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CASE REPORT
Cardiovascular surgery

Hepatic encephalopathy due to aorto-right ventricular fistula responsive to percutaneous repair: a case report

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Background Encephalopathy due to hyperammonemia is most often found in a setting of cirrhosis. However, it can also result from increased hepatic venous pressures, which can damage zone three hepatocytes and result in elevated serum ammonia.

Case summary This report focuses on the unique case of a 43-year-old woman, who presented with confusion in the setting of hyperammonemia due to congestive hepatopathy from an iatrogenic aorto-right ventricular fistula. The patient underwent percutaneous repair of the fistula with resolution of encephalopathy and notable improvement in symptoms. The patient attended all follow-up appointments and was contacted five and eight months after admittance for updates regarding her recovery and permission to publish this case.

Discussion This exceedingly rare case has not been reported in the literature and highlights the historically narrow differential for hyperammonemic encephalopathy given the prevalence of cirrhosis and potential reversibility of such a case.

Keywords Cardiac • Fistula • Encephalopathy • Congestive hepatopathy • Case report

ESC Curriculum 4.2 Aortic stenosis • 4.1 Aortic regurgitation • 7.4 Percutaneous cardiovascular post-procedure
9.9 Cardiological consultations • 4.10 Prosthetic valves

Learning points

- Patients presenting with unknown causes of hyperammonemia with history of significant cardiac surgery should be considered for workup of anomalous cardiac connections.
- Cardiac left-to-right heart fistulas can lead to chronic hepatic congestion and resultant hyperammonemia for which interventional cardiology can play role in relieving congestion.

Introduction

Congestive hepatopathy can arise from any insult that chronically raises central venous pressure, causing a back-up of blood and damage to the liver through three primary mechanisms: (i) decreased hepatic blood flow, (ii) decreased arterial oxygen saturation, and (iii) increased hepatic venous pressures.[1] This congestion is commonly a result of right-sided heart failure from primary or secondary causes. The resultant sinusoidal hypertension causes primary damage to zone-three hepatocytes responsible for conversion of ammonia to glutamine.[1] Damage can thus lead to elevations in serum ammonia, a nitrogenous substance associated with neurotoxicity and largely implicated

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throughout history as the root cause, co-actor, or correlate for hepatic encephalopathy.[2]

We present a patient with a unique source of hepatic congestion through elevated right heart pressures from an iatrogenic aorto-right ventricular fistula (ARVF), ventricular septal defect (VSD), and acquired tricuspid regurgitation (TR). This caused congestive hepatopathy seen on ultrasound and disruption in ammonia metabolism causing hyperammonemia and its associated signs and symptoms.

Timeline

Past medical history

Date	Event
4/2011	Evaluated due to congenital bicuspid aortic valve with aortic root dilatation and aortic regurgitation. 23-mm St. Jude's mechanical valve replacement and tricuspid valvular annuloplasty.
4/6/2021	Secondary aortic valve replacement with 19 mm On-X valve complicated by aorto-right ventricular fistula, severe tricuspid regurgitation, and peri-membranous ventriculoseptal defect.
5/8/21–5/23/21	Admitted for confusion and fall from bed. Inpatient rehabilitation with physical therapy and occupational therapy (PT/OT).
5/30/21–6/7/21	Admitted for elevated right (>25 mmHg) and left sided pressures. Inpatient rehabilitation with PT/OT. Decision to manage cardiac fistula outpatient.
6/29/21–7/5/21	Admitted for confusion and fall from bed. Computerized tomography (CT) brain and neurology consult reveal no findings necessitating further neurologic workup. Ammonia elevated (92). Psychiatric medications adjusted. Recommendation to continue cardiac management outpatient.
7/19–7/28/21	Admitted for confusion and multiple falls. Ammonia elevated (59 mcmol/L). Started on lactulose due to elevated ammonia with improvement in symptoms.
9/21/2021	Patient ran out of lactulose and became progressively more confused.

