhosis; schistosomiasis; 3-oxo steroid 5-ß reductase deficiency	

* one patient also had hepatic carcinoma

Table 2 Immunosuppression Regimen

Anhepatic phase in the operating room[1]
Cyclosporin A 2 mg/Kg i. v.
Methylprednisolone 1000 mg i. v.
Azathioprine 2 mg/Kg i. v.
Maintenance after transplantation[2]
Cyclosporin A 2 mg/hr
Methylprednisolone tapering dose (50 mg q. i. d. to 20 mg daily over 5 days)

[1] Except for re-transplantation when azathioprine was omitted and cyclosporin A continued in the regular dose as determined following the previous OLT

[2] These were changed to oral cyclosporin A and prednisone when the patient was capable of oral intake

Results

Nervous system manifestations before OLT were present in 31 patients (69%) (Table 3). Thirteen patients (29%) had a history of previous encephalopathy and 4 (9%) had encephalopathy at the time of OLT. Brain atrophy was seen on CT or MRI in 8 (18%) while 8 patients had normal cranial imaging, and the result was not known in one patient. Cranial imaging before OLT had not been performed in the remainder of the patients. Five patients (11%) complained of fatigue with no further qualification of the symptom and 4 (9%) had a history of episodic loss of consciousness. Less frequent manifestations included intermittent headache (7%), peripheral neuropathy (4%) and seizures (2%).

The NS manifestations following OLT are summarised in Table 4. Encephalopathy was seen in about two-thirds of patients with immediate onset following operation 71%; 58% of these patients either died or had a second OLT and the remainder made slow recovery. In 21% of patients the onset of encephalopathy was delayed from 1 to 50 days (average 11 days). Three patients (11%) had intermittent confusion and agitation. One

Table 3 Pre-transplant Nervous System Manifestations

Encephalopathy	17
Historical	13
Current	4
Brain atrophy on imaging	8
Fatigue	5
Episodic alteration in level of consciousness	4
Headache	3
Neuropathy (glove and/or stocking)	2
Partial empty sella	1
Diffuse white matter disease	1
Old idiopathic facial nerve (Bell's) palsy	1
Abducens nerve palsy	1
Seizures	1

Table 4 Number (%) of Post-orthotopic Liver Transplantation Nervous System Manifestations

Encephalopathy		28 (62.2)
early with no recovery	11	
early with slow recovery	8	
delayed	6	
intermittent confusion and agitation	3	
Seizures		9 (20)
focal and generalised	5	
focal	2	
myoclonus	1	
unspecified	1	
Neuropathy		3 (6.7)
"stocking" sensory loss	1	
critical illness	1	
brachial plexus injury	1	
Tremor		2 (4.4)
Headache		2 (4.4)
Fatigue		2 (4.4)
Others:		1 each
Facial palsy, visual hallucinations, traction-detached retina, transient enuresis, nervousness, restlessness, intermittent dizziness and critical illness myopathy		

third of the patients with post-operative encephalopathy had experienced encephalopathy pre-operatively (either immediately before surgery or previously), while the remainder developed it for the first time after OLT. The clinical features associated with encephalopathy included primary hepatic dysfunction, multi-organ failure, sepsis, renal failure, prolonged surgery, multiple blood transfusion, transient hepatic dysfunction, hypomagnesæmia, hypercalcæmia, sedation and analgesia. Seizures followed OLT in nine patients (20%). There were focal and generalised seizures in five patients (55%), with multifocal myoclonus in two and status epilepticus in one of them. Associated clinical features included multiorgan failure, systemic sepsis, hepatic or renal dysfunction, increased serum level of Cyclosporin A, intracerebral hæmorrhage (Fig. 1A, B, D) and *Aspergillus* abscess (Fig. 1C). Cranial imaging was performed in 15 patients (Table 5). All patients had CT and one had MRI in addition. In 11 patients the imaging was abnormal. One of these had white matter changes and brain atrophy similar to previous imaging before OLT. Others showed abnormalities not known previously. Imaging was normal in 4 patients. Of the 15 patients who underwent cranial imaging (Table 5) only two had cerebrospinal fluid (CSF) analysis (patients 1 and 12). The

