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Case Report

Fatal neurological complication after liver transplantation in acute hepatic failure patient with hepatic encephalopathy

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Liver transplantation is a current definitive treatment for those with end-stage liver disease. Hepatic encephalopathy is a common complication of hepatic failure, which can be improved and aggravated by various causes. It is important to differentiate hepatic encephalopathy from other diseases causing brain dysfunction such as cerebral hemorrhage, which is also related to high mortality after liver transplant surgery. A 37-year-old patient was presented with acute liver failure and high ammonia levels and seizure-like symptoms. Computed tomography (CT) of his brain showed mild brain atrophy, regarded as a symptom of hepatic encephalopathy, and treated to decrease blood ammonia level. Deceased donor liver transplantation was performed and liver function and ammonia level normalized after surgery, but the patient showed symptoms of involuntary muscle contraction and showed loss of pupil reflex and fixation without recovery of consciousness. Brain CT showed brain edema and bilateral cerebral infarction, and the patient died after a few days.

The purpose of this case report is to emphasize the importance of preoperative neurological evaluation, careful transplantation decision, and proper perioperative management of liver transplantation in patients with acute hepatic encephalopathy.

Key Words: Acute Hepatic Failure, Brain edema, Hepatic encephalopathy, Liver Transplantation, Seizure

Liver transplant surgery is the only treatment for patients with end-stage liver disease or acute liver failure, particularly, those patients with fulminant hepatic failure. Hepatic encephalopathy (HE) is common in these patients and sometimes it is accompanied by serious complications that may affect reversibility or the postoperative prognosis. Hepatic encephalopathy may present various clinical aspects ranging from sleep disorder and mood changes to epileptic seizure.

After liver transplant surgery from a brain dead donor, nervous system complications occur at a rate of 10 to 75% and [1] are known to increase the patients' morbidity and mortality. This case report is to determine the neurological evaluation, diagnosis, and treatments that may be attempted before performing liver transplant surgery in patients with liver failure accompanied by hepatic encephalopathy.

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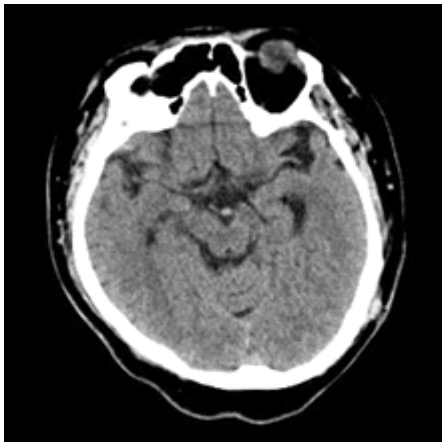

Fig. 1. Brain CT was performed on the day before surgery when the consciousness was semi-coma. As a results of reading, no specific finding was observed other than mild brain atrophy.

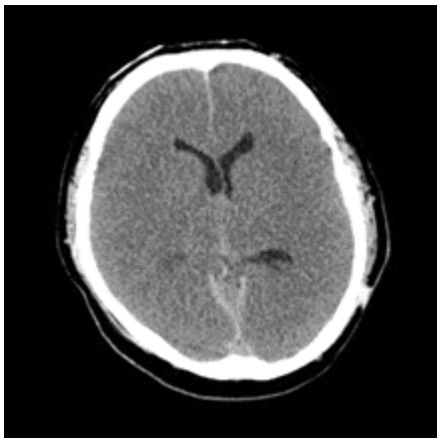

Fig. 2. On the first day after surgery, brain CT revealed severe cerebral edema and cerebral infarction. At this time, the patient showed bilateral pupil dilatation and fixation without recovery of consciousness.

CASE

A 37-year-old male patient was transferred to the hospital with the toxic hepatitis. This patient had chronic alcoholic hepatitis and diabetes and he had been drinking water boiled with burdock (Arctium lappa) and bitter melon for 10 days before coming to the hospital. At the time of admission, he also had symptoms of anxiety and a confused state of mind. He was classified as having serious Grade III hepatic encephalopathy based on a classification of hepatic encephalopathy symptoms according to the West Haven grading system. Blood tests showed the following levels: ammonia 207 umol/L, creatinine 1.31 mg/dL, bilirubin 16.2 mg/dL, and prothrombin time (international normalized ratio, INR) 10.33, resulting in a MELD (Model for End-stage Liver Disease) score of 43. The patient's consciousness gradually changed to a semi-coma state, and a lactulose enema was performed. A brain Computed Tomography (CT) showed mild cerebral atrophy (Fig. 1) and he was registered as a status 1 on the liver transplant waiting list in the Korean Network for Organ Sharing (KONOS).

