Case Report

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A glimpse into multimodal neuromonitoring in acute liver failure: a case report

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Introduction: Acute liver failure (ALF) is a rapidly progressing, life-threatening syndrome characterized by liver-related coagulopathy and hepatic encephalopathy (HE). Given that higher HE grades correlate with poorer outcomes, clinical management of ALF necessitates close neurological monitoring. The primary objective of this case report is to highlight the diagnostic value of utilizing multimodal neuromonitoring (MNM) in a patient suffering from ALF.

Case report: A 56-year-old male patient with a history of chronic alcoholism, without prior chronic liver disease, and recent acetaminophen use was admitted to the hospital due to fatigue and presenting with a mild flapping tremor. The primary hypothesis was an acute hepatic injury caused by acetaminophen intoxication. In the following hours, the patient's condition deteriorated, accompanied by neurological decline and rising ammonia levels. The patient's neurological status was closely monitored using MNM. Bilaterally altered pupillary light reflex assessed by decreasing in the Neurological Pupil Index values, using automated pupillometry, initially suggested severe brain oedema. However, ultrasound measurements of the optic nerve sheath diameter showed normal values in both eyes, P2/P1 noninvasive intracranial pressure waveform assessment was within normal ranges and the cerebral computed tomography-scan revealed no signs of cerebral swelling. Increased middle cerebral artery velocities measured by Transcranial Doppler and the initiation of electroencephalography monitoring yielded the presence of status epilepticus.

Discussion: The utilization of MNM facilitated a more comprehensive understanding of the mechanisms underlying the patient's clinical deterioration in the setting of HE. Nonetheless, future studies are needed to show feasibility and to yield valuable insights that can enhance the outcomes for patients with HE using such an approach. Given the absence of specific guidelines in this particular context, it is advisable for physicians to give further consideration to the incorporation of MNM in the management of unconscious patients with ALF.

Keywords: acute liver failure, cerebral ultrasound, EEG, pupillometry

Introduction

Acute liver failure (ALF) is a rare, distinct, and progressively life-threatening syndrome characterized by the development of liver-related coagulopathy and altered consciousness attributed to hepatic encephalopathy (HE), in the absence of pre-existing liver disease[1]. In developed nations, the reported incidence of this condition is estimated to fall within the range of 1–6 cases per million individuals. Particularly within Europe, data derived from population-based studies revealed an annual incidence rate spanning from 0.62 to 1.13 cases per 100 000 people[2–6]. Notably, drug-induced liver injury stands as the predominant aetiology of ALF, whereas viral infections are prevalent in developing countries[1,4].

HE is a critical manifestation of ALF and can be assessed using the West Haven criteria, a bedside assessment tool that quantifies neurological dysfunction[7]. Higher HE grades correlate

HIGHLIGHTS

- Clinical management of acute liver failure necessitates close neurological monitoring.
- In patients with acute liver failure abnormal pupillary function can be present but bilateral non-reflecting mydriasis may be due raised intracranial pressure or increased ammonia levels.
- The patient's neurological status can be closely monitored using multimodal neuromonitoring for a more comprehensive understanding of the mechanisms underlying the patient's clinical deterioration in the setting of hepatic encephalopathy.
- A gradual loss of pupillary light reflex could be caused by ammonia-stimulated sympathetic ganglia, causing dilation, neuromuscular blocking agent accumulation in hepatic failure, paralyzing the iris sphincter, or high vasopressor doses.

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with worse outcomes and serve as indicators for liver transplantation[8]; acetaminophen intoxication is one of the most common causes leading to the development of cerebral oedema and HE in patients with ALF[4,5]. Among the life-threatening manifestations, cerebral oedema stands out due to its high mortality risk[9]. The clinical management of ALF demands meticulous neurological assessment, and in cases of coma, the implementation of neuromonitoring, either noninvasive or invasive, becomes imperative. The integration of these monitoring tools holds the potential to provide a more precise understanding of clinical deterioration in ALF patients. Nevertheless, there is limited data regarding the role of multimodal neuromonitoring (MNM) within this context.

