Liver transplantation results in complete neurologic recovery from malignant hypertension secondary to fulminant hepatic failure: A case report

George Tsoulfas1‡, Nahel Elias1‡, Warren S. Sandberg2‡, Dicken S.C. Ko1‡, Tatsuo Kawai1‡, A. Benedict Cosimi1‡, Parmenion P. Tsitsopoulos3‡, Polyxeni Agorastou4‡, Martin Hertl1‡

1 Department of Surgery, Transplant Unit, MGH, Boston, MA, U.S.A.
2 Department of Anesthesia and Critical Care, MGH, Boston, MA, U.S.A.
3 Department of Neurosurgery, Aristotle University of Thessaloniki, Thessaloniki, Greece
4 Department of Medicine, Aristotle University of Thessaloniki, Thessaloniki, Greece

Summary

Background: Uncontrolled intracranial hypertension can lead to cerebral herniation and death in patients with acute liver failure.

Case Report: A 26-year-old female was admitted for acute liver failure following inadvertent acetaminophen overdose. The pH on admission was 6.9. Her neurologic status precipitously deteriorated and she was listed for liver transplantation. An intracranial pressure (ICP) monitoring catheter was inserted, which revealed a pressure >60 mmHg. After neurointensive care treatment, ICP was lowered and an emergency left lobe living donor liver transplant was performed. Intraoperative management of the ICP, which rose to 80mmHg during the explant phase, was achieved by therapy with barbiturates and hypothermia. After surgery, hepatic function improved initially, but 7 days post transplantation the graft showed signs of acute failure. The pathology report of a liver biopsy suggested acute rejection and liver retransplantation using a deceased donor liver was then carried out. The postoperative course was uneventful and the patient recovered completely without any residual neurologic deficits.

Conclusions: This case states that favourable outcomes can result from sub-optimal starting points, and that the human brain has the ability to overcome extremely adverse conditions. Critical in this effort is the role of proper neuromonitoring which helps implement the appropriate treatment measures.

Key words: liver transplantation • living donor liver transplantation • intracranial pressure • intracranial hypertension

Word count: 1827
Tables: –
Figures: 2
References: 25

Author’s address: Georgios Tsoulfas, 66 Tsimiski St., Thessaloniki, Greece, e-mail: tsoufasg@gmail.com
BACKGROUND

In fulminant hepatic failure, brain edema and intracranial hypertension are major causes of morbidity and mortality [1]. The etiology is not fully understood, although both vasogenic and cytotoxic factors have been implicated. In particular, accumulation of glutamine has been considered a cause of cerebral edema and hypertension in patients with fulminant hepatic failure [2]. Moreover, toxic substances released by the hepatocytes and Kupffer cells during the manipulation of the necrotic liver at hepatectomy, and additional products of ischemia/reperfusion injury released during reperfusion of the graft, have been also suggested as possible contributing factors [3]. The consequence is cerebral vasodilation, resulting in intracranial hypertension with increased risk of brain herniation and brain death.

Some groups include intracranial pressure (ICP) monitoring in the protocol of fulminant hepatic failure patient management, but available data on peri-transplant intracranial hypertension and its effects are inconclusive [4–6]. Furthermore, current evidence suggests that extreme elevations of ICP are associated with a dismal prognosis [7,8].

CASE REPORT

A 26-year-old female was admitted with acute liver failure secondary to acetaminophen overdose, while being treated for ankylosing spondylitis. At the time of admission the patient was encephalopathic stage II, disoriented to time and place. The encephalopathy started developing 1–2 days after the acetaminophen overdose. Her initial lab tests showed Acetaminophen values of 59mg/L (normal range: 10–25 mg/L), pH: 6.96, blood glucose level as low as 30 mg/dl, Prothrombin Time (PT) >50 secs, and Total bilirubin of 5.8 mg/dL with a direct of 2.8 mg/dL. The patient was transferred to the intensive care unit (ICU) and placed on the waiting list for emergency deceased donor liver transplantation. Her encephalopathy was particularly concerning given the fact that it is a poor prognostic factor [9].