After lactulose enema treatment, the blood ammonia level was reduced to 166 umol/L but it increased rapidly, which resulted in the patient being placed on ventilator after endotracheal intubation and application of continuous renal replacement therapy (CRRT) to reduce the blood ammonia level. The next day, a brain-dead patient matching our study patient was identified and the patient was prepared for an emergency liver transplantation.

One hour before entering the operating room, seizure-like symptoms such as myoclonic seizure on the left leg, blinking eyelids and eyeball deviation were observed for 5 minutes. At that time, the mean arterial blood pressure was maintained stably at 70 mmHg. The seizure symptoms dis-

appeared after an intramuscular injection of 1 mg Lorazepam. The endotracheal tube and central venous catheter were maintained and the patient had continuous intravenous infusion and was sedated with remifentanil and dexmedetomidine to suppress voluntary extubation. At that time, the symptoms were considered to be caused by hepatic encephalopathy so the patient was immediately taken into surgery without performing additional neurological evaluation.

After entering the operating room, the patient still showed the same symptoms. After anesthetic induced using IV anesthesia (Propofol 50 mg IV), the anesthetic condition was maintained using the inhalation anesthetic Desflurane.

Blood tests were performed at the intraoperative pre-anhepatic phase, the anhepatic phase, and the neo hepatic phase, and ammonia levels were determined to be 240, 209, and 182 umol/L respectively (Table 1). BIS (Bispectral index), which monitors the anesthetic depth through an electroencephalogram analysis, was attached before anesthetic induction, and the initial value was identified as 84. The values were maintained between 30 and 55 for the first 2 hours after starting the surgery, and it was identified as 0 right before liver extraction at 4 hours of surgery. Subsequently, the BIS value was less than 10 and from 30 minutes after refusion until the end of surgery, it continued to be 0. The patient's systolic arterial blood pressure during the surgery was 90-100 mmHg and higher. The mean arterial blood pressure was 50-85 mmHg and over, the heart rate was 75-95 bpm, oxygen saturation was 97-100%, and the body temperature was maintained at 36.0 ºC and over. The total operation time took 7 hours and 30 minutes (Table 2). While maintaining the endotracheal intubation, the patient was sedated with continuous intravenous infusion with dexmedetomidine and remifentanil and moved to the intensive care unit. Even during the sedation after entering the intensive care unit, he showed symptoms of involuntary muscle contraction, so an additional 2 mg of Lorazepam IV was given. One day after surgery, the blood tests showed the ammonia level reduced to less than 150 mol/L so the administration of sedative was stopped. The consciousness of the patient was checked by attempting

Table 1. Perioperative clinical laboratory findings

	Preoperative period	Pre-anhepatic period	Anhepatic period	Neohepatic period	Postoperative day 1
Ammonia (umol/L)	314	240	209	182	108
Total Bilirubin (mg/dL)	15.5	14.1	12.9	9.4	8.2
Prothrombin time (INR)	6.58	8.84	4.20	4.54	1.85
Creatinine (mg/dL)	2.62	3.38	3.22	3.25	2.15

INR: Internationalized ratio

Table 2. Perioperative vital signs

	Pre-operative	Pre-anhepatic period	Anhepatic period	Neo-hepatic period	Post-operative (After 2 hours post-operative)	Post-operative (After 2 hours post-operative)
Systolic ABP (mmHg)	150-170	80-130	70-100	100-120	140-165	6-65
Diastolic ABP (mmHg)	65-80	40-75	30-55	40-60	60-80	40-45
Mean ABP (mmHg)	70-85	60-75	45-60	60-65	70-85	45-50
HR (bpm)	100-120	70-90	90-100	60-80	65-80	60-70
SPO_2 (%)	98-100	97-100	100	100	99-100	88-96
Mental status	Semicoma	Under general anesthesia			sedation	coma
BIS	22-46		0-10	0		