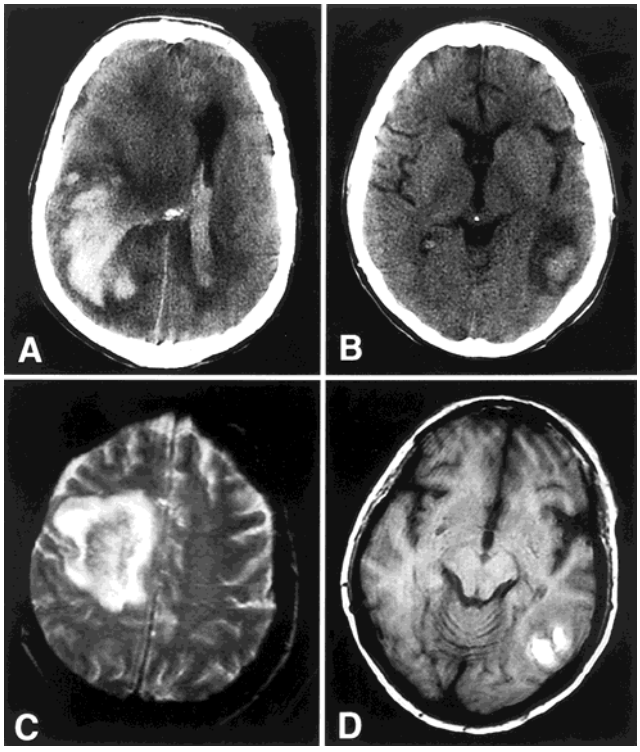

Fig. 1 Non-contrast CT (A, B) and 1.5 Tesla MRI T2 (C) and TI (D) weighted images of brain. Biopsy specimen from right frontal lesion (C) showed *Aspergillus*.

Table 5 Post-OLT Cranial Imaging Findings

Pt	NS Manifestations	Imaging
1	Confusion, seizures, depression	Intracerebral hæmorrhage with extension into ventricles
5	Seizures, generalized weakness and hemiplegia, *Aspergillus* on brain biopsy	Cerebral infarction, intracerebral hæmorrhage,"ring-enhancing" lesion
12	Encephalopathy, mutism, tremor, myopathy	normal
16	Encephalopathy, headache, enuresis	normal
18	Encephalopathy, seizures	normal
19	Encephalopathy, seizures, hemiplegia	white matter changes and brain atrophy similar to pre-OLT
28	Encephalopathy, critical illness neuropathy	mild cerebellar atrophy
29	Coma	subarachnoid bleed, œdema, poor differentiation in grey & white matter
38	Seizures, encephalopathy	extensive white matter hypodensity
39	Seizures, encephalopathy	intracerebral hæmorrhage with extension into ventricles
40	Encephalopathy	mild brain atrophy
41	Encephalopathy, neuropathy	mild brain atrophy, focal R-basal ganglia infarction
43	Encephalopathy, dizziness	normal
44	Agitation	moderate brain atrophy
45	Encephalopathy	cerebral œdema

Table 6 Associated Factors in Patients Developing Nervous System Complications

	NS Complication yes	no	p value (Fisher exact test)
Age			
< 16 years	9	2	0.58
≥ 16 years	31	3	
Gender			
male	23	3	0.9
female	17	2	
Post-operative serum magnesium level			
normal	11	5	0.015*
abnormal	18	0	
Post-operative serum sodium level			
normal	16	8	0.07
abnormal	9	0	
Post-operative serum calcium level			
normal	19	5	0.16
abnormal	11	0	
Femoral axillary veno-venous by-pass			
performed	24	3	0.83
not performed	13	2	
Hypotension during surgery			
present	21	2	0.67
absent	19	3	
Duration of surgery			
< 8 hours	21	5	0.5
≥ 8 hours	16	3	
Variceal bleeding before transplant			
present	19	0	0.12
absent	20	4	
Ascites			
present	32	2	0.39
absent	5	1	
Pre-transplant nervous system manifestations			
present	27	2	0.33
absent	13	3	

* significant

CSF from patient 1 showed xanthochromia and slight elevation of protein and that from patient 12 was normal. Electroencephalography was performed in 9 patients. It showed mild to marked slowing in six patients (with additional epileptiform abnormalities in one), electrocerebral silence in two patients (both died), and no report was available for one patient. Cerebrospinal fluid was analysed to exclude CNS infection in 5 patients (including patients 1 and 12) with systemic sepsis. It showed elevated protein content in 3, hæmorrhage in one and no abnormality in one patient. One patient had quadriparesis and rhabdomyolysis, considered to be toxic myopathy on muscle biopsy but retrospectively diagnosed as critical illness myopathy [5].