The patient’s condition remained quite stable for several days; however, eight days after admission she rapidly deteriorated with worsening coagulopathy, while she also progressed to stage III encephalopathy. Her INR was >10 despite increasing fresh frozen plasma transfusions. It became obvious that she was in need of an urgent hepatectomy and liver transplantation. Head Computed Tomography (CT) scan revealed diffuse brain edema with obliteration of the sulci, compression of the basilar cisterns, and inferior displacement of the cerebellar tonsils (Figure 1).

Given the concern for intracranial hemorrhage due to the presence of coagulopathy, the patient was given recombinant factor VII along with fresh frozen plasma, which led to a decrease of the INR to 1.8 and the ability to place the ICP monitoring bolt system without bleeding. A right frontal ICP monitoring bolt system was placed in the subarachnoid space with the opening ICP values above 60mmHg (normal ICP 8–15mmHg and normal CPP >70mmHg). However, after the use of pentobarbital, mannitol and hypothermia to 33°C, the ICP was lowered to 20–25 mmHg.

The decision was made to proceed with liver transplantation from a living donor. The donor’s left lobe (weight 440 grams, 1% recipient’s body weight) was used. Intraoperatively, the patient was stable until the portal vein was clamped prior to the removal of the native liver. At that point the ICP rose to 80 mmHg for 5 minutes but the systemic blood pressure autoregulated to 180/110 mmHg (Figure 2). The patient was supported with volume and vasopressors (noradrenaline) and cerebral perfusion pressure (CPP) was maintained above 60 mmHg during the remaining surgery.

The pathology report of the explant revealed massive hepatic necrosis with severe cholestasis. Postoperatively, the patient developed diabetes insipidus, which resolved spontaneously. Liver allograft function initially improved but it deteriorated again after one week. Allograft biopsies showed portal and lobular inflammation consistent with early stages of acute cellular rejection. Clinically the patient had significantly elevated transaminases levels (in the 400 range), as well as an elevated bilirubin, despite an immunosuppression regimen consisting of Prednisone taper, Tacrolimus aiming at a level of 10 and Mycophenolate Mofetil. The tacrolimus was kept at that level to avoid worsening of the neurologic status, however given the possibility of rejection, the dose was increased to achieve a level of 13–15, and a steroid bolus was given as well. Despite aggressive treatment, the hepatic dysfunction continued to progress. The decision to relist the patient for retransplantation was made, and 10 days after the living donor transplant, she underwent a second orthotopic liver transplantation from a 72-year-old deceased donor.
The recovery period following the second transplant surgery was significant for continuous improvement of the liver function and gradual resolution of the cholestatic picture. During the early post transplant period, due to hypoxic brain damage, the patient developed severe neurologic deficits and she required prolonged intubation and neurointensive care treatment for several weeks. However, she gradually made a remarkable recovery by improving across the board in all cognitive domains. At the time of discharge from rehabilitation, one month after the last surgery, her neurologic status was normal with no deficits. At the last follow-up (48 months post transplant) no graft dysfunction was noted and her neurologic picture remained unchanged.

**DISCUSSION**

In patients with fulminant hepatic failure, the overall mortality rate is close to 80% [10]. A major contributing factor to this is cerebral edema and its consequences; that is significantly elevated ICP, a decrease in CPP and imminent brainstem herniation [11]. Intracranial hypertension can also develop during orthotopic liver transplantation. In the study of Bismuth et al., 13 of 116 patients with fulminant hepatic failure (11%) became brain dead and two patients had significant neurologic sequelae postoperatively [12]. Intracranial hypertension commonly occurs during dissection of the failing liver and graft reperfusion [5,13]. Keays et al demonstrated that ICP reaches its peak during the pre-clamp phase of the operation and the graft reperfusion period (median 54 mmHg, range 46–62) [5]. This was also evidenced in our case.

Controversy persists regarding the use of ICP monitoring in patients with advanced liver disease, mainly due to the associated coagulopathy. The American Association for the Study of Liver Diseases stated that ICP monitoring is potentially useful in the decision to exclude patients from emergency liver transplantation [14]. However, others have reported their ability to manage acute liver failure effectively without the use of ICP monitoring [15].