Inpatient (9/26/21–10/8/21)

Date	Event
9/26/21 (Day 0)	Admitted due to confusion and recurrent falls. The CT brain without contrast shows no acute process. Ammonia elevated (122 mcmol/L). Medications reviewed and patient restarted on inpatient lactulose and rifaxamin.

Continued

Continued

Inpatient (9/26/21–10/8/21)

Date	Event
9/27/21 (Day 1)	US liver showing bi-directional flow in main portal vein
10/2/21 (Day 6)	CT abdomen/pelvis with evidence of congestive hepatopathy.
10/4/21 (Day 8)	Transesophageal echocardiogram with continued evidence of aorto-right ventricular fistula and tricuspid regurgitation.
10/5/21 (Day 9)	CT angiography demonstrates fistula between aorta and right ventricle.
10/8/21 (Day 12)	Percutaneous plugging of fistula by interventional cardiology with 10-mm Amplatzer™ Vascular Plug II.
10/9/21 (Day 13)	Patient discharged.

Since discharge

Date	Event
10/14/21 (5 days post-discharge)	Patient reports feeling well at outpatient follow up appointment with improvement in weight with increased urine output.
12/2/21 (2-month follow-up)	Transthoracic echocardiogram shows no flow through fistula.
2/21/22 (5-month follow-up)	Patient's husband contacted via phone. She reports improved energy. Her mental status remains stable at her baseline and well above her status upon admission. She has been off lactulose for months. Patient being considered for wean from rifaximin.
5/2022 (8-months post-discharge)	Patient continues outpatient follow-up and provides consent for study. Notes continued improvement. Patient remained off lactulose with anticipation for likely discontinuation of rifaxamin.

Case presentation

A 43-year-old woman presented to the emergency department for recurrent falls and confusion. The patient had a significant surgical history including:

- Congenital bicuspid aortic valve complicated by aortic root dilatation and regurgitation, status post-aortic valve replacement with St. Jude 23-mm valve and tricuspid annuloplasty in 2011.
- In 2021, left ventricular hypertrophy and severe aortic stenosis led to a second aortic valve replacement with an On-X valve complicated by an ARVF and TR.
- Right heart catheterization (2 June 2021) showed elevated right heart filling pressures, elevated left heart filling pressures, an ARVF, and dilated right ventricle with normal systolic function.

Two months prior, the patient had presented with confusion and falls. She was noted to have asterixis. Serum ammonia was found to be elevated. She was treated with lactulose until resolution of her symptoms and discharged on it. At that time, her ARVF was not

Table 1 Outpatient medications

Medication	Dose
Iron tablet	324-mg tablet twice daily
Lantus	5-units subcutaneous injection once daily
Lactulose	20-g packet by mouth once daily
Oxcarbazepine	150-mg twice daily
Paroxetine	2-mg tablet by mouth every evening
Sumatriptan succinate	50-mg tablet once daily as needed
Albuterol	90-mcg/act HFA inhaler, 2 puffs every 6 h as needed
Aspirin	81-mg chewable tablet once daily
Atorvostatin	10-mg tablet once daily
Docusate sodium	100-mg capsule every day as needed
Doxepin	1–2 50-mg capsules at bedtime
Fluticasone	50-mcg/actuation spray, 2 sprays each nostril one time a day
Fluticasone propion-salmeterol	250–50-mcg/dose one puff every 12 h
Lamotrigine	200-mg/100-mg/100-mg
Lurasidone	80-mg tablet with dinner
Lurasidone	40-mg tablet every morning
Metoprolol succinate	25-mg tablet once daily
Pantoprazole	40-mg DR once daily by mouth
Prazosin	2-mg capsule at bedtime
Pregabalin	75-mg capsule twice daily
Semaglutide	1-mg/dose injection once weekly
Topiramate	25-mg tablet once daily
Torsemide	20-mg tablet once daily
Warfarin	10-mg tablet once daily

considered as a cause of her encephalopathy. A previous admission called for outpatient management of her ARVF by interventional cardiology. However, there was no mention of her fistula as the cause of her falls and encephalopathy. The cause of her encephalopathy was presumed to be multifactorial. As a result, there were no plans made to correct the aforementioned cardiac abnormalities during that admission. She experienced a progressive worsening in her somnolence despite compliance with the previously efficacious lactulose dose. Unfortunately, the patient ran out of lactulose and was hospitalized rapidly due to severe encephalopathy.

