

Liver transplantation rapidly stops cerebral ammonia uptake in fulminant hepatic failure

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Fulminant hepatic failure (FHF) is a relatively uncommon but often fatal condition.¹ Common aetiological precipitants include paracetamol overdose (39%), other drug reactions (13%), or viral hepatitis (12%), with 17% of cases remaining unexplained.^{2,3} Most cases occur among young women, with a median age at presentation of 38 years.² Despite significant improvements in the provision of intensive and supportive care, many patients still die. Often, liver transplantation is the only option for treatment.

A life-threatening complication of FHF is the development of severe encephalopathy with cerebral oedema. This can lead to increased intracranial pressure (ICP) and cerebral herniation. The genesis of this cerebral oedema is imperfectly understood. Current evidence suggests roles for inflammatory mediators, radical oxygen species and loss of autoregulation of cerebral blood flow with resultant hyperaemia. Another important factor, considered pivotal to the development of brain oedema, is the significant increase in cerebral glutamine concentrations driven by elevated blood concentrations of ammonia.^{4,5}

Elevated ammonia levels have been shown to be an independent risk factor for the development of increased ICP,^{6,7} encephalopathy^{7,8} and possibly mortality.⁹ Levels greater than 200 $\mu\text{mol/L}$ have been shown to correlate with an increased risk of cerebral herniation.¹⁰ Ammonia is demonstrably taken up by the brain among patients with FHF,¹¹⁻¹⁵ with reports of significant transcerebral arteriovenous difference in ammonia concentration first published nearly 50 years ago.¹⁶

A recent study examined the transcerebral arteriovenous difference of ammonia before and after cooling in the context of FHF¹⁷ with measurements taken on three occasions — once before and twice after induction of therapeutic hypothermia. To our knowledge, there are no reports of how rapidly liver transplantation can restore transcerebral ammonia homeostasis. Here, we describe a case of FHF, with frequent simultaneous jugular bulb venous (JBV) and peripheral arterial blood monitoring of ammonia during hypothermia for severe encephalopathy and coma before and after liver transplantation.

Clinical record

A 33-year-old woman with no significant personal or family medical history presented to another hospital with FHF. She

ABSTRACT

This report describes the effect of liver transplantation on transcerebral ammonia uptake in a case of fulminant hepatic failure. A young woman with fulminant hepatic failure and coma received monitoring of transcerebral ammonia uptake before and after orthotopic liver transplantation. Before liver transplantation, median transcerebral ammonia uptake was 8 $\mu\text{mol/L}$. After liver transplantation, ammonia uptake decreased to 0 $\mu\text{mol/L}$. Fulminant hepatic failure is associated with transcerebral ammonia uptake, which is fully and rapidly corrected by liver transplantation.

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described 3 weeks of increasing nausea, vomiting and jaundice, with 3 days of abdominal pain and distension and mild confusion. She had no history of mushroom or herbal medicine ingestion or of paracetamol use or overdose. She was not pregnant and had no identifiable illness contacts. There was no recent history of foreign travel. She had no features of chronic liver disease on history or examination. There was no evidence suggestive of haemochromatosis, Wilson disease or autoimmune disorders.

On investigation, the patient was found to have a serum bilirubin level of 210 $\mu\text{mol/L}$ (reference range [RR], < 18 $\mu\text{mol/L}$), an alanine aminotransferase concentration of 1378 U/L (RR, < 34 U/L), a γ -glutamyl transpeptidase level of 89 U/L (RR, < 38 U/L), an alkaline phosphatase level of 107 U/L (RR, 32–91 U/L) and an international normalised ratio of 2.3. She was hyperammonaemic, with a blood ammonia level of 116 $\mu\text{mol/L}$ (RR, 11–35 $\mu\text{mol/L}$). All investigations for identifiable causes of FHF were negative. An abdominal Doppler ultrasound showed no evidence of hepatic venous, arterial or ductal obstruction.

Four days after admission, she was transferred to the tertiary intensive care unit of the regional liver transplantation centre with worsening hepatic encephalopathy and coagulopathy. She required endotracheal intubation and mechanical ventilation, ongoing blood product support, and renal replacement therapy for anuric renal failure. Owing to her severe encephalopathy and progressive

Table 1. Simultaneous arterial and venous measurements of cerebral metabolism before and after liver transplantation