ABP: Arterial blood pressure; HR: Heart rate; BIS: Bispectral index

to wake the patient, but the patient was in a semi-coma. For 2 hours after being moved to the intensive care unit, the arterial blood pressure and heart rate were maintained high at 140-180/50-80 mmHg and 100-125 times/min, respectively, so 6 mg/hr of Nicardipine was injected by drip infusion, and as a result, the arterial blood pressure and heart rate were maintained stably at 120-130/50-70 mmHg and 60-100 times/min. However, at 12 hours after the surgery, the blood pressure and heart rate were reduced to 60/40 nnHg and 60 bpm and the patient's pupils were fully dilated (5 mm, both sides) and fixed. The drip infusion of Nicardipine was discontinued. After 0.2 mcg/kg/min of Norepinephrine was given, the arterial blood pressure and heart rate recovered to 120-140/65-80 mmHg and 80-90 times/min, respectively. In order to determine the cause of hypotension, the patient's body fluid and hemodynamic status were checked and heart function was evaluated through removable transthoracic echocardiography, but no abnormal findings were observed. To find out the cause of pupil dilation and fixation, emergency brain computed tomography was performed and as a result, the findings of severe cerebral edema and bilateral cerebral infarction were identified (Fig. 2).

For brain edema treatment, 15% Mannitol (1g/kg) was injected intravenously. A consultation with the neurosurgery department about the patient's case determined that it would difficult to prevent the irreversible progression of brain edema, and impossible to treat. Eventually, the patient was pronounced as brain dead at 9 days after the surgery.

DISCUSSION

In this case, a patient with acute hepatic failure accompanied by hepatic encephalopathy showed mimetic convulsion symptoms such as involuntary muscle contraction and ocular deviation symptoms. Brain computed tomography of the patient taken the day before transplant surgery showed mild brain atrophy. Due to high blood ammonia level, the patient was diagnosed with a hepatic coma caused by hyperammonemia. The blood ammonia was reduced using continuous lactulose edema and continuous renal replacement therapy. A compatible brain-dead patient was found and the patient received a liver transplantation. After the transplantation, the patient's liver function and conditions recovered but he was still in semi-coma. One day after the surgery, it was confirmed that the patient's pupils were dilated and fixed so emergency brain computed tomography was performed and it showed severe brain edema and bilateral cerebral infarction. These findings were untreatable, lethal and irreversible neurological complications. The patient was pronounced as brain dead 9 days after the liver transplant surgery.

Hepatic encephalopathy is common in patients with liver failure, and the symptoms occur variously from minimal intellectual functioning impairment to coma. It is reversible and associated with severe complications that may affect the patient's prognosis. The mechanism of hepatic encephalopathy is not well understood, but there are three frequently discussed causes:[2] 1) endogenous neurotoxicity caused by not metabolizing the body's substances such as ammonia in the liver, 2) increased blood-brain barrier permeability observed in acute/chronic epileptic patients and 3) changes in neurotransmitters and receptors.

When the mean arterial blood pressure in a normal person is 50-150 mmHg, the cerebral blood flow is maintained normally through the autoregulatory function of the brain.[4] In patients with acute liver failure, the autoregulatory function of brain is lost and when the brain perfusion pressure increases lightly, it increases the cerebral blood flow through the blood-brain barrier. Conversely, when the arterial blood pressure is a little low, it easily causes ischemic stroke.[5] In particular, when brain edema occurs due to high ammonia level, cerebral blood flow and intracranial pressure are very closely related.[6]

In addition, amino-acid metabolic disorder characteristically presents in liver failure, which causes a change in the ratio of branched chain amino-acid and aromatic amino-acid in plasma. Particularly, there is a hypothesis that aromatic amino-acids, which are a precursor of neurotransmitters, are over-supplied so they compete with normal neurotransmitters at neurotransmitter receptors.

In this case, lactulose and continuous renal replacement therapy were applied as a treatment for hyperammonemia. Recent meta-analysis studies question the effect of lactulose, and L-Ornithine L-Aspartate (LOLA), L-Ornithine

Phenyl Acetate (LOPA), and Rifaximin are instead recommended in patients with liver failure and hyperammonemia.[7-11]

In patients with liver failure accompanied by hepatic encephalopathy, preoperative neurological evaluation may include: 1) neuropsychiatric evaluation, 2) electrophysiological examination of the brain (Electroencephalogram), 3) imaging and 4) clinical blood tests. Neuropsychiatry evaluation methods are Wechsler adults intelligence test, Line tracing test (LTT), and Number connection test (NCT). In electroencephalography, the delta wave and equipotential wave are observed in severe hepatic encephalopathy, but since these waves can't be related with the severity of encephalopathy and they are not pathology-specific in hepatic brain comma, there is a limit to the use of electroencephalography as a diagnostic tool. Imaging examination includes contrast-enhanced CT and positron emission computed tomography (PET-CT). The clinical blood test methods include basic liver function tests as well as blood glucose levels and electrolytes (including calcium, phosphorus and magnesium).

