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Hyperammonaemia Presenting as an Acute Neuropsychiatric Syndrome in an Elderly Patient: A Diagnostic Challenge

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Abstract

Hyperammonaemia is a metabolic derangement characterised by elevated circulating ammonia levels resulting in neurotoxicity and a wide spectrum of neurological manifestations. In adults, particularly the elderly, the clinical presentation may be nonspecific and frequently mimics primary psychiatric or neurodegenerative disorders, leading to delays in diagnosis and management. We report the case of a 77-year-old male patient who presented with progressive neuropsychiatric symptoms initially attributed to alcohol use disorder and psychiatric illness. Despite multiple diagnostic investigations and empirical treatment for several suspected etiologies at the initial hospital, the patient's neurological condition continued to deteriorate. The assessment was further complicated by the presence of an acute infarct in the left capsuloganglionic region on the brain MRI. Due to continued clinical deterioration, the patient was transferred to another tertiary care facility for further evaluation and management. After a thorough review of the clinical course and prior investigations of the patient, the treating physician advised serum ammonia estimation, considering the possibility of an underlying metabolic cause of encephalopathy. The investigation revealed a markedly elevated serum ammonia concentration of 497.7 µg/dL (reference range: 27.2-102 µg/dL), supporting the diagnosis of hyperammonaemia-associated encephalopathy. Following the initiation of ammonia-lowering treatment, the patient showed significant clinical improvement. This case highlights the importance of considering metabolic causes, including hyperammonaemia, in patients presenting with unexplained neuropsychiatric symptoms, as early recognition may facilitate timely management and improve clinical outcomes.

Categories: Neurology, Psychiatry, Internal Medicine
Keywords: altered mental status, delirium, diagnostic challange, elderly patient, hyperammonaemia, hyperammonaemic encephalopathy, metabolic encephalopathy, neuropsychiatric manifestations, serum ammonia

Introduction

Hyperammonaemia refers to an abnormal elevation of ammonia in the bloodstream, resulting either from increased production or impaired detoxification [1]. Under normal physiological conditions, ammonia generated during protein metabolism is converted into urea via the hepatic urea cycle and subsequently excreted [2]. Disruption of this pathway leads to accumulation of ammonia, which exerts neurotoxic effects primarily on astrocytes, resulting in cerebral edema and altered neurotransmission [3].

The clinical manifestations of hyperammonaemia vary widely depending on the acuity and severity of elevation [4]. Acute hyperammonaemia may present with lethargy, vomiting, seizures, and coma, whereas chronic or subacute forms often manifest as cognitive impairment, behavioural disturbances, ataxia, and psychiatric symptoms. In elderly individuals, these features frequently overlap with dementia, delirium, or primary psychiatric disorders, making diagnosis particularly challenging [5,6].

Although hyperammonaemia is a hallmark of inherited urea cycle disorders, it may also arise from acquired causes, including liver dysfunction, medications, infections, and other metabolic disturbances, which may be underrecognised. Early recognition and prompt treatment are essential to minimize the risk of severe neurological complications [7].

Non-hepatic hyperammonaemia arises from diverse mechanisms, including increased ammonia production or impaired elimination [8,9]. Portosystemic shunts may divert ammonia-rich portal blood away from hepatic detoxification [5,8,9], and reduced skeletal muscle mass may decrease extrahepatic ammonia buffering. Ammonia production can be increased during catabolic states such as seizures and trauma [9] and in association with infection or other metabolic stress [5,8]. Gastrointestinal bleeding and excess protein/amino-acid loads can also increase ammonia production. Urease-producing organisms can increase ammonia production and systemic absorption, especially in the presence of urinary obstruction or retention, causing urinary tract infections [9]. Medications, especially valproate, can cause hyperammonaemia by impairing ammonia elimination or increasing its production [4,5,9], and chemotherapeutic agents and

haematological malignancies are also recognised causes [8,9]. Previously unrecognised urea-cycle disorders may present clinically during infection or other metabolic stress [5,7,9]. These mechanisms may result in the accumulation of ammonia even in the absence of overt liver disease.

