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L-Ornithine-L-Aspartate and Intermittent Renal Replacement Therapy in Fulminant Hepatitis A: A Case Report

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Abstract

Hepatitis A is a common viral infection worldwide that is transmitted via the fecal-oral route. Since the introduction of an efficient vaccine, the incidence of infection has decreased but the number of cases has risen due to widespread community outbreaks among unimmunized individuals. Classic symptoms include fever, malaise, dark urine, and jaundice, and are more common in older children and adults. People are often most infectious 14 days prior to and 7 days following the onset of jaundice. We will discuss the case of a young male patient, diagnosed with acute hepatitis A, leading to fulminant hepatitis refractory to conventional therapy and the development of subsequent kidney injury. The medical treatment through the course of hospitalization was challenging and included the use of L-ornithine-L-aspartate and prolonged intermittent hemodialysis, leading to a remarkable outcome. Hepatitis A is usually self-limited and vaccine-preventable; supportive care is often sufficient for treatment, and chronic infection or chronic liver disease rarely develops. However, fulminant hepatitis, although rare, can be very challenging to manage as in the case of our patient.

Keywords: fulminant hepatitis; hepatitis A; L-ornithine-L-aspartate; intermittent renal replacement therapy; continuous renal replacement therapy; a case report.

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Background

Hepatitis A virus (HAV) is a positive-strand RNA virus that is transmitted feco-orally through person-to-person contact (1). Outbreaks are often linked to poor sanitation, overcrowding, or food and water contamination. According to the World Health Organization (WHO), infection rates in developed countries are low. However, high-risk groups include injection-drug users, men who have sex with men,

and people traveling to endemic areas and isolated communities (1). Infection is often asymptomatic in children, but in adults it presents with jaundice, abdominal pain, hepatitis, and hyperbilirubinemia. Diagnosis is through the detection of immunoglobulin M antibodies against HAV. The clinical spectrum of HAV infection ranges from asymptomatic infection to fulminant hepatitis. Clinical manifestations depend on the age of the host: less than 30% of infected young children are symptomatic, while about 80% of infected adults manifest severe hepatitis with remarkably elevated serum aminotransferases. Fulminant hepatitis is rare, with a reported incidence of 0.015 to 0.5% (2). Atypical manifestations include relapsing hepatitis, prolonged cholestasis, and complicated cases with acute kidney injury (2). Extrahepatic manifestations include autoimmune hemolytic anemia, aplastic anemia, pure red cell aplasia, pleural or pericardial effusion, acute reactive arthritis, acute pancreatitis, acalculous cholecystitis, mononeuritis, and Guillain-Barré syndrome (2). Fundamental management of hepatitis A is active vaccination, supportive care, and liver transplantation for fulminant hepatitis A, which awaits further studies on prognostic predictors and some therapeutic measures (3). Our case highlights the importance of intermittent renal replacement therapy (RRT) in the management of refractory fulminant hepatitis A and the hepatic role of L-ornithine-L-aspartate.

Case Presentation

We herein report the case of a 38-year-old man, with a history of dyslipidemia on rosuvastatin and ezetimibe, who presented for jaundice of 1-day duration, associated with nausea and decreased oral intake since 1 week. Before the presentation, he had two febrile episodes for which he took only two tablets of paracetamol. Three weeks before the presentation, the patient disclosed a previous illness encounter with a coworker who had documented hepatitis A.

Otherwise, he is a nonsmoker, does not consume alcohol, and is vaccinated against COVID-19 (two doses, the last one was 5 months prior to presentation). He had no past surgical history, no known allergies, no drug or substance abuse, and reported a monogamous relationship and protected sexual intercourse with his girlfriend.

On presentation, he was hemodynamically stable and afebrile. On physical exam, he was conscious, cooperative, and oriented to place, person, and time. He had right upper quadrant tenderness and icteric sclera; otherwise, nothing was significant pertaining to general and systemic examination. His initial and follow-up laboratory values are summarized (Table 1). COVID-19 polymerase chain reaction (PCR) was negative. Viral, bacterial, and parasitic serologies (Cytomegalovirus, Epstein-Barr Virus, Hepatitis C Virus Antibody, Hepatitis B Virus Antigen, Herpes Simplex Virus, HIV, syphilis, brucella, and toxoplasma) were all negative, except for HAV IgM: 2.57 (positive) and total HAV: 0.01 (index positive). Anti-mitochondrial antibody (AMA) was negative, and anti-nuclear antibody (ANA) was borderline positive at a titer of 1/100. Ultrasound (U/S) abdomen and pelvis on admission showed only hepatomegaly.

