Living Donor Liver Transplantation for Acute Liver Failure With Fixed Pupils: Are We Fixed?

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Living donor liver transplantation (LDLT) is fraught with the social and ethical dilemma of excising a part of the liver from a healthy first-degree relative. When LDLT is to be done for an acute liver failure (ALF), identification of a suitable donor is a race against time. Herein, we describe a unique challenge faced by the transplant team of whether to proceed with donor hepatectomy from a son, when the recipient (HBV-related ALF) developed non-reactive fully dilated pupils on the table, prior to beginning the surgery. The patient ultimately underwent a LDLT despite fixed dilated pupils by virtue of further workup, which suggested that cerebral blood flow was maintained despite clinical evidence of brainstem herniation. (J CLIN EXP HEPATOL 2017;7:155–157)

Cerebral oedema and intracranial hypertension (ICH) are dreaded complications of acute liver failure (ALF) leading to brainstem herniation and death.¹ In progressive encephalopathy, the size and reaction of the pupil are monitored to assess neurological status. Fixed dilated pupil (FDP) is a clinical sign in diagnosing brain death. However, several cases have been reported in literature highlighting the unpredictability of FDP and brain death. Here, we report the first instance in the setting of living donor liver transplantation for ALF and accentuate the predicament of the transplant team.

CASE REPORT

A 36-year-old male presented with history of progressively increasing jaundice for 22 days and altered sensorium for two days. On examination, the patient was in hepatic encephalopathy grade 4 with bilateral equal mid dilated pupils reacting to light. A provisional diagnosis of HBV related ALF (IgM anti-HBc + HBV DNA: 7.3×10^2 IU/ml; IgM anti-HEV: negative and IgM anti-HAV: negative) was made. Other lab parameters were as follows: haemoglobin: 12.3 gm%; TLC: $12,600 \text{ mm}^{-3}$; platelets: $2.46 \text{ lacs mm}^{-3}$;

bilirubin: 36.2 mg%; AST: 468 IU/ml; ALT: 817 IU/ml; INR: 3.35; sodium: 135 meq/l; potassium: 3.07 meq/L; serum creatinine: 0.9 mg%.

The patient was managed according to institute protocol for ALF. Trachea was electively intubated in view of encephalopathy using thiopentone, fentanyl and atracurium and mechanical ventilation instituted targeting an endtidal CO₂ of 30–32 mmHg. Invasive haemodynamic monitoring helped guide fluid management. Haemodynamics were maintained on low dose noradrenaline and dopamine infusions. The patient was nursed in slight head up supine position with no physical stimulation. Core temperature was maintained at 34–35 °C. Arterial blood gases, blood sugar and electrolytes were monitored and managed. N-acetyl cysteine (NAC) and 3% NS were started as per protocol. Relatives were counselled to identify a donor for an emergency liver transplant.

Around 24 h post admission, left-sided pupil developed sluggish reaction to light which was managed with intravenous mannitol (0.5 g/kg). A CT head done at this time ruled out significant cerebral oedema and brain stem herniation (Figure 1).

30 h post admission, the patient was shifted to theatre for transplant. Isoflurane was added to the air-oxygen mixture to deepen the anaesthetic plane. Fentanyl and atracurium infusions were continued. Just prior to incision, pupils were checked and found to be fully dilated with no reaction to light.

This created a dilemma for the transplant team of whether to proceed with transplant as the patient had evidently developed a brainstem herniation. Abandoning surgery would take away the only chance of transplant that the patient had. Meanwhile, liver had been mobilised for hepatectomy in the donor. It seemed unwise to proceed

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Abbreviations: ALF: acute liver failure; ICH: intracranial hypertension; LDLT: living donor liver transplantation

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Figure 1 CT head showing mild effacement of sulci, with no midline shift; evidence of mild cerebral oedema.

Figure 2 CT head-angiography showing normal blood flow in the anterior and posterior circulation of the brain, with no reversal of flow.

with donor hepatectomy in the presence of FDP in the recipient.

In the anaesthetised patient, brain death assessment by clinical tests was not possible. It was necessary to do a confirmatory test, so the patient was shifted for a CT head angiography to confirm the status of cerebral blood flow. 32 h post admission, the contrast imaging revealed normal cerebral perfusion and we could proceed with the transplant (Figure 2). The 11 h long surgery was uneventful with minimal haemodynamic fluctuations. However, pupils remained fixed and dilated throughout and the patient was shifted to ICU on mechanical ventilation post procedure for further management as per protocol.