In patients without overt liver disease, hyperammonaemia may be overlooked as clinicians are more familiar with its association with hepatic dysfunction, whereas non-cirrhotic causes are less well recognized and its neurological manifestations may mimic other psychiatric, neurological or structural brain disorders [8,10].

Diagnosing hyperammonaemia in elderly patients can be challenging because its neurological and psychiatric manifestations are often nonspecific and may overlap with those of other neurological or psychiatric conditions [7]. In this case, the coexistence of cerebrovascular abnormalities on neuroimaging added complexity to the evaluation of progressive neuropsychiatric deterioration, as the clinical manifestations were not clearly attributable to a focal neurological event alone. Following persistent clinical deterioration despite extensive diagnostic evaluation and empirical treatment at the initial hospital, the patient was transferred to a critical care facility for further management. Reassessment prompted investigation for an underlying metabolic cause of encephalopathy, revealing markedly elevated serum ammonia levels despite the absence of significant abnormalities in serial liver biochemical parameters. The subsequent clinical improvement following ammonia-lowering treatment highlights the importance of considering hyperammonaemia in the differential diagnosis of persistent, unexplained encephalopathy, even in the absence of overt hepatic biochemical abnormalities.

Case Presentation

A 77-year-old male patient was brought to the medical intensive care unit with a 20-day history of progressive behavioural changes, confusion, irritability, and irrelevant speech, accompanied by retrograde memory disturbances. The patient also had a five- to six-month history of slow-stepping gait, bilateral hand tremors, muscular rigidity and difficulty walking. One day prior to admission, he developed urinary incontinence. He had also wandered away from home and was subsequently found disoriented and undressed. Approximately one hour before admission, an episode of tongue biting was reported, raising suspicion of seizure activity. There was no history of fever, head trauma, or prior similar episodes.

His past medical history was significant for chronic alcohol use (with his last reported alcohol intake two days prior to admission), long-term tobacco consumption, hypertension, and type 2 diabetes mellitus, for which he was receiving regular treatment. Four days prior to admission, he had been evaluated by a psychiatrist and initiated on risperidone (2 mg) with trihexyphenidyl (2 mg), clonazepam (0.5 mg), and thiamine supplementation for presumed psychiatric illness.

On admission, the patient was stuporous with incoherent speech and a shuffling gait. He was not oriented to time, place, or person. His Glasgow Coma Scale (GCS) score was 9/15, comprising an eye-opening response of 2 (opens eyes to pain), a verbal response of 2 (incomprehensible sounds), and a motor response of 5 (localises to pain) [11]. The patient's vital signs recorded at the time of admission are presented in Table *1*.

Parameter	Recorded value	Normal reference range
Temperature	98.6 °F	97–99 °F
Pulse Rate	92 beats/min	60–100 beats/min
Blood Pressure	130/80 mmHg	<120/80 mmHg
SpO_2	100%	95–100%
GRBS	167 mg/dL	<140 mg/dL

TABLE 1: Vital signs recorded at the time of admission

SpO_2: Peripheral oxygen saturation; GRBS: General random blood sugar.

Initial laboratory investigations revealed elevated erythrocyte sedimentation rate (36 mm/hour; reference range: 0 to 20 mm/hr) and mild hyperbilirubinaemia (total bilirubin 1.4 mg/dL; reference range: 0-1.2 mg/dL). Based on the clinical presentation, history of alcohol use and parkinsonian features, a provisional diagnosis of alcohol use disorder with neuropsychiatric manifestations along with Parkinson's disease was made.

The patient was started on intravenous thiamine at a dose of 200 mg three times daily (as chronic alcohol use can contribute to thiamine deficiency through inadequate nutritional intake and impaired absorption,

increasing the risk of Wernicke's encephalopathy - a neurological disorder caused by thiamine deficiency) [12]. Pantoprazole was prescribed for gastric protection, and ondansetron was administered for symptomatic relief of nausea. Lorazepam was administered to manage agitation and possible alcohol withdrawal, while insulin therapy was initiated for glycaemic control and cilnidipine was started for blood pressure management. Levetiracetam was started prophylactically in view of altered sensorium, an episode of tongue biting, and the associated risk of seizures. Additionally, levodopa-carbidopa (Syndopa Plus) was introduced for suspected parkinsonian features, while ursodeoxycholic acid was prescribed as supportive therapy in view of mild hepatic dysfunction.