The primary objective of this case report is to provide a detailed account of the use of MNM in a patient suffering from ALF and multiple organ failure (MOF), with a specific focus on its diagnostic utility.

Case report

A 56-year-old male patient was admitted to the hospital with fatigue, a history of bipolar disorder, and recent acetaminophen use (four grams per day for 2 weeks related to rib pain) at the upper limit of the maximum recommended dosage[10]. Upon admission, the patient exhibited mild encephalopathy and a mild flapping tremor, with no other discernible symptoms. Initial laboratory investigations disclosed findings consistent with acute renal injury, including elevated serum creatinine (296 µmol/l) and urea levels (68 mg/dl), as well as acute hepatitis, as indicated by significantly elevated levels of aspartate aminotransferase (AST) at 16427 IU/l, alanine transaminase (ALT) at 6200 IU/l, and a prolonged international normalized ratio (INR) of 3.07. The primary working diagnosis was acute hepatic injury secondary to acetaminophen intoxication, which was consistent with recent medical history, and with unremarkable results in viral serological tests and autoimmune panels. Upon admission to the intensive care unit, the patient received intravenous N-acetyl-cysteine at a dose of 100 mg/kg per day. Persistent Grade I HE and normal pupillary function were assessed using the Neurologic Pupil Index (NPi) via the NPi-200 device (Neuroptics) were documented. On the second day of hospitalization, the patient developed diffuse gastric bleeding, necessitating endoscopic therapy with Hemospray. Subsequently, a neurological deterioration to Grade IV HE occurred, accompanied by a significant increase in ammonium levels (from 132 mcg/dl to 1574 mcg/dl within 48 h). This deterioration prompted endotracheal intubation and the initiation of norepinephrine infusion at a rate of 0.3 mcg/kg per minute. In light of these developments, a decision was made to prioritize the patient for urgent liver transplantation (LT). Notably, NPi values decreased compared to the previous day but remained within the normal range for both eyes (Table 1). Transcranial Doppler (TCD) examination revealed bilaterally elevated middle cerebral artery (MCA) velocities with a normal pulsatility index. In response to the patient's severe metabolic acidosis and hyperlactatemia, continuous veno-venous hemofiltration and plasmapheresis were initiated. The timeline of these events is represented in Fig. 1.

At 18 h after the first plasmapheresis session, ammonia levels continued to rise (1785 mcg/dl), and the patient developed vasoplegic shock that proved refractory to high doses of vasopressors (norepinephrine > 1.5 mcg/Kg*min) and acute bilateral chest infiltrates, resulting in severe respiratory failure (PaO_2/FiO_2 <100), despite protective lung ventilation. A decision was made to proceed with a second plasmapheresis session in addition to administering ceftriaxone, ampicillin, and amikacin. Sedatives were increased, and neuromuscular blocking agents were initiated (i.e. rocuronium 0.5 mg/kg*h), along with the administration of intravenous vasopressin (0.03 IU/min). Ultrasound assessment revealed no signs of vascular hepatic thrombosis or cardiac abnormalities.

Table 1
Main measured variables over time

	Day 0	Day 1	Day 2	Day 3
PI		1.1 (R); 1.1 (L)	1.1 (R); 1.0 (L)	1.1 (R); 1.1 (L)
FVm		75 (R); 78 (L)	118 (R); 122 (L)	120 (R); 129 (L)
eICP, mmHg				16
ONSD, mm				5.2 (R); 5.3 (L)
NPi	4.4 (R); 4.6 (L)	4.8 (R); 4.5 (L)	1.9 (R); 1.6 (L)	0.6 (R); 0.7 (L)
B4C				P2/P1 <1
EEG			SE	BS to suppressed
Ammonium, mcg/dl	132		1574	1785

B4C, Brain4Care; EEG, electroencephalography; eICP, estimated intracranial pressure; FVm, mean flow velocities (measured on the middle cerebral artery); L, left; NPi, neurological pupil index; ONSD, optic nerve sheath ultrasound; PI, Pulsatility Index; R, right; SE, status epilepticus.