Twelve patients died before discharge, five in the first and three in the second week post-OLT; 11 (92 %) of them had encephalopathy post-OLT. The association of various factors with development of NS complications is shown in Table 6; NS complications related to morbidity or mortality are shown in Table 7. Abnormal serum magnesium was seen post-operatively in 33 %, with a statistically significant association with the development of NS complications post-OLT. All except one patient had hypomagnesæmia (average 0.55 mmol/l, range 0.29–0.68 mmol/l). One patient had slight hyponatræmia (serum Na level 134 mmol/l) and eight had hypernatræmia (serum Na from 146 to 157 mmol/l). The association of the presence of NS complications post-OLT with poor outcome (death or re-transplantation) was statistically significant by χ^2 but not by Fisher's exact test. There was no significant association of any pre-transplant neurological manifestation with development of postoperative NS complications. The condition of the patients at the time of death is shown in Table 8. Multiorgan failure was seen in 5 (42 %) with coagulopathy resulting in disseminated intravascular coagulation (DIC) in two, perforation of false aneurysm of superior vena cava and septic shock in one each. Primary non-function of the transplanted liver was seen in three (25 %) with DIC in one patient. One patient with renal dysfunction had yeast septicæmia and pulmonary hæmorrhage and another patient had pulmonary aspergillosis and systemic bacterial sepsis. One patient with coagulopathy developed subarachnoid hæmorrhage and another patient developed intracerebral hæmorrhage.

The most common cause of liver failure necessitating OLT was hepatitis C, either alone or in combination with hepatitis B, hæmachromatosis, hepatic carcinoma or alcohol-related hepatic disease. Time from onset of hepatic failure to first OLT ranged from 1 day to 15 years. Nine patients (22 %) had OLT within 1 year (5 in the first half and 4 in the second half) and 29 (70.7 %) had OLT within 4 years of onset of hepatic failure. Retransplantation was performed in 5 to 18 days.

Discussion

A wide variety of neurological complications can occur after OLT. In our series, the incidence of neurological complications after OLT until discharge, retransplantation or death was 75 %. Review of the literature shows that the incidence of such complications ranges from 19 to 90 % [1, 10, 12, 14, 16, 18, 21, 23]. In contrast to our series, others [1, 10, 12, 18] do not include symptoms such as fatigue, headache, nervousness or dizziness without objective signs as neurological manifestations. This may account for our higher-than-average incidence of complications; in addition, one of our patients had sudden blurring of vision, which was found to be related to traction-detachment of retina, but was included in neurological complications. Neurological manifestations before OLT (mostly encephalopathy) were noted in 69 % of patients; encephalopathy was also the most common NS manifestation after OLT, the next most frequent being seizures. The presence of post-OLT NS manifestation in

Table 7 Mortality and Morbidity with Nervous System Complications

Variable	Outcome		p value (Fisher's Exact Test)
	Discharged	Died/Re-transplanted	
NS manifestation post-OLT			
present	24	16	0.14
absent	5	0	(χ^2=0.02) (statistically significant)
Previous œsophageal variceal bleed			
present	12	6	0.75
absent	15	6	
Ascites			
present	23	9	0.86
absent	6	2	
Veno-venous by-pass			
yes	22	5	0.25
no	8	5	
Hypotension during OLT			
yes	19	3	0.16
no	14	7	
Serum magnesium post-OLT			
normal	14	6	0.16
hypomagnesæmia	10	5	
Serum calcium post-OLT			
normal	19	6	0.45
hypercalcæmia	5	4	
hypocalcæmia	2	0	