Despite these measures, the patient's neurological status worsened, with the development of visual hallucinations and persistent disorientation. This prompted escalation of care and further diagnostic evaluation.

Neuroimaging (MRI of the brain) revealed an acute infarct in the left capsuloganglionic region, along with diffuse cerebral atrophy and chronic small-vessel ischaemic changes, which may have contributed to some of the patient's neurological manifestations, particularly gait and motor disturbances. However, the overall clinical presentation was predominantly characterised by progressive global neuropsychiatric manifestations rather than a clearly defined focal neurological syndrome.

The neuroimaging findings may have contributed to the patient's neurological manifestations, further complicating the diagnostic evaluation of the altered mental status and neuropsychiatric symptoms. Laboratory investigations revealed elevated inflammatory markers and deficiencies of vitamin B12 and D, with the corresponding values presented in Table *2*.

Investigation	Reference range	Reported value
C-reactive protein (CRP)	0–6 mg/L	66.6 mg/L
Erythrocyte Sedimentation Rate (ESR)	0 to 20 mm/hr	46 mm/hr
25-hydroxyvitamin D	30–100 ng/mL	23.6 ng/mL
Vitamin B12	180–914 pg/mL	115 pg/mL

TABLE 2: Laboratory investigations showing elevated inflammatory markers and vitamin deficiencies

CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate.

In view of the acute neurological deterioration and the overall clinical findings, possible viral encephalitis was also considered in the differential diagnosis.

Accordingly, Vitamin D and vitamin B12 supplementation was added to address the identified deficiencies, while aspirin and atorvastatin (75/20 mg combination) were prescribed for secondary prevention in view of the acute infarct identified on MRI. Additionally, empiric antiviral therapy with acyclovir (500 mg three times daily) and broad-spectrum antibiotics, including ceftriaxone (2 g twice daily) and vancomycin (500 mg twice daily), were initiated. Despite these interventions, the persistence of altered mental status raised concern for multifactorial encephalopathy.

To investigate potential hepatic involvement, serial liver function tests were performed throughout the hospital stay. No significant abnormalities in liver function were detected, apart from transient mild bilirubin elevation during the initial assessment as presented in Table *3*.

LFT parameter	Biological reference range	Investigations			
		I	II	III	IV
Total Bilirubin	0-1.2 mg/dL	1.4 mg/dL	0.5 mg/dL	0.6 mg/dL	0.6 mg/dL
Direct Bilirubin	0-0.2 mg/dL	0.4 mg/dL	0.2 mg/dL	0.2 mg/dL	0.3 mg/dL
Serum Glutamic Pyruvic Transaminase (SGPT)	15-40 U/L	17 U/L	18 U/L	16 U/L	16 U/L
Serum Glutamic-Oxaloacetic Transaminase (SGOT)	15-35 U/L	29 U/L	28 U/L	25 U/L	15 U/L
Alkaline Phosphatase (ALP)	53–128 U/L	61 U/L	92 U/L	89 U/L	80 U/L

TABLE 3: Serial liver biochemical parameters and their reference ranges

LFT: Liver function test.

A serum protein profile was assessed and was within normal limits, with a serum albumin level of 3.7 g/dL (reference range: 3.5-5.2 g/dL). Additionally, CT imaging of the abdomen revealed no significant abnormalities. Other routine investigations, including complete haemogram, renal function tests (RFTs), coagulation profile (INR), serum creatine-kinase and complete urine analysis, were within normal limits. Urine culture showed no bacterial growth.