Immunosuppression, broad spectrum antibiotics, anti-fungal agents and N acetyl cysteine were continued post operatively. Inotropes were gradually tapered and stopped. Around 7 h post surgery, sluggish pupillary reaction to light was first observed.

Over the next few days, the patient showed gradual improvement. On POD₂, pupils were sluggishly reacting to light. Graft function was satisfactory as assessed by laboratory parameters. Nasogastric feeds were started and increased as per tolerance. Tenofovir was added to prevent HBV recurrence. Breathing efforts were observed in the next few hours.

The patient regained muscle power over the next week. On POD₃, eye opening to command was present. Ventilatory support was continued and trachea was finally extubated on POD₅. An episode of absence seizures occurred on POD₇ for which levetiracetam was started after neurology consult.

Further course was uneventful and the patient was shifted to ward on POD₁₁ and discharged from hospital on POD₂₉ with no neurological sequelae. Presently, the patient is on regular OPD follow-up and doing well.

DISCUSSION

Progressive cerebral oedema in ALF could lead to brainstem herniation,¹ limiting the survival of comatose patients awaiting liver transplantation before a suitable donor is identified.² A significant group of patients with ALF could be in grade III/IV encephalopathy and may have ICH necessitating constant monitoring of size and reaction of pupils. Sustained development of FDP is commonly considered a sign of brainstem herniation due to rise in ICP and irreversible brain damage in patients with ALF.³

Following the development of FDP, it seemed that our patient had forgone the opportunity of transplant and it seemed practical not to proceed with donor hepatectomy as ensuring the safety of the healthy ASA1 donor is a priority of the transplant team. LT for an ALF is a race against time. It was crucial to confirm the status of the brain before cancelling the only chance the patient had of having a transplant.

Assessment by bedside tests like TCD and ONSD were ruled out as we felt that being operator-dependant, in the present case, they could provide only supportive information. Hence, we decided to perform a CT head which ruled out brain stem herniation and a CT angiography which showed normal cerebral blood without any reversal and hence we proceeded with LDLT.

Several cases have been reported in literature highlighting the unpredictability of FDP and brain death.^{4,5} Pupils could dilate and become non-reactive following administration of high doses of sympathomimetics such as dopamine,⁶ noradrenaline or parasympatholytic drugs. FDPs

can be associated with other miscellaneous causes of anoxia like cardiac arrest, hypothermia, excessively deep anaesthesia, various poisonings like cyanide, methanol, propranolol as well as barbiturate overdose. Hypothermia induced in our patient was as per ALF protocol and depth of anaesthesia was monitored with Bi-Spectral Index monitoring. In non-ALF patients, induced hypothermia does not significantly impact pupillary signs.⁷ The patient had been on low doses of inotropes which usually do not lead to pupillary changes, in our experience.

Nondepolarizing neuromuscular blocking drugs (NMBD) normally do not cross the intact blood brain barrier (BBB).⁸ However, there have been reports of NMBDS to cross the disrupted or poorly developed blood brain barrier in the critically ill and in neonates leading to dilated non-reactive pupils.⁹ In ALF, although the BBB is largely structurally intact, increased pinocytotic activity, endothelial swelling, inflammatory and oxidative stress could lead to disruption of BBB.¹⁰

However, our patient was still receiving muscle relaxant postoperatively when some pupillary response was observed. We had attributed the gradual and sustained change in pupil size and reaction to progressively rising ICP. However, it could perhaps be explained by the vasopressor usage as it was restored after discontinuation of dopamine and noradrenaline infusions after surgery.

Our dilemma was solved by performing ancillary test of CT head angiography which confirmed the presence of normal cerebral blood flow,^{10,11} ruling out brain stem herniation.

In conclusion, this case highlights the dilemma created in a case with FDP since a major decision regarding donor hepatectomy and transplanting patients with ALF had to be taken. Although the reason for FDPs still remains an enigma in this case, CT angiography of the brain helped in resolving the issue in favour of going ahead with transplantation. Although we are not suggesting that ALF

patients with fixed dilated pupils can be routinely transplanted and we understand that this may be a unique case, we do recommend that in all such cases of suspected brain death where clinical tests of brain death cannot be performed, cerebral imaging and angiography may help in making the correct diagnosis.

CONFLICTS OF INTEREST

The authors have none to declare.

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