NPi progressively deteriorated, eventually evolving into bilateral non-reactive mydriasis. Suspecting intracranial hypertension, intravenous mannitol (1 g/kg) was administered, mean arterial pressure increased to 90 mmHg, and mild hyperventilation induced, reducing $PaCO_2$ from 38 to 33 mmHg. TCD consistently showed elevated MCA velocities; noninvasive intracranial pressure (ICP) assessment via cerebral ultrasound indicated an ICP value of 16 mmHg, and optic nerve sheath diameter (ONSD) measurements remained within normal ranges. Using B4C (Brain4care Corp), a noninvasive device to assess intracranial compliance, a P2/P1 ratio below 1 was observed. Cerebral CT-scan results showed no signs of brain oedema (Fig. 2). Continuous EEG monitoring was initiated, revealing generalized periodic discharges progressing toward myoclonic status epilepticus. Intravenous leviracetam and high-dose midazolam (0.5 mg/Kg*h) were administered. Despite all therapeutic efforts, the patient remained in a refractory shock state. The EEG tracing progressively transitioned into a burst-suppression pattern and rapidly shifted to an iso-electric tracing after a few hours, accompanied by bradycardia, ultimately leading to cardiac arrest.

Discussion

In this case report, we wanted to emphasize the potential role of multimodal neuromonitoring (MNM) in assessing the severity and elucidating the underlying mechanisms of neurological deterioration in a patient with ALF. Initially, pupillary abnormalities led to the suspicion of severe cerebral oedema; however, they were found to be a consequence of significantly elevated ammonium levels. None of the other monitoring tools indicated substantial alterations in cerebral hemodynamics, ICP, or cerebral compliance. Ultimately, electroencephalogram (EEG) monitoring identified status epilepticus, which remained unresponsive to pharmacological interventions.

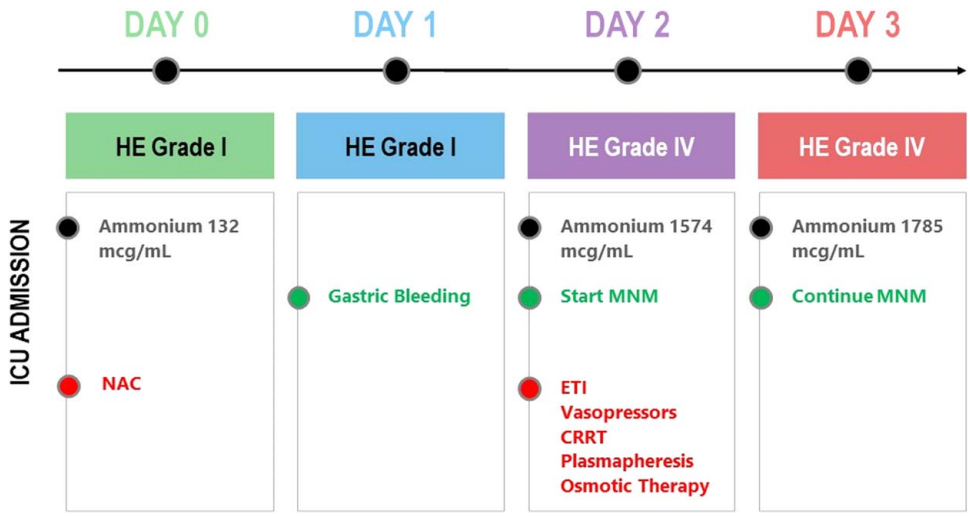

Figure 1. Main events during hospitalization. HE, hepatic encephalopaty; NAC, N-acetyl-cysteine; ETI, endotracheal intubation; CRRT, continuous renal replacement therapy; MNM, multimodal neuromonitoring.