Over the subsequent days, the patient developed increasing somnolence, peripheral ankle oedema, worsening cognitive impairment, and constipation. Symptomatic treatments included a laxative and purgative preparation (Duphalac Bulk - containing lactulose, wheat dextrin, fructo-oligosaccharides, and polydextrose) to relieve constipation and furosemide for peripheral oedema. During furosemide administration, serum electrolyte levels were monitored to identify potential electrolyte disturbances. Serial measurements revealed a decline in serum potassium levels monitored on consecutive days, as presented in Table *4*, following which furosemide was discontinued and oral potassium supplementation with Potklor syrup (15 mL diluted in one glass of water, three times daily; each 15 mL containing 20 mEq of potassium) was initiated.

Serum electrolyte	Biological reference range	Investigations				
		I	II	III	IV	V
Sodium (Na^+)	136-145 mmol/L	137 mmol/L	140 mmol/L	137 mmol/L	140 mmol/L	137 mmol/L
Potassium (K^+)	3.6-5.1 mmol/L	3.0 mmol/L	3.3 mmol/L	3.7 mmol/L	4.0 mmol/L	4.1 mmol/L
Chloride (Cl^-)	98-107 mmol/L	99 mmol/L	104 mmol/L	100 mmol/L	101 mmol/L	98 mmol/L

TABLE 4: Serial serum electrolyte levels during furosemide therapy and following potassium chloride supplementation

Serum potassium levels subsequently showed gradual improvement, following which Potklor syrup was discontinued. Low-dose risperidone (0.5 mg twice daily) was also administered for behavioural disturbances. Antihypertensive therapy was modified, with cilnidipine discontinued due to suspected drug-induced peripheral ankle oedema and nifedipine initiated in its place [13].

Pimavanserin (34mg once daily) was subsequently initiated to manage persistent psychotic symptoms. However, the patient's clinical condition continued to deteriorate, prompting consideration of drug-induced sedation and ongoing metabolic or neurological pathology as potential contributing factors.

Despite extensive diagnostic evaluations, empirical treatment for suspected infectious and neurological conditions, and continued symptomatic management at the initial hospital, the patient's clinical condition progressively deteriorated, with persistent altered sensorium and worsening neuropsychiatric manifestations. After 23 days of hospitalisation, the patient was transferred to the medical intensive care unit of a critical care hospital for further evaluation and management.

Definitive diagnosis and management

Upon reviewing the patient's clinical course, prior investigations, neuroimaging findings, and response to treatment, the treating physician suspected that an underlying metabolic disturbance might be contributing to the persistent encephalopathy, a possibility that had not yet been explored. A serum ammonia level was therefore requested as part of the further diagnostic evaluation. The investigation revealed a markedly elevated serum ammonia concentration of 497.7 µg/dL (reference range: 27.2-102 µg/dL), supporting the diagnosis of hyperammonaemia-associated encephalopathy.

Following the identification of hyperammonaemia (497.7 µg/dL; approximately 292 µmol/L), urgent ammonia-lowering therapy was initiated. Given the marked elevation and the patient's neurological deterioration, haemodialysis was undertaken to promote ammonia clearance, alongside supportive care. Pharmacological treatment consisted of oral lactulose (25 mL thrice daily; 3.335 g/5 mL formulation), targeted to achieve two to three soft stools per day, and rifaximin (550 mg twice daily). Serum ammonia levels declined progressively, from 497.7 µg/dL at presentation to 98.4 µg/dL after three sessions of haemodialysis.

After ammonia-lowering therapy was initiated, the patient demonstrated progressive clinical improvement, becoming conscious, alert, and able to follow commands. His neurological status continued to improve during hospitalisation, and he was subsequently considered clinically stable for discharge. At the time of discharge, the patient was prescribed oral levetiracetam 500 mg twice daily, levodopa-carbidopa (Syndopa Plus 125 mg) once daily, Lactulose syrup was titrated down from the initial dose of 25 mL three times daily to 25 mL twice daily (3.335 g/5 mL formulation), and rifaximin 550 mg twice daily. The patient's existing antihyperglycaemic and antihypertensive medications were also continued as part of the discharge regimen. At follow-up 10 days after discharge, serum ammonia had fallen further to 70.7 µg/dL. The serial changes in serum ammonia after successive haemodialysis sessions and at post-discharge follow-up are shown in Figure *1*.