The patient's contributing past history included bipolar and post-traumatic stress disorders requiring the centrally acting medications in *Table 1*. Remaining history was non-contributory.

Vitals were within normal limits. Admission exam was significant for obesity, slowed mentation, slurred speech, regular rate, and rhythm with a III/VI holosystolic murmur at upper right sternal border with radiation to carotids, mechanical S2 with near-obliteration of S1, bilateral asterixis, and ecchymosis on the chest. Her exam was negative for jugular venous distension, organomegaly, laboured respirations, or peripheral edema.

Given her findings and history of outpatient treatment with lactulose, ammonia levels were measured and markedly elevated at 122 mcmol/L on admittance (*Table 2*). Further investigation showed elevated transaminases and serum bilirubin.

Table 2 Labs

	7/2/21	7/24/21	9/26/21	9/29/21	10/7/21
Serum chemistry					
Sodium (135–145 mmol/L)			139		
Potassium (3.6–5.0 mmol/L)			4		
Chloride (98–109 mmol/L)			103		
CO_2 (22–31 mmol/L)			26		
Anion gap (6–10 mmol/L)			10		
Glucose random (65–200 mg/dL)			147		
Urea nitrogen (6–23 mg/dL)			12		
Creatinine (0.51–0.95 mg/dL)			1.06		
EGFR African American (mL/min/1.73 m^2)			>60		
EGFR non-African American (mL/min/1.73 m^2)			57		
Calcium total (8.4–10.2 mg/dL)			9.3		
Phosphorus (2.4–4.5 mg/dL)			2.8		
Magnesium (1.6–2.6 mg/dL)			1.8		
Ammonia (13–40 mcmol/L)	92	59	122	41	69
Liver studies:					
AST (10–35 units/L)			40		
ALT (10–35 units/L)			22		
Alkaline phosphatase (35–104 units/L)			411		
Routine coagulation					
Fibrinogen (190–400 mg/dL)			314		
Protime (10.2–13.0 s)			57.6		
INR (0.9–1.1)			5		
PTT (25.1–36.5 s)			58		
Complete blood count					
WBC (4.22–10.33 × 10^9/L)			4.19		
RBC (3.93–5.22 × 10^{12}/L)			4.1		
Hemoglobin (11.2–15.7 g/dL)			11.2		
Hematocrit (34.1–44.9%)			36.3		
MCV (79.4–94.8 femtoliters)			88.5		
MCH (26.5–32.6 pg)			27.3		
MCHC (32.3–36.5 g/dL)			30.9		
RDW-CV (11.4–14.4%)			19.9		
Platelets (160–383 × 10^9/L)			243		
MPV (8.8–12.2 femtoliters)			10.4		
Urine studies					
Urinalysis			Negative for nitrites and bacteria on admittance and four days after admittance		
Organic acid urine screen			No significant abnormalities detected		

EGFR, estimated glomerular filtration rate; RDW-CV, red cell distribution width; MCHC, mean corpuscular hemoglobin concentration; MPV, mean platelet volume; MCV, mean corpuscular volume