The main concern with the use of ICP monitoring is the risk of intracranial hemorrhage, which in patients with coagulation disorders may have catastrophic consequences [16,17]. The incidence of hemorrhage varies. In a multicenter nationwide study that included 262 patients with fulminant liver failure, an overall prevalence of intracranial bleeding of 20% was noted after the placement of ICP monitors [18]. They also suggested that epidural transducers, although less precise, may be the safest choice for ICP monitoring since the incidence of bleeding, including fatal hemorrhage, was much less when compared with the subdural bolts and the intraparenchymal catheter [18]. However, the production of epidural transducers has been discontinued in the decade since that...
the present report, reported a case of complete tracranial pressure [8]. Gottlieb et al., similarly to reverse the course of brain edema and lower incidence to support that liver transplantation can be considered for patients with fulminant hepatic failure, as malignant intracranial hypertension typically leads to brain death and is considered a contraindication for liver transplantation [7,8]. Nevertheless, their use has been frequently associated with obstacles [23]. Nevertheless, their use has been frequently associated with obstacles [23].

Regarding medical management of the elevated ICP, the standard treatment is hyperventilation, osmotic therapy with mannitol and/or hypertonic saline, as well as elevating the patient’s head and chest to a 30° angle from the horizontal level. In refractory cases, barbiturates are given (e.g., pentobarbital bolus of 3–5 mg/kg, followed by infusion at a rate of 1–3 mg/kg/hr). Significant improvements have also been seen with the use of moderate hypothermia by means of lowering the patient’s core temperature to 32–33°C [21]. Interestingly, in the study of Jalan et al., the use of moderate hypothermia increased CPP and improved cerebral flow [22]. In our patient, the use of hyperventilation and hypothermia had minimal effect on ICP; however, after pentobarbital administration a dramatic (about 50%) reduction in the ICP was encountered.

Generally, patients with persistent ICP >40 mmHg and CPP <50 mmHg are poor candidates for liver transplantation and have a poor prognosis, as malignant intracranial hypertension typically leads to brain death and is considered a contraindication for liver transplantation [7,8]. There have been efforts to use artificial liver support for patients with fulminant hepatic failure, however, their use has been frequently associated with obstacles [23]. Nevertheless, there is evidence to support that liver transplantation can reverse the course of brain edema and lower intracranial pressure [8]. Gottlieb et al., similarly to the present report, reported a case of complete neurological recovery following acute liver failure and extreme elevation of ICP [24].

This case is significant because it demonstrates that favorable outcomes can result even from suboptimal starting points, as shown by the complete recovery of a patient with a measured ICP of 80 mmHg. We believe that ICP monitoring in this situation was critical, as it helped maintain adequate cerebral perfusion pressure. Pre-existing coagulopathy was aggressively and successfully reversed and the decision was made to insert the ICP monitor, as it has been shown in several trials to be a useful guide in improving ICP and CPP [25]. ICP monitoring allowed us to estimate the status and severity of the neurologic insult, and address it in a way that would allow us to proceed with the first living donor transplant. Furthermore, the complete recovery of a patient with an ICP of 80 mmHg, even if only temporarily, indicates that continuous measurements of the ICP are critical in helping us understand the progression of the neurologic injury and its significance. Finally, it is another example of how these cases can be approached safely and treated successfully by a team of doctors from different specialties.

**Conclusions**

High ICP in patients requiring liver transplantation should not be seen solely as an exclusion criterion for liver transplantation. Extreme elevations of ICP should not discourage surgeons from proceeding to transplantation. The endpoint for any study on ICP monitoring, in addition to survival, should also be the clinical picture itself and the extent of neurological deficits on survivors. While recognizing that no definitive recommendations can be made based on case reports, a case like this demonstrates the need for controlled trials to properly evaluate the significance of ICP monitoring in guiding therapeutic interventions in this very challenging group of patients, as well as determine to what extent the outcome of liver transplantation is affected.

**Conflicts of interest**

There are no conflicts of interest from any of the authors.

**References:**