Neurological complications in recipients after living donor liver transplantation

Thesis
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بسم الله الرحمن الرحيم

قَالُوا سُبْحَانَكَ لاَ عِلْمَ لَنَا إِلاَّ مَا
عَلَّمْتَنَا إِنَّكَ أَنتَ الْعَلِيمُ الْحَكِيمُ

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The Beneficent and Merciful of All"**

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List of Abbreviations

AEDs	:	Antiepileptic Drugs
AFB	:	Acid Fast Bacilli
AIDP	:	Acute Inflammatory Demyelinating Polyneuropathy
BBB	:	Blood Brain Barrier
Cho	:	Choline
CIDP	:	Chronic Inflammatory Demyelinating Polyneuropathy
CIM	:	Critical Illness Myopathy
CIP	:	Critical Illness Polyneuropathy
Cis	:	Calcineurin Inhibitors
CK	:	Creatinine Kinase
CMV	:	Cytomegalovirus
CNS	:	Central Nervous System
COA	:	Co Enzyme A
CPM	:	Central Pontine Myelinolysis
Cr	:	Creatine
CS	:	Cyclosporine
CSF	:	Cerebrospinal Fluid
CT	:	Computerized Tomography
CVST	:	Cerebral Venous Sinus Thrombosis
Cx	:	Culture and sensitivity
DDLT	:	Deceased Donor Liver Transplantation
DM	:	Diabetes Mellitus
EBV	:	Epstein-Barr Virus
EEG	:	Electroencephalography
EMG	:	Electromyography
EPS	:	Extrapyramidal symptoms
ESLD	:	End Stage Liver Disease
FLAIR	:	Fluid Attenuated Inversion Recovery
FTA-ABS	:	Fluorescent Treponemal Antibody Absorbed Test
GABA	:	Gamma Amino Butyric Acid
GBS	:	Guillian Barre Syndrome
GVHD	:	Graft Versus Host Disease
HBS	:	Hepatobiliary Scintigraphy

List of Abbreviations

HBV	:	Hepatitis B virus
HCC	:	Hepatocellular Carcinoma
HCV	:	Hepatitis C virus
HE	:	Hepatic Encephalopathy
HEV	:	Hepatitis E virus
HHV-6	:	Human herpes virus-6
HIE	:	Hypoxic Ischemic Encephalopathy
HIV	:	Human Immune deficiency virus
HSCT	:	Hematopoietic stem cell transplantation
HSV	:	Herpes Simplex Virus
ICH	:	Intracerebral Hemorrhage
ICU	:	Intensive Care Unit
INH	:	Isoniazide
IRS	:	Immune Reconstitution Syndrome
IV	:	Intravenous
JC Virus	:	John Cunningham Virus
LDLT	:	Living Donor liver transplantation
LOC	:	Level of Conciousness
LP	:	Lumbar puncture
LT	:	Liver Transplantation
MHA-TP	:	Microhemagglutination Treponemal Test
MMF	:	Mycophenolate Mofetil
MRI	:	Magnetic Resonance Imaging
MRV	:	Magnetic Resonance Venography
NAA	:	N-acetyl Aspartate
NC	:	Neurological Complications
NCS	:	Nerve Conduction Study
OHE	:	Overt Hepatic Encephalopathy
OLT	:	Orthotopic Liver transplantation

List of Abbreviations

PBC	:	Primary Biliary Cirrhosis
PCR	:	Polymerase Chain Reaction
PET	:	Positron emission tomography
PML	:	Progressive Multifocal Leucoencephalopathy
PSC	:	Primary Sclerosing Cholangitis
PTLD	:	Posttransplant Lymphoproliferative Disorder
RPLE	:	Reversible Posterior Leucoencephalopathy
SHE	:	Subminimal Hepatic Encephalopathy
SIP	:	Sickness Impact Profile
SPSS	:	Statistical Package for Social Sciences
SSEP	:	Somatosensory Evoked Potential
SSRI	:	Selective Serotonin Reuptake Inhibitors
TBI	:	Traumatic Brain Injury
TMP/SMX	:	Trimethoprim/Sulfamethoxazole
TSH	:	Thyroid Stimulating Hormone
VDRL	:	Venereal Disease Research Laboratory
VZV	:	Varicella Zoster Virus
WML	:	White Matter Lesions
WNV	:	West Nile Virus

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Abstract

Background and Objective:Neurological complications (NC) affects up to one third of patients after Liver transplantation (LT). The aim of this study is to assess the incidence, risk factors and clinical presentation of NC after liver transplantation in patients who underwent living donor liver transplantation (LDLT) in Egypt.