*Normal values in parentheses

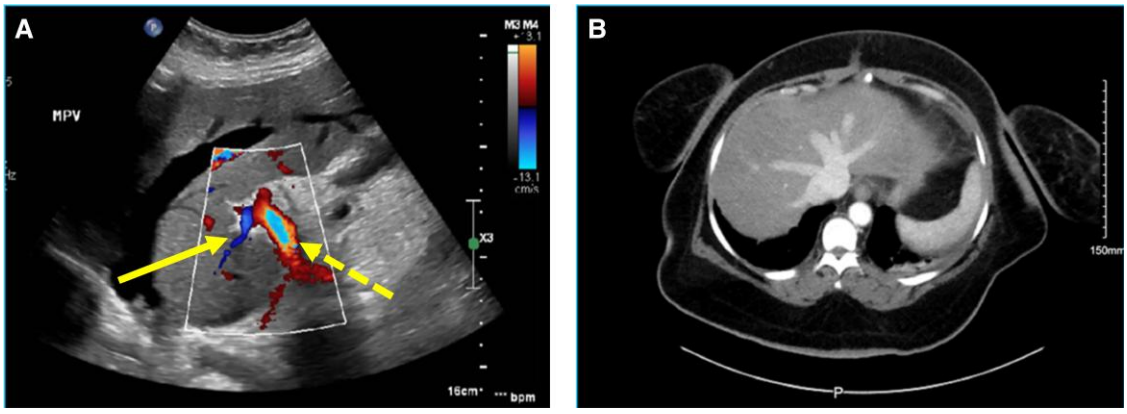


Figure 1 Hepatic congestion demonstrated by liver ultrasound with dilated hepatic veins (solid arrow) and bidirectional flow in main portal vein (dashed arrow) (*A*). CT abdomen/pelvis with evidence of congestive hepatopathy with hepatic steatosis and hepatomegaly (*B*).