A clinical decision was taken to admit the patient to the ICU for close monitoring and start him on supportive treatment. Serial Prothrombin Time and Partial Thromboplastin Time were ordered every 6 h and home medications were stopped. On day 3 of presentation, he started deteriorating. He developed grade 2 hepatic encephalopathy (HE) for which he was started on lactulose 30 cc thrice daily (tid) targeting 2–4 bowel movements per day and rifaximin 200 mg two tablets tid with no improvement. A brain computed tomography (CT) scan was done showing mild cerebral edema but no midline shift. Based on our expert hepatologist's recommendation, the patient was started on methylprednisolone 500 mg daily, IV pulse therapy for 3 days for a possible concomitant autoimmune hepatitis, and ursodeoxycholic acid (UDCA) 250 mg Per Os (PO) tid for pruritis.

On day 7, he got intubated for worsening encephalopathy (Glasgow Coma Scale 7). L-ornithine, L-aspartate was added in NG tube 1 sachet tid. The patient also developed progressive acute renal failure (ARF) refractory to conventional treatment as IV hydration, for which he was started on daily sustained low-efficiency daily dialysis (SLED) for 6–8 h each, as a bridge to Continuous Renal Replacement Therapy (CRRT). However, due to limited sources and logistic issues, the patient was not transferred to another hospital, so we continued SLED for five sessions without bridging to CRRT. The repeated level of ANA at that time turned out to be normal.

Despite all measures, the neurological state was not improving; hence, a brain MRI was requested on day 7, which showed abnormal signals in the cortex and basal ganglia, including the thalamus, compatible with mild cerebral edema with no increase in intracranial pressure (ICP) and this could be reversible (metabolic in etiology). Electroencephalogram (EEG) done on day 10 showed diffuse slowing compatible with metabolic origin. All brainstem reflexes were preserved with response only to painful stimuli.

On day 8, the patient became febrile. All infectious workup was negative, including urine analysis, urine culture, and blood cultures, except for infiltrates on chest X-ray with no documented increase in oxygen requirement on the ventilator. He was started by an ID specialist on piperacillin/tazobactam 4.5 g IV q 6 h for hospital-acquired pneumonia.

At this stage and due to the worsening of the patient's clinical status, the hepatologist decided to start him on N-acetylcysteine (NAC) two sachets twice per day for its possible role in hepatic improvement even in non-acetaminophen-induced hepatitis.

During his ICU stay (day 11), the patient developed one episode of coffee ground emesis for which he was started

Table 1: Summary of laboratory values follow-up, during and after hospitalization.

	Day 1	Day 7	Day 10	Day 30
Hb (g/dL)	16	13.9	11.9	9.3
WBC ($\times 10^9$/L)	6.8	15.5	21.9	14.5
Platelets ($\times 10^9$/L)	202	422	178	131
BUN (mg/dL)	23	42	135	26.5
Cr (mg/dL)	0.9	1.84	3.63	1.7
Na (mEq/L)	133	157	135	134.4
K (mEq/L)	3.8	4.6	4.1	3.88
Cl (mEq/L)	106	116	100	99.2
Co2 (mEq/L)	24	17.6	13.6	19.08
Ammonia (mg/L)	-	164	275	43
Albumin (g/dL)	4	3	2.7	2.8
SGOT (U/L)	4052	245	196	100
SGPT (U/L)	7338	1778	611	138
Alkaline Phosphatase (U/L)	100	102	86	101
GGT (U/L)	49	32	34	37
Bilirubin (Total/Direct) (mg/dL)	9.3/5.8	19/15.38	26/24.3	19.2/18.9
INR	2.68	2.8	5.35	1.4
PTT (seconds)	40.1	60.5	90.6	42
Amylase (U/L)	25	28	-	-
Lipase (U/L)	30	32	-	-

on IV continuous proton-pump inhibitors (PPI) and underwent urgent gastroscopy that showed erosive antral gastritis (which bled secondary to high INR level, see Table 1). He subsequently received several fresh frozen plasma (FFP) units. The emesis, then, ceased.

During the treatment course, our patient also developed watery diarrhea secondary to Clostridium difficile colitis that was treated with 10 days of oral vancomycin 125 mg q 6 h after finishing piperacillin/tazobactam course.

After taking the family's consent, the patient was planned to be transferred to a CRRT specialized center, as a bridge to liver transplantation. He was off sedation since the EEG date. The liver-matched donor was chosen with anticipation of possible live-related liver transplantation. The hepatologist and liver transplant specialist along with the general surgeon were kept on standby.