The pathophysiology of HE in ALF is intricate, involving multiple pathways and factors contributing to its onset and progression[11]. Ammonium, a by-product of protein metabolism, has long been considered the primary neurotoxin in the pathogenesis of HE. In healthy individuals, the liver detoxifies ammonium by converting it to urea, which is then excreted by the kidneys. However, in ALF patients, compromised liver function leads to ammonium accumulation in the bloodstream and subsequent entry into the central nervous system (CNS)[12]. Elevated ammonium levels lead to alkalinization of the intracellular pH and disrupt the blood-brain barrier, enabling the entry of other toxins and inflammatory mediators into the CNS. Additionally,

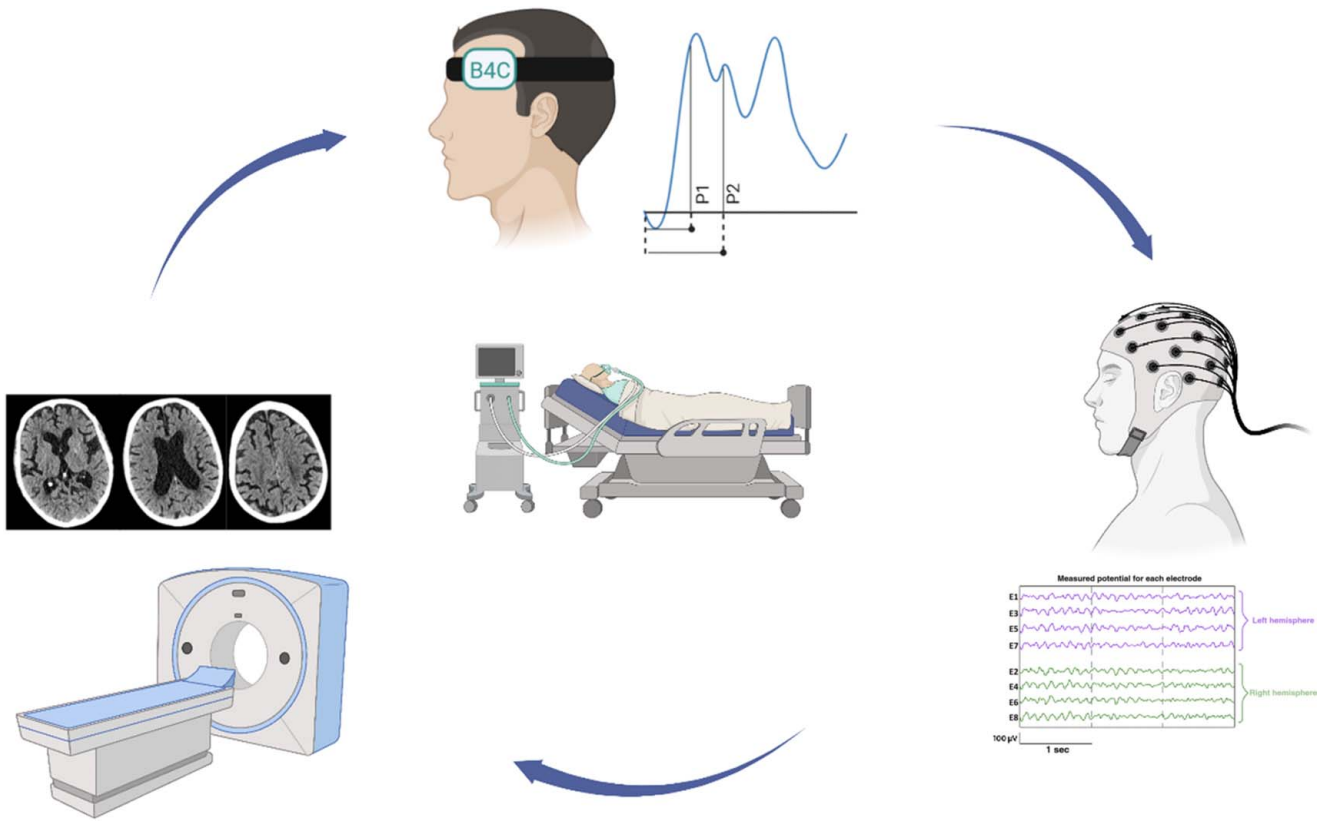

Figure 2. Cerebral computed tomography-scan showing no signs of brain oedema. Electroencephalography tracing of status epilepticus. Normal P2/P1 ratio on noninvasive intracranial pressure waveform analysis. Figure created by BioRender.