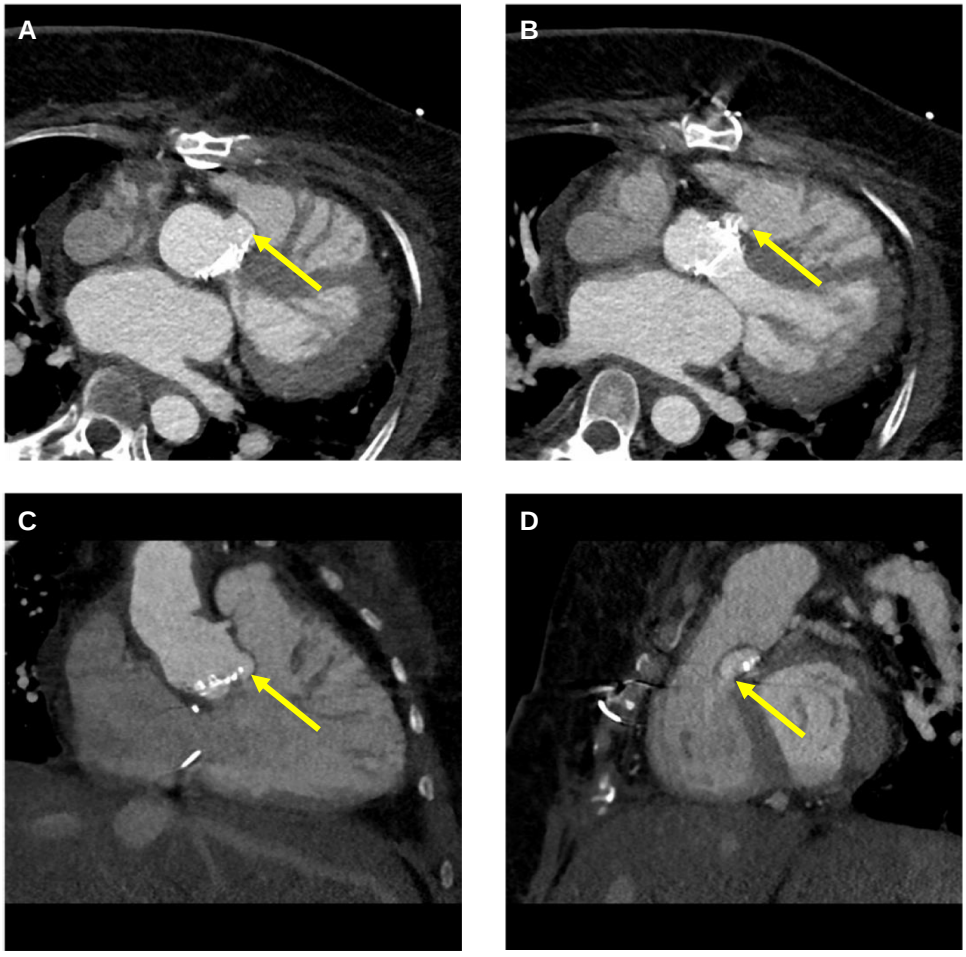


Figure 2 Post contrast axial computerized tomography (CT) images demonstrating aortic pseudoaneurysm (*A*) and fistula (*B*) between aorta and right ventricle. Post-contrast coronal CT image (*C*) demonstrating aortic pseudoaneurysm. Post-contrast sagittal CT image (*D*) demonstrating presence of pseudoaneurysm and fistula.

Table 3 Examples of non-hepatic and hepatic causes of hyperammonemia

Non-hepatic causes	Hepatic causes
Drugs*	Cirrhosis
Urea cycle disorder[a]	Acute liver failure
Organic acidurias	Portosystemic bypass of liver due to congenital abnormality
Metabolic defect	Portosystemic bypass of liver due to acquired abnormality
Reye's syndrome	
Urinary tract infection	

*Ex: 5 fluorouracil, sodium valproate
[a]Due to a defect in any of the six enzymes needed to complete the cycle (most commonly ornithine transcarbamylase)

Liver ultrasound showed 'dilated hepatic veins and bidirectional flow in the main portal vein may relate to cardiac disease' (*Figure 1A*, Supplementary material online, *Video S1*).

Computerized tomography (CT) abdomen/pelvis revealed evidence of congestive hepatopathy with hepatic steatosis and hepatomegaly (*Figure 1B*).

Transthoracic and transesophageal echocardiograms confirmed the presence of an ARVF and TR as noted in the patient's history (see Supplementary material online, *Video S2*). Additionally, it revealed dilation of the right heart chambers and an estimated left ventricular ejection fraction of 55%. The CT angiography of the chest confirmed presence of the fistula, peri-membranous VSD, and small pseudoaneurysm (*Figure 2*).

Our differential for the patient included congestive hepatopathy due to elevated right atrial pressures, cirrhotic hyperammonemia, a urease-producing urinary tract infection, medication-induced hyperammonemia in setting of polypharmacy, or possible errors in the urea cycle.

Hepatology assessed the liver through ultrasound and CT imaging. Although they did not rule out the possibility of hepatic fibrosis from NAFLD or chronic congestion, they did not deem further investigation with biopsy or elastography appropriate at that time. Biopsy would not affect management as therapy was already directed toward lowering right atrial pressure. Urinalysis was conducted twice throughout her hospital course and was negative for nitrites and bacteria. A defect in any of the six enzymes required to complete the urea cycle can result in increased levels of ammonia.[3] Urine tests for organic acids were unrevealing. The patient had an extensive list of medications (*Table 1*). However, drug-induced hyperammonemia was decided to be unlikely as only oxcarbazepine,[4] and topiramate[5] shows very rare instances of hyperammonemia. Only a few cases are reported for each drug. These cases are most often seen in combination with other psychotropic or antiseizure medications, which our patient did not take. For example, cases of topiramate-induced hyperammonemia can be a result of co-administration with valproic acid.[5] Our patient did not take valproic acid. Liver enzymes revealed an elevated alkaline phosphatase with intact transaminases. These findings suggested a congestive process further supported by the ultrasound findings and elevated right atrial pressure, well above the baseline of >12 mmHg needed to result in hepatic congestion. The presence of the fistula, VSD, and TR were sufficient to explain the cause.

She started inpatient treatment with lactulose titrated for 4–5 daily bowel movements. Five days into her hospitalization, she began rifaximin 550 mg twice daily. With treatment, her encephalopathy and asterixis began to improve. Her initial struggle with reporting her name and location waned. The patient began answering all questions correctly with increased speed and confidence. Her asterixis eventually resolved.