Day	Time (h)	TpT (h)	Ammonia (µmol/L)		pH		Bicarbonate (mmol/L)		Base excess		Glucose (mmol/L)		Lactate (mmol/L)		SpO ₂ (%)		PaCO ₂ (mmHg)		
			Arterial	Venous	Arterial	Venous	Arterial	Venous	Arterial	Venous	Arterial	Venous	Arterial	Venous	Arterial	Venous	Arterial	Venous	Arterial
Before transplantation																			
1	0	-77	61	53	7.45	7.38	27	29	2.8	4.3	6.5	5.8	1.6	1.4	99	63	40	51	
1	4	-73	111	75	7.39	7.35	25	28	0.5	2.3	5.3	4.9	2.7	2.3	97	70	43	52	
2	15	-62	99	93	7.35	7.33	26	29	0.2	0.9	5.5	5.1	2.9	2.4	98	73	49	52	
2	27	-50	66	57	7.27	7.24	14	16	-13.0	-11.0	9.6	9.3	12.3	11.2	97	64	31	39	
3	39	-38	46	41	7.48	7.42	23	26	-0.4	1.2	4.8	4.4	3.5	3.2	99	52	32	40	
3	45	-32	76	53	7.52	7.52	25	28	1.8	4.3	4.5	4.5	3.7	3.22	98	51	30	39	
3	51	-26	66	66	7.51	7.44	26	28	2.6	3.5	6.7	6.5	3.8	3.6	99	38	32	42	
3	56	-21	55	56	7.49	7.44	24	28	0.9	3.4	5.7	5.5	3.9	3.3	99	46	32	42	
4	62	-15	55	47	7.50	7.45	25	27	1.7	3.1	6.4	5.9	3.2	2.8	98	44	32	40	
After transplantation																			
5	84	6	44	58	7.45	7.41	24	27	0.5	2.3	7.7	7.2	2.6	1.9	97	51	33	43	
5	90	12	42	42	7.42	7.36	26	29	1.4	3.8	6.6	6.4	1.7	1.4	96	56	41	52	
5	96	18	48	42	7.47	7.4	26	29	2.9	4.3	6.6	6.3	2.1	1.78	96	50	36	47	
5	101	23	48	53	7.46	7.39	25	28	1.1	2.7	7.2	6.8	2.8	2.0	98	49	35	46	
6	107	29	34	36	7.43	7.37	25	28	1.0	2.0	6.9	6	2.4	1.6	95	42	39	50	
6	119	41	34	33	7.44	7.40	26	28	1.4	3.6	7.6	7.6	1.8	1.5	97	53	38	48	
6	125	47	38	37	7.44	7.38	25	28	1.2	3.1	9.1	8.8	2.0	1.6	97	48	38	49	
7	131	53	34	38	7.43	7.38	26	28	1.5	3.0	7.3	7.3	1.8	1.5	97	49	39	48	
7	137	59	58	50	7.45	7.39	26	27	1.5	2.2	9.7	9.2	1.8	1.6	97	45	38	46	
7	143	65	43	49	7.48	7.42	27	29	3.2	4.2	6.9	6.6	1.3	1.3	92	45	36	45	
7	149	71	47	40	7.45	7.39	24	26	0.1	1.4	10.0	9.7	1.7	1.6	96	50	36	44	
8	155	77	42	40	7.46	7.43	22	25	-1.4	0.3	8.8	8.6	2.2	1.2	98	60	32	38	
8	161	83	25	29	7.44	7.37	24	25	1.0	2.0	9.3	9.0	2.6	1.4	96	47	39	47	

TpT = time before or after (pre- or post-) transplantation.

Table 2. Arterial and jugular bulb venous (JBV) sampling before transplantation

Transcerebral uptake calculated from arterial and JBV differences	Median decrease (range)	<i>P</i>
Ammonia (μmol/L)	8 (–1 to 36)	0.017
pH	0.05 (0.00–0.07)	0.012
Bicarbonate (mmol/L)	–3 (–2 to –4)	0.008
Base excess	–1.6 (–0.7 to –2.5)	0.008
Glucose (mmol/L)	0.4 (0.0–0.7)	0.008
Lactate (mmol/L)	0.4 (0.2–1.1)	0.008
Oxygen saturation (%)	47 (25–61)	0.008
PaCO ₂ (mmHg)	–9 (–3 to –11)	0.008

Table 3. Arterial and jugular bulb venous (JBV) sampling after transplantation

Transcerebral uptake calculated from arterial and JBV differences	Median decrease (range)	<i>P</i>
Ammonia (μmol/L)	0 (–14 to 6)	0.81
pH	–0.06 (0.03 to 0.07)	0.013
Bicarbonate (mmol/L)	–3 (–1 to –3)	0.008
Base excess	–1.5 (–0.7 to –2.4)	0.002
Glucose (mmol/L)	0.3 (0.0–0.9)	0.003
Lactate (mmol/L)	0.3 (0.0–2.4)	0.002
Oxygen saturation (%)	47 (38–53)	0.008
PaCO ₂ (mmHg)	–10 (–6 to –11)	0.001