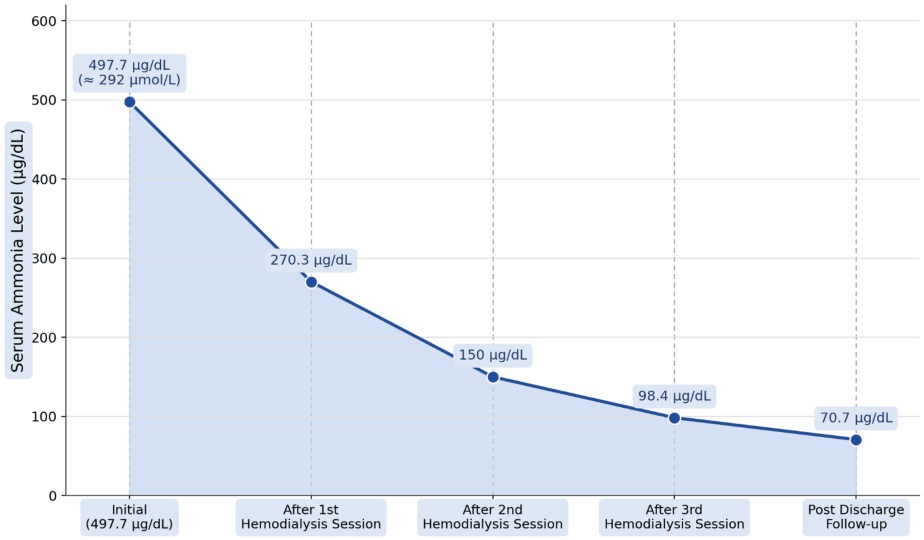


FIGURE 1: Serial trend of serum ammonia levels during ammonia-lowering treatment and subsequent follow-up

Consolidated summary of clinical evaluation and management

Table *5* summarizes the patient's clinical course in chronological order, including the progression of neurological manifestations, the evolving diagnostic considerations, key investigations, and the corresponding treatments, from admission through follow-up.

Hospitalisation phase	Clinical course and diagnostic evaluation	Therapeutic interventions and medication changes
	A 77-year-old male patient was admitted with a 20-day history of progressive behavioural changes, confusion, irritability, irrelevant speech, and memory disturbances. The history also included a five to six-month duration of slow-stepping gait, bilateral hand tremors, muscular rigidity, and difficulty walking. Urinary	Initiation of intravenous thiamine (200 mg three times daily), pantoprazole, ondansetron, lorazepam for agitation/possible alcohol withdrawal, and levetiracetam (500 mg twice