Interventional cardiology was consulted to consider repair after cardiovascular surgery raised concerns about repeat surgery. She was taken by the former for successful percutaneous plugging of her ARVF with a 10-mm Amplatzer™ Vascular Plug II. She continued to have severe TR, but the remainder of her hospital course was unremarkable. She was discharged one day after repair. Upon discharge, minimal changes were made to the outpatient medications recorded in *Table 1*. In addition to continuing her previous dose of lactulose (20-g packet daily), she was prescribed rifaximin 550 mg oral, twice daily. As the patient was placed on a heparin drip leading up to her procedure, she was bridged back to her prior warfarin dose (10 mg daily) before leaving. Lastly, her torsemide dose was increased from 20 to 40 mg.

Five days post-discharge, she felt well with improvement in weight from increased urine output. Echocardiogram performed six weeks after surgery did not show significant changes from prior to surgery but showed no flow through the fistula. Five months after surgery, she reports improved energy. Her mental status remains stable at her baseline and well above her status upon admission. She has been off lactulose for months and is being considered for wean from rifaximin as of this writing (eight months after surgery).

Discussion

Ammonia can reach toxic levels due to increased production or decreased elimination.[6] In addition to classification as congenital or acquired, origins of hyperammonemia can be separated into hepatic and non-hepatic causes (*Table 3*).[7] Hepatic origins of hyperammonemia are most common with 90% of its cases due to severe liver disease. In fact, 60–80% of patients with liver cirrhosis are estimated to develop hepatic encephalopathy.[7] In cirrhosis, portal hypertension and resulting portal-systemic shunts allow various toxins to bypass the liver, contributing to the build-up of intestinal toxins such as ammonia, manganese, and cytokines in the systemic circulation.[7]

This case is unique in that the patient presented with signs and symptoms classically attributed to cirrhotic hepatic encephalopathy with resolution after correction of an ARVF and no evidence for hyperammonemia due to increased production.

Only four cases of ARVF after transcatheter aortic valve replacement had been reported thus far[8–10] with rare occurrences documented since then.[9,10] Although our patient originally underwent an open procedure, this highlights the rarity of developing an ARVF after valve replacement. If symptomatic, most patients presented late with increased fatigue or dyspnea.[9–14] There have also been reports of late formations of pseudoaneurysms after prosthetic valve replacement,[15] which can lead to ARVF[13] or aorto-RA fistula.[16] None of these cases reported hyperammonemia leading to encephalopathy.

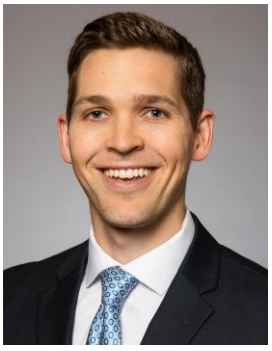
To the best of our knowledge, there is no reported case of a patient with an iatrogenic ARVF suffering hyperammonemia and encephalopathy due to hepatic congestion. This rarity was reflected in the relative delay in diagnosis between trips to the emergency department, initial hospitalization, and eventual repair. While medical management was initially sufficient, her progressive decline despite adequate bowel movements highlighted the need for repair. Only through her procedure has the patient seen substantial improvement and resolution in her mental status.

Conclusions

An ARVF represents a rare complication of aortic valve replacement. As demonstrated by this case, these fistulas can result in elevated right

atrial pressures that may cause symptomatic hepatic congestion and encephalopathy. Patients presenting with unknown causes of hyperammonemia in the setting of significant cardiac surgery history should be considered for workup of anomalous cardiac connections causing hepatic congestion with ultrasound or CT imaging. Finally, patients who suffer the rare complication of ARVF should be considered for repair if medical treatment fails, and interventional cardiology deems the patient a good candidate. Close consultation with cardiovascular surgery is also recommended.

Lead author biography



Craig Kemper is a fourth year medical student at the University of Texas Southwestern Medical Center in Dallas, Texas. He will continue his training as a resident in otolaryngology at the Baylor College of Medicine in Houston, Texas.

Supplementary material

Supplementary material is available at *European Heart Journal – Case Reports*.

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Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

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Data availability

The data underlying this article are available in the article and in its online supplementary material.

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