Meanwhile, the patient received SLED and other supportive care as per guidelines. The patient showed significant improvement clinically and biochemically on day 17 post-admission. The patient was successfully extubated on day 17 and was able to communicate with the medical team and his family. His laboratory parameters showed gradual improvement along with liver function tests (Table 1). Hence, the decision for liver transplantation and transfer to a higher center was deferred.

After receiving 13 days of nutritional, psychological support, and physiotherapy (i.e., day 30 of hospitalization), the patient was successfully discharged home on UDCA and lactulose with marked improvement of his laboratory values (Table 1) and was scheduled for short-interval clinic visits with follow-up laboratory test.

Discussion

Acute liver failure (ALF) is defined as an acute liver insult with catastrophic consequences without any pre-existing

liver disease. Its two main cardinal features are: encephalopathy and coagulopathy (4). ALF is rare with an incidence of less than 1%. Main etiologies are drug-induced, viral, immunologic, and other causes (4).

The risk of ALF in acute hepatitis A is less than 1%. The majority of HAV-related ALF has a spontaneous resolution rate (~70%) and the remaining 30% requires an urgent liver transplant or else results in death. Cerebral edema is one of the feared complications of ALF and one of the leading causes of death (4).

The poor prognostic indicators include a serum creatinine level >2 mg/dL, an ALT > 2600 U/L, and the need for intubation. Underlying preexisting liver conditions like nonalcoholic fatty liver disease and alcoholic steatohepatitis could be risk factors for rapid progression (5).

On his third day of admission, the patient had neurologic deterioration, because of which he was started on lactulose and rifaximin for HE, as well as UDCA for pruritis as per standard of care. Methylprednisolone's use apprehending underlying autoimmune hepatitis in our opinion was inappropriate and was taken with factual judgment at that time.

As the encephalopathy worsened and the patient became unresponsive with a GCS of 7, he had to be intubated and ventilated for airway protection.

L-ornithine L-aspartate (LOLA) one sachet tid was started for HE refractory to conventional therapy. At this stage, he was referred for an urgent call for liver transplant.

LOLA is a combination of two natural amino acids, ornithine and aspartate. It can be administered orally or parenterally with major effect on the reduction of the grade of HE in clinical trials. It also had encouraging effects on psychomotor function in cirrhotic patients with minimal hepatic encephalopathy (MHE) and chronic grade 1 HE (6).

Several randomized controlled clinical trials (RCT) reviewed by Butterworth et al. have revealed that the use of LOLA increases the removal of ammonia by residual hepatocytes and skeletal muscle of patients with cirrhosis.

Direct hepatoprotective effects of LOLA were also demonstrated in these RCT, where reduction of the plasma concentrations of liver enzymes was seen, as well as improvement of liver function and amelioration of symptoms of HE in patients with cirrhosis (7, 8).

Several mechanisms appear to be responsible for the protective actions of LOLA and are related to this agent's components: L-ornithine and L-aspartate, as well as their metabolites: glutamate, glutamine, and glutathione (7).

Mechanisms of actions of LOLA

The detoxification of ammonia by the liver is based on two metabolic pathways: the synthesis of urea and the synthesis of glutamine (7, 9). LOLA acts by delivering important substrates for both pathways.

L-ornithine is an important activator of the urea cycle that will lead to the elimination of ammonia (7, 9). It also increases the synthesis of glutamine in the liver and the skeletal muscle, which leads to the elimination of excess ammonia. It may also be involved in the direct hepatoprotective effects of LOLA. Glutamine has also been shown to have antioxidant properties that help in the protection of the liver.

Another pathway of hepatoprotective actions of LOLA consists of the production of nitric oxide (NO) from L-arginine. This has been shown to result in improved hepatic microcirculation (6, 7).

Circulating L-arginine is produced from L-ornithine as shown in studies of patients with HE or cirrhosis who were treated with LOLA (7).

There is a limited role for liver biopsy in ALF. However, liver biopsy is strongly indicated in cases of suspicion of malignant infiltration and cases of alcoholic hepatitis, especially when considering a liver transplant. However, our patient was not stable enough to undergo a liver biopsy and was assigned for an urgent liver transplant. Meanwhile, the patient was maintained on LOLA in addition to lactulose and rifaximin. NAC was added for its predicted beneficial effect and role in non-acetaminophen-induced ALF (NAI-ALF).

N-Acetylcysteine is known to be the precursor of glutathione, a very important detoxifying agent. NAC is a potent antioxidant that helps in eliminating free oxygen radicals and replenishing cytoplasmic and mitochondrial glutathione stores (10). NAC has also been proven to have vasodilatory and inotropic effects, which help ameliorate the oxygenation and perfusion of vital organs during shock states (11). It is as an antidote to acetaminophen. But the guidelines of the American Association for the Study of Liver Diseases (AASLD) published in 2011 suggested that it may also be of importance in NAI-ALF (11).