Table 4. Difference in transcerebral uptake before and after transplantation

	Transcerebral uptake	<i>P</i> (exact)
Ammonia (μmol/L)	8	0.009
pH	–0.01	0.209
Bicarbonate (mmol/L)	0	0.471
Base excess	–0.1	0.556
Glucose (mmol/L)	0.1	0.695
Lactate (mmol/L)	0.1	0.845
Oxygen saturation (%)	0	0.647
PaCO ₂ (mmHg)	1	0.292

multiple organ failure, she was placed on the waiting list for urgent liver transplantation.

Supportive management followed the local FHF protocol — mechanical ventilation, targeted to a PaCO₂ of 30–35 mmHg; induced hypernatraemia (150–155 mmol/L) with an infusion of 20% sodium chloride; induced moderate hypothermia at 34–35°C; 10% dextrose infusion administered to maintain normoglycaemia; vasopressor support to maintain a mean arterial pressure of 65–70 mmHg; and sedation with intravenous propofol. A retrograde JBV catheter was inserted to enable JBV monitoring of oxygen saturation and transcerebral ammonia, lactate and glucose uptake. Nasogastric norethisterone (5 mg three times/day) to prevent menstrual bleeding and prophylactic antimicrobial therapy were administered (meropenem and vancomycin from the time of intubation and liposomal amphotericin after Day 5). Renal replacement therapy was provided by continuous venovenous haemodiafiltration with 3 L/h

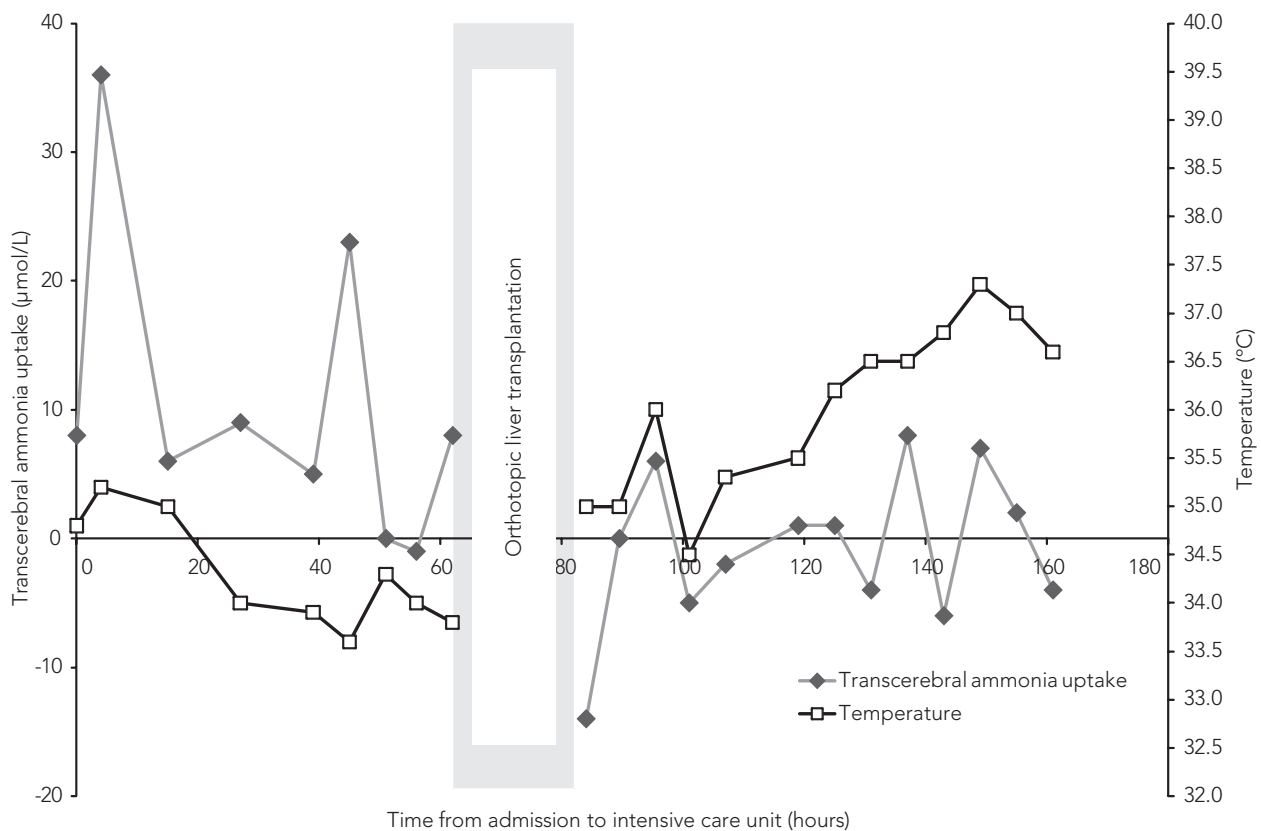
exchanges. Gastric ulcer prophylaxis and other routine intensive care measures were also provided. She remained comatose while supported by such treatment for 8 days, after which she received orthotopic liver transplantation (OLTx). Histology of her native liver at the time of OLTx showed complete necrosis with no viable liver cells. She was discharged to the general ward on Day 26 and home on Day 37 with intact cerebral function.