For patients on the liver transplant waiting list, brain computed tomography is performed for neurological evaluation and is useful for excluding potential causes of intracranial hypertension, but sensitivity to brain hemorrhage is not high.[12] In addition, after persistent intracranial hypertension, the results may not be detected by imaging until later. Brain magnetic resonance angiography or positron emission tomography (PET-CT) may be applied but this cannot be performed in high-risk patients group whose vital signs are unstable due to liver failure.

Patients with liver failure may present complications such as ascites, variceal hemorrhage, hepatic coma and gestational syndrome. These are the important factors that can cause post-operative neurological complications. In particular, pre-operative hepatic coma has very high correlation with post-operative neurological morbidity. According to a recent study of Ramesh K. et al., ALFED (Acute liver failure early dynamic) model is applied to patients with acute liver failure, and using the grade of hepatic encephalopathy and the blood ammonia level, prothrombine time (INR) and bilirubin level obtained by collecting the arterial blood, the score can be calculated.[13] In this patient, the pre-operative ALFED score ranged between 4 and 6, which belonged to the high-risk group. In this case, the post-operative mortality was 88.5% in the derivation cohort and 85% in the validation cohort.

Patients with hepatic comma and bilateral cerebral edema should maintain the neck in a central position and the head raised 20-30 degrees for venous return, and it is important to alleviate symptoms of anxiety. Through continuous electroephalography (EEG), the seizure situation including subclinical seizures should be recognized early. It was found that using phenytoin in patients with acute liver failure prophylactically is not helpful for cerebral edema or survival rate.[14] In the case of this patient, after performing the endotracheal

intubation in the intensive care unit before surgery, the patient's neck was maintained in the central position and his head was raised 20-30 degrees. However, it is regrettable that additional brain CT scan and EEG test were not performed.

Recently, many hospitals have started to apply a epidural intracranial pressure monitoring system at the frontal lobe in patients with hepatic encephalopathy grade III and IV.[15] To prevent complications including hemorrhage, strict correction of coagulation disorder in patients is required before surgery. When increased intracranial pressure is confirmed, drugs such as mannitol and barbituate may be administered to lower the intracranial pressure. At this time, the recommended dose of barbituate is 3-5 mg/kg (maximum 500 mg) first for 15 minutes intravenously, followed by 0.5-2.0 mg/kg/h drip infusion. Treatment with barbiturate should be carried out by monitoring the continuous intracranial pressure and arterial blood pressure. Despite these attempts, increased intracranial pressure is not well-controlled, hypothermia therapy may be considered.[16,17]

In this patient, if the severe brain comma condition had been recognized through electroencephalogram and the intracranial pressure increase had been identified through the intracranical pressure monitoring system at the intensive care unit before surgery, mannitol and barbituate could have been tried and if necessary, pre-operative hypothermia therapy might have been performed. However, since no tests for other neurological complications were performed except the brain computed tomography, the cerebral edema and intracranial pressure increase were not recognized earlier in this patient, leading him to be diagnosed simply with hepatic encephalopathy caused by hyperammonemia. Considering all this, it is regrettable that the administration of mannitol or barbituate and hypothermia therapy were not even tried. In addition, when he showed pre-operative seizure-like symptoms, it is possible that brain lesions had become more severe. However, consequently, since they showed cerebral infarction and cerebral edema findings, there may be other causes that need to be considered. At the liver transplant surgery during 45 minutes of anhepatic period, considering that the mean arterial blood pressure were maintained low as 50-60 mmHg and BIS values were maintained low between 0 and 10, it may suggest that the cerebral perfusion pressure was already not maintained properly, which may be a direct cause of the lethal results for this patient who might have already had an impaired blood-brain barrier. Afterward, at the refusion period, in the course of administering epinephrine IV to treat the low blood pressure, the already developed brain lesions progressed further because a luxury perfusion occurred.

With this case, we realized that in the future when a patient in the liver transplant waiting list is accompanied by hepatic encephalopathy, it is necessary to check the neurological condition through multiple evaluations, and to pay more attention to the hemodynamic stabilization in order to maintain the intraoperative cerebral

perfusion pressure. In addition, applying treatments such as LOLA, LOPA, and Rifaximin should be considered in advance of surgery in patients with liver failure who are accompanied by hyperammonemia.

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