Table 2

Potential role of multimodal neuromonitoring to detect cerebral abnormalities in patients with hepatic encephalopathy

	TCD	NIRS	AP	EEG	B4C	ONSD
Brain oedema	PI > 1.4 Vd < 20 cm/sec eICP > 20 mmHg	rSO_2 < 60%	NPi <3	Slowered and/or attenuated Background	P2/P1 > 1.0	> 5.5/6.0 mm
Seizures	Increased FVm	rSO_2 normal or <60%	NPi > 3	Seizures	P2/P1 < 1.0	< 5.5 mm
Focal injury	As for brain oedema but unilateral	δrSO_2 > 10%	δNPi > 0.7	Asymmetric power and/or background	P2/P1 > 1.0	Asymmetric ONSD

AP, automated pupillometry; B4C, Brain4Care; EEG, electroencephalography; eICP, estimated intracranial pressure; FVm, mean flow velocities (measured on the middle cerebral artery); NIRS, near-infrared spectroscopy; NPi, neurological pupil index; ONSD, optic nerve sheath ultrasound; P1, percussion wave; P2, tidal wave; PI, pulsatility index; rSO_2, regional cerebral saturation; TCD, transcranial doppler; Vd, diastolic flow velocity; δNPi, difference in NPi values between both eyes; δrSO_2, difference in rSO_2 values between both hemispheres.

ammonium contributes to astrocyte swelling, potentially leading to cerebral oedema and increased ICP[11,13]. Moreover, glutamine, one of the product of ammonium metabolism, can be transported into mitochondria, followed by its hydrolysis, resulting in elevated intracellular ammonium levels, ultimately leading to mitochondrial injury[14,15]. In addition to ammonium, cytokines and chemokines play a main role in the development of HE. These mediators are released in response to liver injury and contribute to systemic inflammation, further exacerbating neuroinflammation and cerebral oedema[11]. Oxidative stress is another factor in the pathogenesis of HE. Excessive production of reactive oxygen and nitrogen species during ALF leads to cellular damage and dysfunction within the CNS[16]. Furthermore, imbalances in inhibitory and excitatory neurotransmitters, such as gamma-aminobutyric acid (GABA) and glutamate, have been observed in HE patients. Elevated GABA levels can result in neuronal inhibition and cognitive impairment, while increased glutamate levels can lead to excitotoxicity, hyper-excitability, and neuronal damage[9,17].

In patients with ALF and elevated ammonia levels, abnormal pupillary function is frequently observed. Bilateral non-reactive mydriasis may be indicative of increased ICP[12]. Our case demonstrated a gradual loss of pupillary light reflex, possibly attributed to: (1) ammonia-stimulated sympathetic ganglia[18] causing dilation, (2) accumulation of neuromuscular blocking agents (NMBAs) in hepatic failure[19–21] which paralyze the iris sphincter, or (3) high vasopressor doses[22]. Automated pupillometry can reveal altered pupillary features in severe HE patients[23]; however, changes in pupillary function alone should not guide therapy or LT decisions but should be incorporated into a MNM approach. Various noninvasive neuromonitoring techniques, including EEG, TCD, ONSD, and P2/P1 measurements, could prove valuable in this context. ONSD and TCD are reliable noninvasive methods for identifying patients at risk for elevated ICP (Table 2).