Methods: Between November 2011 and December 2013, 149 patients from diffrent centers were observed for one month after LDLT and evaluated by full general and neurological examination, assessment of encephalopathy by West Haven classification, full laboratory investigations including drug levels, and brain CT and/or MRI.

Results: 46 patients (30.9%) developed neurological complications 30 of which (20.1%) developed side effects related to Tacrolimus (FK-506) and 2 patients (1.3%) developed side effects related to cyclosporine. The most common neurological complications were Encephalopathy (14.1%) while the least were both Central pontine myelinolysis and Meningoencephalitis (0.7%). Patients were classified into complicated and noncomplicated groups. The mean Serum level of Tacrolimus (FK-506) was higher in complicated than noncomplicated patients yet both were within the normal therapeutic range with no statistically significant difference. A highly significant association was found regarding the relation between FK-506 and neurological complications in both groups. Neither the age nor the preoperative risk factors (diabetes mellitus, hypertension) had significant correlation with the early postoperative neurological complications. In all patients, there was no statistical significant correlation between FK506 and the other studied parameters while there was a positive correlation between FK506 and total bilirubin ($r= 0.226$; $p= 0.006$). FK506 was positively correlated with both direct bilirubin ($r= 0.160$; $p= 0.053$) and ammonia ($r= 0.146$; $p= 0.078$) no statistical significant correlation were found between cyclosporine and different studied parameters. In neurologically complicated patients, FK506 was positively correlated with both total bilirubin ($r= 0.272$; $p= 0.089$) and direct bilirubin ($r= 0.281$; $p= 0.079$) yet still insignificant (borderline insignificant). Finally, no correlation was observed between the primary cause of liver disease and the NCs reported.

Conclusion: There was a high incidence of neurological complications after LT, the most common complications following LT were encephalopathy, delirium, hallucinations, delusions and seizures. NC can occure even with normal serum levels of FK506.

Key words: Liver Transplantation, Neurological complication, Encephalopathy, Immunosuppression

Introduction

Liver transplantation has become a lifesaving therapy for many types of end stage liver disease, however during the past decade; a critical shortage of cadaveric organs for adults in need of liver transplants has developed. During this time, the waiting period for liver transplantation and the rate of death among patients on waiting lists have been increased. Therefore, living donor liver transplantation (LDLT) has become an important tool to treat end stage liver disease due to the lack of such cadaveric donors ***(Lee et al., 2008).*** Over the past several decades, advances in surgical techniques, organ preservation, immunosuppressive therapy, and early detection of postoperative complications have increased survival rates after liver transplantation ***(Caiado et al., 2007).***

Liver transplantation (LT) is the only curative treatment in patients with end-stage liver disease. The first LT was performed in 1963 ***(Starzl et al., 1963)***. Initially, the most common reason for death post-LT was an acute or chronic rejection of the graft. Then, the introduction of immunosuppressive treatment increased the survival rate from 20% to nearly 80% ***(Starzl et al., 1985)***, but postoperative complications remain a significant source of morbidity and mortality ***(Mazariegos et al., 1999)***. Of all the complications post-LT, the neurological complications (NC) are particularly relevant, since they affect up to a third of transplanted patients ***(Wang et al., 2000)***.

With the rapid development of transplant technique and immunosuppressive therapy, orthotopic liver transplantation (OLT) has been carried out all over the world and accepted as one of the most effective treatments for the patients with end-stage liver diseases. However, postoperative complications are still the most important causes resulting in death of patients undergoing OLT ***(Dhar et al., 2008)***.

The incidences of posttransplant cerebrovascular complications or intracranial hemorrhage were 2.2%–3.9% in United States ***(Saner et al., 2006)***, 3.3% in United Kingdom ***(Lewis et al., 2003)***, 3.7% in Chile ***(Uribe et al., 2003)***, 6% in Spain ***(Pujol et al., 1994)***, 6.5% in Hong Kong ***(Wang et al., 2000).***