relation to fatal outcome approached statistical significance when the χ^2 method was used (p=0.02); however, because of small numbers involved we used Fisher's exact test which showed that post-operative hypomagnesæmia was the only association with the development of NS complications that was statistically significant. Hypomagnesæmia is common after transplantation of kidney [22] and lung [9]. In liver transplant recipients a major factor causing hypomagnesæmia is chelation of magnesium with the citrate contained in hæmo-derivatives, which are usually transfused massively [7]. During cardiac operations, hypomagnesæmia is associated with clinically significant morbidity resulting from cardiac dysrhythmias and it was shown to impair selectively the release of nitric oxide from the coronary endothelium, hence promoting vasoconstriction and thrombosis in the early postoperative period [15]. After OLT, no significant cardiac arrhythmias were directly attributable to hypomagnesæmia [7]. To our knowledge, the development of NS complications after liver transplantation caused by hypomagnesæmia, and the underlying mechanisms, have not been clearly established. More interestingly, it is not known whether correction of hypomagnesæmia would affect the outcome in these patients. These factors may require further study.

Table 8 Condition of Patients at the Time of Death *

Multiorgan failure	5
Transplanted liver dysfunction	3
Renal dysfunction	2
Intracranial hæmorrhage	2
TOTAL DIED	12

* see text for further details

Age (pædiatric versus adult), gender, post-operative abnormal serum calcium, femoro-axillary veno-venous by-pass or hypotension during surgery, duration of surgery, previous œsophageal bleeding, ascites or NS manifestations pre-transplant, did not achieve statistical significance for the prediction of complications after OLT. Most complications occurred during the early post-OLT period. Mortality during the first week was 42 % and during the second week 25 %. It is likely that mortality would have been greater if five patients had not received a second OLT.

In our series, the commonest cause of liver failure necessitating OLT was hepatitis C-related liver disease, either alone (41 %) or in combination with other disease (10 %) including hepatitis B, hepatic carcinoma, hæmochromatosis or alcohol-related liver disease. Notably, the incidence of hepatitis B-related liver failure was only 2 %. Three patients had Wilson's disease; two were discharged alive after OLT while one had primary non-function of transplanted liver, probably related to hyperacute rejection, and died despite retransplantation of liver. The data regarding any recurrence of Wilson's disease-related failure in transplanted liver in these patients is not available. One patient left for retransplantation abroad and the outcome is not known.

Liver transplantation has now been established as an important therapeutic consideration for almost every patient with severe, irreversible liver disease [4, 12]. Ner-

vous system complications occur frequently post-OLT and cause significant morbidity and mortality [1, 10, 12, 14, 17, 18, 21, 23]. Non-infectious lesions are common in the early post-OLT period; they are usually related to hepatic dysfunction, multi-organ failure, metabolic abnormalities, sedation or analgesia. Multifocal seizures and myoclonus are usually a manifestation of metabolic abnormalities but focal and/or secondarily generalized seizures usually indicate an intracranial hæmorrhagic or infectious lesion [2, 3]. Infectious lesions, cyclosporine toxicity, neuromyopathy and other NS lesions occur relatively later post-OLT. *Aspergillus sp*. is a common cause of intracranial infectious lesion. Bacterial involvement of the CNS is rare in liver transplant recipients compared with systemic sepsis, and viral infections, including cytomegalovirus, may also involve the CNS [16].

In conclusion, neurological complications commonly follow OLT and are a significant source of morbidity and mortality in liver transplant recipients. The major NS manifestation in our patients was encephalopathy followed by seizures. Attempts to establish the diagnosis are often technically difficult because of the patient's poor clinical status. Moreover, significant systemic and metabolic abnormalities may obscure symptoms of an underlying lesion in the CNS. We suggest routine preoperative neurological evaluation and careful post-operative examination to help define the causes and consequences of NS complications in OLT recipients. We observed an association of hypomagnesæmia with development of NS complications after OLT and that the presence of NS complications may adversely affect morbidity and mortality. It is not known whether prevention or correction of hypomagnesæmia might alter the outcome in these patients. We did not identify any clear preoperative predictor of neurological complication developing after OLT. Nevertheless, a reasoned approach to the recognition and diagnosis of CNS lesions after OLT, prompt treatment and use of invasive procedures in selected patients, will help improve the management of OLT recipients.

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