Day 1 – Admission to the initial hospital	incontinence and an episode of tongue biting were reported before admission. The patient had a history of chronic alcohol use, hypertension, and type 2 diabetes mellitus. Initial examination revealed stupor, incoherent speech, shuffling gait, and disorientation to time, place, and person. Initial laboratory investigations revealed mildly elevated ESR and mild hyperbilirubinemia and the Initial clinical considerations included alcohol-related neuropsychiatric manifestations and Parkinsonism.	daily) for seizure prophylaxis. Levodopa 100 mg–carbidopa 25 mg (in two divided doses) was initiated for suspected parkinsonian features. Insulin therapy was initiated for glycaemic control, and cilnidipine was administered for antihypertensive management. Ursodeoxycholic acid was prescribed in view of mild hepatic dysfunction.
Early hospitalisation – Neurological evaluation	MRI of the brain revealed an acute infarct in the left capsuloganglionic region, diffuse cerebral atrophy, and chronic small-vessel ischemic changes. Further laboratory investigations revealed elevated inflammatory markers and deficiencies of vitamin B12 and vitamin D	Vitamin B12 and vitamin D supplementation initiated. Aspirin and atorvastatin commenced for secondary stroke prevention.
Evaluation for suspected infection	In view of the acute neurological deterioration, persistent altered sensorium, and elevated inflammatory markers, an infective etiology, including possible viral encephalitis, was considered.	Empirical antimicrobial therapy was initiated with acyclovir (500 mg three times daily), ceftriaxone (2 g twice daily), and vancomycin (500 mg twice daily).
Subsequent hospitalisation – Evaluation of hepatic and systemic parameters	Serial liver biochemical and other systemic laboratory investigations were performed at multiple time points during hospitalisation to monitor the patient's clinical and biochemical parameters. Liver biochemical investigations showed no significant abnormalities apart from transient mild bilirubin elevation. The serum protein profile, complete hemogram, renal function tests, complete urinalysis, serum creatine kinase, coagulation profile, and urine culture were within normal limits, with the urine culture showing no bacterial growth. Additionally, CT imaging of the abdomen revealed no significant abnormalities.	Supportive management was continued while further evaluation was undertaken.
Later hospitalisation – Progressive clinical deterioration and supportive management	The patient subsequently developed increasing somnolence, worsening cognitive impairment, peripheral ankle edema, constipation, and persistent behavioural and psychotic manifestations. Serial electrolyte monitoring revealed a decline in serum potassium levels during furosemide therapy, with subsequent improvement following potassium supplementation.	Duphalac Bulk initiated for constipation. Furosemide administered for peripheral edema and subsequently discontinued following the decline in serum potassium levels. Oral potassium supplementation with Potklor syrup was initiated and subsequently discontinued following improvement in potassium levels. Cilnidipine discontinued due to suspected medication-associated peripheral ankle edema and replaced with nifedipine. Low-dose risperidone (0.5 mg twice daily) initiated for behavioural disturbances. Pimavanserin (34 mg once daily) subsequently introduced for persistent psychotic symptoms.
After 23 days at the initial hospital – Transfer to the critical care hospital (Day 24)	The patient's clinical condition continued to deteriorate, with persistent altered sensorium and worsening neuropsychiatric manifestations. Following 23 days of hospitalization at the initial hospital, the patient was transferred to the medical intensive care unit of another critical care hospital for further evaluation and management.	The patient was transferred for further diagnostic assessment and management of persistent encephalopathy.
Following transfer – Definitive diagnosis of hyperammonaemia	In view of persistent unexplained encephalopathy, serum ammonia was measured and found to be markedly elevated at 497.7 µg/dL (approximately 292 µmol/L; reference range: 27.2–102 µg/dL), supporting the diagnosis of hyperammonaemia-associated encephalopathy.	Haemodialysis was initiated, alongside lactulose (25 mL orally thrice daily; 3.335 g/5 mL formulation), targeting 2–3 soft stools per day, and rifaximin (550 mg twice daily).
Clinical improvement and follow-up	The patient demonstrated progressive clinical improvement, becoming conscious, alert, and able to follow commands.	Following ammonia-lowering treatment, he was considered clinically stable for discharge and continued to show improvement at the 10-day post-discharge follow-up.

TABLE 5: Chronological summary of the clinical course, diagnostic evaluation, and therapeutic interventions during hospitalisation

CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; MRI: Magnetic resonance imaging; INR: International normalized ratio; RFT: Renal function test; CT: Computer tomography.

The details of key medications administered during the patient's hospital stay, including their doses.

S. No.	Drug name	Dose	Route of administration (ROA)	Frequency	Start day	Stop day
1	Inj. Lorazepam	0.5 mg	IV	OD	Day 1	Day 14
2	Inj. Levetiracetam	500 mg	IV	BD	Day 1	Ongoing at discharge
3	Tab. Syndopa	100 mg + 25 mg	RTF	In two divided doses	Day 1	Ongoing at discharge
4	Tab. Ursodeoxycholic acid	300 mg	RTF	BD	Day 1	Day 10
5	Inj. Acyclovir	500 mg	IV	TID	Day 5	Day 11
6	Inj. Ceftriaxone	2 g	IV	BD	Day 5	Day 13
7	Inj. Vancomycin	500 mg	IV	BD	Day 5	Day 13
8	Syp. Duphalac Bulk	10 mL	RTF	TID	Day 14	Day 18
9	Inj. Furosemide	20 mg	IV	OD	Day 15	Day 21
10	Tab. Risperidone	0.5 mg	Oral	BD	Day 15	Day 22
11	Tab. Pimavanserin	34 mg	RTF	OD	Day 16	Ongoing at discharge
12	Syp. Lactulose	25 mL (3.335 g/5 mL formulation)	RTF	TID	Day 24	Ongoing at discharge
13	Tab. Rifaximin	550 mg	RTF	BD	Day 24	Ongoing at discharge