Measurements

Simultaneous blood samples were taken from the radial arterial catheter and from the retrograde JBV catheter. They were taken at regular intervals after insertion of the JBV catheter. These samples were tested for ammonia, oxygen, carbon dioxide, bicarbonate, base excess, lactate and glucose levels, and pH. Blood gas samples, and lactate and glucose levels were analysed by using an ABL800 Flex analyser (Radiometer Medical ApS, Brønshøj, Denmark). Ammonia concentrations were measured using the timed end-point method (DxC analyser, Beckman Coulter, Brea, Calif, USA). Measurements continued until the fourth post-operative day, when the patient’s consciousness level began to improve and the JBV catheter was removed.

The results of the simultaneous sampling are presented in Table 1. They show ammonia uptake before transplantation period, with a median decrease in ammonia concentration of 8 μmol/L from arterial to JBV concentration. This change was associated with evidence of continued lactate and glucose uptake with a median transcerebral decrease in lactate concentration of 0.4 mmol/L and a median decrease in glucose concentration of 0.4 mmol/L. To estimate the transcerebral metabolism of the analysed substances, the peripheral arterial and JBV concentrations of ammonia, pH, oxygen, carbon dioxide, bicarbonate, base excess, lactate, and glucose were compared at each time point using the Wilcoxon signed-rank test, before and after transplantation

Figure 1. Transcerebral ammonia uptake and temperature over the peritransplantation period



Graphic representation of changes in temperature and transcerebral ammonia uptake according to body temperature (right-hand scale) before and after liver transplantation. There is a clear change with liver transplantation despite a return to normal body temperature.

(Table 2 and Table 3, respectively). To determine if there was a significant difference between cerebral uptakes after transplantation, the transcerebral arteriovenous differences for each substance were compared before and after transplantation using the Mann–Whitney rank-sum test (Table 4). Statistical analyses were performed using SPSS, version 17 (IBM Corporation, New York, NY, USA).

The changes in transcerebral ammonia metabolism over time are presented in Figure 1. They show a clear and rapid change in ammonia uptake with transplantation such that cerebral ammonia uptake decreased to zero after transplantation, while all other facets of lactate, glucose and oxygen uptake remained the same.

Discussion

To our knowledge, this is the first report of the effects of OLTx on transcerebral ammonia uptake in a patient with FHF treated with therapeutic cooling. We monitored ammonia levels, blood gases, and lactate and glucose levels in arterial and JBV blood in a young woman with

FHF before and immediately after OLTx. We found a significant difference between peripheral arterial and JBV concentrations of ammonia during modest therapeutic cooling, which disappeared within 6 hours of return from theatre after OLTx. In contrast, none of the other observed variables representing cerebral metabolism showed a significant change in uptake or release after transplantation, with continued oxygen, glucose and lactate uptake and carbon dioxide release with an associated increase in bicarbonate and base excess.

Ammonia is produced by the gut, through the digestion of protein and the action of bacterial metabolism¹⁸ and is synthesised in the proximal tubule of the kidney.¹⁹ During intensive exercise or seizures, skeletal muscle can also produce ammonia.¹⁸ Evidence suggests it has a crucial role in renal acid handling and in gastrointestinal bleeding.²⁰ Ammonia produced by the gut enters the liver, where it is metabolised to urea. The urea cycle within the liver is extremely efficient at this process, and usually there is no correlation between venous and arterial ammonia in the systemic circulation.^{10,21} In some situations, however, the

metabolic capacity of the liver will be exceeded, or the liver may be unable to metabolise ammonia, as occurs in some inborn errors of metabolism. Ammonia elimination becomes dependent on the kidney, which reduces production and increases urinary excretion,²⁰ and to a lesser extent skeletal muscle and the brain. The latter organs metabolise ammonia, producing glutamine.^{21–23} When the liver and kidneys fail, hyperammonaemia occurs and the increased ammonia is taken up by the brain, where it contributes to cerebral oedema.¹⁷