A retrospective study conducted on patients with NAI-ALF showed that patients who received NAC had an increased survival rate with their native liver as compared to patients who were not treated with NAC.

Despite all these therapeutic measures, the patient only showed mild improvement in encephalopathy and his renal function worsened. Therefore, the decision was made to start intermittent hemodialysis as our dialysis center does not provide CRRT for two main purposes: removal of ammonia through hemofiltration and improvement of renal function.

More than 80% of patients with fulminant hepatitis develop ARF, which negatively influences the overall prognosis (12). The pathophysiology of the ARF in hepatitis is not well known and different mechanisms are suggested (12). First, volume depletion related to nausea, vomiting, and diarrhea leads to stimulation of the renin-angiotensin system and prerenal acute kidney injury. Second, immune complex – mediated nephritis in the case of hepatitis A may lead to

different types of glomerular disorders, including membranous nephropathy, mesangial proliferative, and membranoproliferative glomerulonephritis. Third, endotoxemia related to hepatitis will lead to systemic hypotension, renal vasoconstriction, the release of cytokines, and the activation of neutrophils, which will contribute to renal injury (12). ARF is considered a cause of hyperammonemia if it occurs early with ALF decreasing the excretion of ammonia by 20%. Ammonia is a major regulator of acid-based homeostasis (13), and extracellular pH and plasma potassium concentration play an important role in the regulation of ammonia synthesis and transport (13). Hypokalemia can precipitate encephalopathy by stimulating ammonia-genesis in the tubule (14) and bicarbonate-containing fluids induce cerebral vasodilation, facilitate ammonia entry in the brain, and thereby lead to intracranial hypertension (15).

Ammonia is a 17 g/mol non-protein-bound element with a diffusive clearance similar to urea; both continuous and intermittent modalities of RRT are efficient to remove it from the plasma but with different rates (13, 15). The timing to start dialysis in adults with ALF, hyperammonemia, and cerebral edema is still unknown (13, 15). Some references recommend dialysis when ammonia levels approach 200 micromol/L (16). It has been suggested to consider it when the ammonia level is three times more than the upper limit of normal or when patients are severely encephalopathic, even before the advancement of AKI (13). Continuous RRT (CRRT) used alone or with intermittent hemodialysis is considered the method of choice because it provides uninterrupted clearance for ammonia reducing post-hemodialysis rebound caused by a deferred ammonia shift from extravascular compartments (13, 15). It allows a gradual reduction in serum osmolality and less shift of water across the blood–brain barrier to prevent the worsening of cerebral edema in patients with high ICP. It also allows temperature control and slow correction of metabolic abnormalities such as hyponatremia (15). However, Cardoso et al. demonstrated that there was no statistically significant difference in ammonia reduction between the CRRT and intermittent hemodialysis groups; however, the use of CRRT was associated with a reduction in 21-day transplant-free all-cause mortality, whereas intermittent hemodialysis was associated with an increase in mortality (17). Despite the recommended use of the CRRT, our patient has been treated with daily long sessions of intermittent dialysis with good outcomes. So, in the absence of CRRT availability, intermittent hemodialysis might still be a good option.

Conclusion

Hepatitis A virus continues to be a global health issue, with the highest rates in lower-income countries. Fulminant hepatitis is rare, yet it is the most feared complication due to the difficulty in management and the overall poor prognosis. Treatment of HE focuses on the reduction of ammonia produced in the colon. In this context, LOLA promotes ammonia clearance and increases production of glutamine, making it an excellent therapeutic alternative and could have contributed to the patient improvement along with dialysis. The use of CRRT to reduce ammonia levels in the treatment of cerebral edema has been reported in the literature, yet, in our case, the use of intermittent hemodialysis was effective despite established guidelines about the importance of CRRT in this situation. Thus, our case proves the importance of RRT in fulminant hepatitis-A with ARF refractory to standard treatment and also proves that intermittent hemodialysis can possibly be an efficient alternative, in resource-limited settings. Further research and studies are needed to determine the impact of SLED in this type of scenario.

Declarations

Funding and Conflicts of Interest/competing Interests

No funding was received for conducting this study. The authors have no relevant financial or nonfinancial interests to disclose.

Consent for Publication

Consent was taken from the patient.

Availability of Data and Material

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' Contributions

All authors contributed to this study and approved the final manuscript.

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