TABLE 6: List of key medications and their treatment durations

OD: Once daily; BD: Twice daily; TID: Three times daily; IV: Intravenous; PO: Per oral; RTF: Ryle's tube feeding.

Discussion

This case highlights the diagnostic complexity of hyperammonaemia presenting as an acute neuropsychiatric syndrome in an elderly patient with multiple comorbidities. The clinical trajectory was marked by progressive encephalopathy, initially attributed to alcohol use disorder, psychiatric illness, cerebrovascular disease, and possible infectious etiologies. The eventual identification of markedly elevated serum ammonia levels late in the clinical course underscores a critical diagnostic oversight and reflects a broader challenge in recognising non-hepatic or atypical hyperammonaemia in adult populations [10,14].

A central issue in this case was phenotypic overlap. The patient exhibited confusion, hallucinations, irritability, and cognitive decline-features that are commonly encountered in delirium, dementia, alcohol withdrawal, and primary psychiatric disorders [5,6]. Additionally, neuroimaging demonstrated an acute infarct and chronic ischemic changes, which further anchored the diagnostic reasoning toward a cerebrovascular etiology. While these findings were clinically relevant, they did not fully account for the rapidly progressive and fluctuating neurological deterioration, which is more characteristic of metabolic encephalopathy [5,8]. The coexistence of cerebrovascular pathology and metabolic disturbance therefore presented a diagnostic challenge, as both conditions may have contributed to the patient's neurological manifestations.

From a pathophysiological standpoint, ammonia readily crosses the blood-brain barrier and is detoxified in astrocytes via conversion to glutamine [15,16]. Excess ammonia leads to intracellular glutamine accumulation, resulting in osmotic astrocyte swelling, cerebral oedema, and impaired neuronal signaling

[15,16]. Furthermore, ammonia disrupts neurotransmitter balance, particularly glutamatergic and gamma-aminobutyric acid (GABA)ergic pathways, contributing to altered consciousness and behavioural disturbances [15,16]. These mechanisms explain the patient's progression from agitation and hallucinations to somnolence and reduced responsiveness observed between days six and 10 of hospitalisation.

Importantly, the absence of overt hepatic failure suggests that hyperammonaemia in this patient may have arisen through non-cirrhotic or multifactorial mechanisms. Chronic alcohol consumption may have contributed to impaired hepatic mitochondrial function and altered urea cycle activity, potentially compromising ammonia detoxification even in the absence of advanced cirrhosis. Furthermore, exposure to multiple medications, including sedatives, antipsychotics, and anticonvulsants, may have aggravated central nervous system depression and complicated the clinical assessment. Concurrent infection, catabolic stress, and possible nutritional deficiencies may also have contributed to increased ammonia production or impaired clearance [7,9].

Despite these potential contributors, the underlying cause of the hyperammonaemia could not be determined with certainty. Chronic alcohol use and nutritional deficiencies were regarded as relevant background factors, but a direct link between either of them and the ammonia elevation could not be established. Routine abdominal CT showed no significant abnormalities, and there was no evidence of urinary tract infection. Further evaluation for specific inborn errors of metabolism and occult portosystemic shunting was not undertaken. Overall, the available clinical and investigative findings suggest that the hyperammonaemia may have involved several interacting factors, although its precise pathophysiological basis remains uncertain.