Optic nerve sheath diameter reflects changes in ICP as the subarachnoid space surrounds the optic nerve. However, ONSD measurement is operator-dependent, and the optimal ONSD cut-off for detecting elevated ICP remains unclear, with most studies involving traumatic brain injury patients[24]. TCD can indicate reduced mean and diastolic MCA velocities and a high pulsatility index (PI) in cases of intracranial hypertension[25]. ICP can be non-invasively estimated using a validated formula, which exhibits high sensitivity for excluding intracranial hypertension[26]. Noninvasive estimation of brain compliance, based on ICP waveforms (P1: arterial pulsation, P2: cerebral venous flow, P3: aortic valve closure), also revealed a normal P2/P1 ratio, suggesting normal brain compliance and the absence of brain oedema[27,28]. In our patient, several monitoring tools suggested the absence of intracranial hypertension, and high MCA velocities could have indicated cerebral hyperaemia, as observed in hypercapnia, severe hypertension, or ongoing seizures[29–31].

EEG plays a valuable role in monitoring the progression of HE and in detecting subclinical seizures or non-convulsive status epilepticus, which may necessitate antiepileptic treatment, as was the case with our patient[32–34]. Nevertheless, it remains uncertain whether early seizure detection and treatment can prevent neurological damage and minimize increases in ICP in this context. In HE, EEG changes can range from a low alpha rhythm frequency mixed with bilateral theta activity to progressive deceleration with theta-delta activity. In severe HE patients, arrhythmic delta activity may decrease and progress to electrocerebral silence[34]. Epileptic activity significantly impacts brain hemodynamics, altering cerebral blood flow and the cerebral metabolic rate of oxygen. During seizures, heightened neuronal activity increases energy demands[35], leading to increased cerebral blood flow and volume. This could result in elevated MCA velocities on TCD without a concurrent increase in ICP. Prolonged or recurrent seizures can lead to oxygen supply-demand mismatches, resulting in tissue hypoxia and ischaemia, thereby exacerbating neuronal injury and contributing to the progression of epilepsy and the severity of brain injury during HE[35]. While we did not utilize noninvasive brain oxygenation monitoring, such as near-infrared spectrophotometry (NIRS), it is important to note that cerebral NIRS monitoring has limitations, including susceptibility to extra-cerebral contamination, limited spatial resolution (typically the forehead area), sensitivity to ambient light interference, and device measurement variability, which may restrict its utility in HE patients[36]. Very scarce and inconclusive data are available for the role of cerebral NIRS in this context.

Importantly, there are various limitations to consider with respect to MNM. First, the precise role of MNM in patients with HE remains ambiguous, except for its exclusion as routine ICP monitoring. Therefore, additional research is warranted to elucidate the feasibility and potential clinical benefits of its routine application in the management of ALF patients within this context. Second, this approach requires diverse equipment that may not be accessible in every centre. Third, some monitoring tools, such as EEG and TCD, demand specialized expertise for their execution and interpretation. Finally, some techniques, such as B4C, are still primarily research-oriented, are not currently available in Europe and require further validation for widespread clinical application.

Conclusions

Compared to existing literature, to our knowledge, our is the first case report that strengthens the potentiality of MNM in ALF cases in ICU settings. Multimodal neuromonitoring plays a pivotal role in the management of patients with HE, by identifying intracranial hypertension, subclinical seizures, or status epilepticus, and thus optimizing cerebral perfusion and oxygenation. This comprehensive approach facilitates the early detection of neurological complications in these patient and allows for individualized treatment strategies which can help to reduce morbidity. As future perspective, multimodal neuromonitoring could positively contribute to the interdisciplinary decision-making process for placing a patient on the transplant list, offering a more comprehensive understanding of the patient's overall clinical condition.

Further studies are needed to better understand the real impact of MNM on the management of ALF patients.

Ethical approval

The study was approved by the Ethics Committee of the Hôpital Universitaire de Bruxelles (HUB), Site Erasme (P2023/219).

Consent

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Author contribution

S.Z.: conceptualization, collecting data, writing. A.A.O.: conceptualization, collecting data, writing. E.C.d.S.L.: collecting data, writing. G.M.T.: collecting data, writing. M.S.: collecting data, writing. E.D.S.: collecting data, writing. F.S.T.: supervision, validation.

Conflicts of interest disclosure

The authors declare that they have no financial conflict of interest with regard to the content of this report.

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Data availability statement

Publicly available.

Provenance and peer review

Not invited.

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