The relationship between ammonia, glutamine, cerebral oedema and FHF has been the subject of much debate. Elevated cerebral glutamine levels among FHF patients were first noticed in necropsy specimens,²⁴ but have been confirmed in vivo with functional magnetic resonance imaging techniques,^{25,26} and are localised to astrocytes.^{18,22,23,27} Astrocytes compose about one-third of cerebral volume and ubiquitously interact with all of the other structures of the brain, providing important signalling and regulatory roles.²⁸ Astrocytes become swollen and distorted in FHF with the elevated intra-astrocytic concentrations of glutamine (increasing from 5 to 18 mmol/kg of cerebrum²⁹), increasing intracellular osmolarity and causing net intracellular water influx.^{22,28}

Hyperammonaemia has been demonstrated to be the causative mechanism responsible for glutamine accumulation as first suggested in rat models,³⁰ then in wider experimental settings.^{18,22,23,27} Evidence for the cerebral uptake of ammonia in FHF was first published in 1963, with a study showing a significant difference between femoral arterial and jugular venous ammonia concentrations.¹⁶ Ammonia is converted by the astrocyte directly to glutamine, causing cell swelling, inflammatory mediator release, oxidative and nitrosative stress and consequent apoptosis.^{23,27} Rising ammonia concentrations effectively paralyse aerobic respiration leading to elevated astrocytic and cerebral lactate levels.^{18,31} Local neurones convert glutamine into glutamate to be released at the synapse, where it activates *N*-methyl-D-aspartic acid receptors. It is normally taken up by astrocytes and recycled into glutamine, but elevated astrocytic glutamine concentrations lead to down-regulation of astrocyte glutamate receptors and an increase in local glutamate concentrations, and may explain the aetiology of seizures in FHF.^{22,23,27}

The syndrome of hyperammonaemic encephalopathy with the attendant risk of cerebral oedema and increased ICP in FHF shares many characteristics with syndromes of hyperammonaemic encephalopathy, which occur as a consequence of inborn errors of metabolism affecting the enzymes of the urea cycle.²⁸ In both cases, elevated ICP and

brain stem compression can occur. This does not occur in chronic states of hepatic encephalopathy, despite chronically elevated levels of blood ammonia.²⁸ Explanations for this include increased extracerebral ammonia metabolism,^{10,21} activation of additional mechanisms of osmoregulation and down-regulation of *N*-methyl-D-aspartic acid receptors.^{22,31}

An elegant in-vivo cerebral microdialysis experiment demonstrated that, in patients with FHF, there is a significant correlation between arterial ammonia levels and cerebral glutamine content.⁶ Following on from this, investigators have also demonstrated significant correlations between ICP and glutamine concentration, offering convincing clinical evidence of the central role that ammonia plays in the pathogenesis of cerebral oedema and elevated ICP via glutamate, with consequent morbidity and mortality. The association between ammonia and outcome is well established,^{7,10} and arterial ammonia concentration has been shown to be a reasonable predictor of outcome.⁹ Experiments using positron emission tomography have shown that the blood–brain barrier is more permeable to ammonia among patients with cirrhosis, and that cerebral metabolism of ammonia is increased, suggesting that other mediators play a role in priming the brain for hyperammonaemia.^{32,33}

A small Italian study demonstrated the potent effects of OLTx in the rapid return of disordered cerebral autoregulation and correction of cerebral oxygen metabolism.³⁴ Two studies by the same group examined changes in cerebral ammonia uptake with cooling of the FHF patient¹² and cooling of the liver transplant patient.¹⁷ They conclude, through analysis of paired arterial and JBV samples, that ammonia uptake is significantly decreased by cooling.

Our study is the first to show how quickly OLTx can correct the problem of cerebral ammonia uptake. In our case, correction appears to have occurred within 24 hours, with transcerebral ammonia uptake at that time being reduced from a median of 8 to 0 $\mu\text{mol/L}$. These observations suggest that it may be safe to begin slow rewarming towards normothermia within 24 hours of successful OLTx.

Conclusions

This case report confirms that, even with moderate hypothermia (34–35°C) and its attendant degree of ammoniaemic control, there can be persistent ammonia uptake in patients with FHF. Such persistent ammonia uptake likely contributes to cerebral oedema, suggesting the need for deeper hypothermia. Transcerebral ammonia uptake, however, can be rapidly reversed within 24 hours of OLTx suggesting that, after such period of postoperative recovery, slow rewarming may be safe.

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