In addition to the metabolic disturbance, the patient's neurological presentation may have been influenced by coexisting cerebrovascular disease and pharmacological burden. MRI findings of an acute left capsuloganglionic infarct, diffuse cerebral atrophy, and chronic small-vessel ischaemic changes may have contributed to the patient's cognitive and neurological manifestations. Furthermore, the patient received multiple medications during hospitalisation, including sedatives such as lorazepam, antipsychotics such as risperidone, and antiparkinsonian medication, levodopa/carbidopa. The cumulative effects of sedative and psychotropic medications may have further impaired cognition and alertness [17]. This pharmacological burden, in combination with the underlying cerebrovascular pathology, may have compounded the altered sensorium and obscured the clinical trajectory, making it challenging to distinguish the manifestations of hyperammonaemic encephalopathy from those associated with other neurological and medication-related factors.

Another notable feature of this case was the delay in measuring serum ammonia during the initial hospitalisation, despite persistent, unexplained encephalopathy. After the patient was transferred to a critical care hospital on day 24, the treating physician reconsidered the differential diagnosis and looked for a metabolic cause, which led to the identification of severe hyperammonaemia. Non-hepatic hyperammonaemia may be under-recognised in clinical practice, particularly in patients without obvious liver disease, and this can delay both ammonia measurement and diagnosis [8]. This case underscores that serum ammonia should be considered early in the evaluation of unexplained altered mental status, especially when the clinical course is disproportionate to the structural findings or fails to respond to standard therapy [8,10].

The therapeutic response further supports the clinical relevance of hyperammonaemia in this patient. The management approach involved a combination of haemodialysis, lactulose, and rifaximin, addressing both systemic ammonia clearance and intestinal ammonia production. Lactulose and rifaximin facilitate the reduction of intestinal ammonia absorption and production, while haemodialysis provides an additional means of systemic ammonia removal (Master's Thesis: Meier C. Non-cirrhotic Hyperammonemia and Adult-Onset Metabolic Disorders: Under-Recognised Presentation Among Emergency Clinicians; 2024) [5,7]. The progressive improvement in serum ammonia levels observed during treatment, alongside the patient's favourable neurological recovery, may be associated with the potential reversibility of hyperammonaemic encephalopathy [18]. However, given the coexisting cerebrovascular pathology, multiple medication exposures, and other comorbidities, the neurological improvement may also reflect the combined effects of ammonia-lowering therapy and concurrent supportive care. This case highlights the value of an individualised approach that treats hyperammonaemia while accounting for the other possible contributors to encephalopathy, particularly when the underlying etiology remains uncertain.

This case also illustrates the risk of diagnostic anchoring and premature closure. Initial attribution of symptoms to alcohol use disorder and psychiatric illness may have delayed consideration of metabolic causes. As the clinical picture evolved, additional diagnoses - including viral encephalitis and Parkinson's disease - were entertained, reflecting diagnostic uncertainty but also contributing to therapeutic complexity. A more structured approach to encephalopathy, incorporating early metabolic screening, may have expedited diagnosis [7].

However, some limitations of this case should also be acknowledged. The exact quantity, frequency, and duration of the patient's alcohol consumption could not be established. Although brain MRI identified an

acute infarct in the left capsuloganglionic region, the precise age and temporal relationship of the infarct to the onset of neurological manifestations could not be determined. Furthermore, EEG evaluation was not conducted, limiting the ability to exclude non-convulsive seizure activity. Although routine hepatic and abdominal evaluations did not reveal significant abnormalities, dedicated vascular imaging to exclude an occult portosystemic shunt was not performed. Further metabolic investigations to explore potential underlying causes of non-hepatic hyperammonaemia were also unavailable. These limitations restrict the ability to establish the precise aetiology and relative contribution of hyperammonaemia to the patient's encephalopathy.

Conclusions

Hyperammonaemia is an important and potentially reversible cause of acute encephalopathy that may present with nonspecific neuropsychiatric symptoms, particularly in elderly patients. This case highlights the importance of considering serum ammonia estimation early in the diagnostic workup of unexplained altered mental status. Timely recognition and appropriate ammonia-lowering treatment may facilitate clinical recovery and improve neurological outcomes. The underlying etiology of hyperammonaemia in this patient remained uncertain and may have involved multiple contributing factors, underscoring the complex and multifactorial nature of hyperammonaemic encephalopathy.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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Disclosures

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