

## CASE REPORTS/CLINICAL VIGNETTES

## Hyperammonemic Coma—Barking Up the Wrong Tree

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Hepatic encephalopathy and myxedema coma share clinical features: coma, ascites, anemia, impaired liver functions, and a “metabolic” electroencephalogram (EEG). Hyperammonemia, a hallmark of hepatic encephalopathy, has also been described in hypothyroidism. Differentiation between the 2 conditions, recognition of their possible coexistence, and the consequent therapeutic implications are of utmost importance. We describe a case of an 82-year-old woman with a history of mild chronic liver disease who presented with hyperammonemic coma unresponsive to conventional therapy. Further investigation disclosed severe hypothyroidism. Thyroid hormone replacement resulted in gain of consciousness and normalization of hyperammonemia. In patients with an elevated ammonia level, altered mental status, and liver disease, who do not have a clear inciting event for liver disease decompensation, overwhelming evidence of hepatic decompensation, or who do not respond to appropriate therapy for hepatic encephalopathy, hypothyroidism should be considered and evaluated.

**KEY WORDS:** hepatic encephalopathy; myxedema coma; urea cycle; hyperammonemia; autoimmune polyglandular syndrome type 2; autoimmune hepatitis.

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## INTRODUCTION

Myxedema coma is a rare syndrome that represents the extreme expression of hypothyroidism. The typical patient presenting with myxedema coma is a woman in her 70s and the cardinal manifestation is deterioration of mental status. Physical findings often include hypothermia without shivering, bradycardia, hypoventilation, macroglossia, hoarseness, dry skin, and delayed tendon reflexes; if hypothyroidism is long standing, there will also be accumulation of fluid rich in mucopolysaccharides in extracellular space manifesting as peripheral nonpitting edema, ascites, pleural and pericardial

effusion. Routine laboratory evaluation may indicate anemia, hyponatremia, hypercholesterolemia, increased serum lactate dehydrogenase and creatine kinase. Typical electrocardiogram findings are varying degrees of blocks, low voltage, prolonged QT interval, and flattened or inverted T waves. Finally, the EEG may show a pattern typical to metabolic coma, including triphasic waves.<sup>1</sup>

Hepatic encephalopathy is a metabolic coma, the hallmark of which is hyperammonemia. Although not all patients with hepatic encephalopathy present with hyperammonemia, and hyperammonemia is not pathognomonic for hepatic encephalopathy, the common practice is to consider patients with a liver disease, hyperammonemia, and coma as suffering from hepatic encephalopathy.

We report a case of hyperammonemic coma unresponsive to conventional therapy. Further investigation disclosed severe hypothyroidism. Thyroid hormone replacement resulted in gain of consciousness and normalization of hyperammonemia.

The differentiation between myxedema coma and hepatic encephalopathy, conditions which share many similarities, is of utmost importance and carries therapeutic implication.

## Case Report

An 82-year-old woman was admitted to the hospital in a state of coma. She had been alert and functioning until 1 week before admission, when she gradually became lethargic and unresponsive.

The patient had a history of hypothyroidism, vitiligo, essential hypertension, depressive disorder, and mild impairment of liver function, which had not been investigated in the past. Her chronic medication included amlodipine, sertraline, furosemide, ramipril, atenolol, and levothyroxine.

On physical examination she was in a state of coma with a Glasgow Coma Score of 5. Her rectal temperature was 36.1°C, heart rate was 56 beats per minute, blood pressure 118/70 mmHg, and respiration rate 20 per minute.

Examination of the abdomen revealed no organomegaly or ascites. No clubbing, spider angiomas, or palmar erythema were noted. Neurologically, she was unresponsive, Achilles tendon reflexes were absent bilaterally, and flapping tremor was not elicited. The rest of the physical examination was unremarkable.

Blood tests revealed macrocytosis of 110  $\mu\text{m}^3$  (78–102  $\mu\text{m}^3$ ), severe vitamin B12 deficiency 74 pg/mL (200–800 pg/mL), and no antiparietal cell antibodies. Creatine kinase was markedly elevated, 1,020 U/L (40–150 U/L), and mild abnormalities in enzymatic, cholestatic, and biosynthetic liver

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function tests were noted: aspartate aminotransferase (AST) 232 U/L (0–35 U/L), alanine aminotransferase (ALT) 65 U/L (0–35 U/L), gamma glutamyl transferase (GGT) 69 U/L (1–94 U/L), alkaline phosphatase (ALP) 142 U/L (30–120 U/L), bilirubin total 0.9 mg/dL (0.3–1 mg/dL), international normalized ration (INR) 1.44, albumin 2.4 g/dL (3.5–5.5 g/dL). Her serum ammonia level was distinctly elevated, 194  $\mu\text{mol/L}$  (6–47  $\mu\text{mol/L}$ ). Urine toxicity screen was negative. Thyroid-stimulating hormone (TSH) level was ordered. Lumbar puncture results were not indicative of infection. A computed tomography scan of the brain was normal. An electroencephalogram showed a “metabolic pattern” of generalized slowing and triphasic waves. Doppler ultrasound revealed a liver of normal span, with coarse nonhomogenous texture. Hepatic veins were normal in diameter and no hepatofugal flow in the portal vein was detected. A liver scan demonstrated colloid shift to the spleen and bone marrow, consistent with chronic liver disease. Further evaluation of liver disease revealed negative serology for HIV, Hepatitis B and C viruses, *Coxiella burnetii* phase 1 and 2, antismooth muscle, anti-LKM, antisoluble liver antigen and antimitochondrial antibodies. An elevated antinuclear factor titer, 1:640 (negative at 1:40) and hypergammaglobulinemia, IgG concentration of 3,200 mg/dL (614–1,295 mg/dL) were suggestive of autoimmune hepatitis type 1. At this point a drop in blood pressure was noted and was evaluated by a 1-mcg ACTH test, which revealed adrenal insufficiency: cortisol 0 minute—150 nmol/Liter (171–536 nmol/L at 8:00 A.M.) and cortisol 30 minutes—200 nmol/L (>550 nmol/L or an increase of > 200 nmol/L). Treatment of hepatic encephalopathy and adrenal insufficiency with lactulose, neomycin, and hydrocortisone was initiated. Blood pressure normalized; however, only a mild improvement in the state of consciousness was noticed; liver function test results worsened and her ammonia level did not change. Thyroid function test results, received 3 days after admission, revealed severe hypothyroidism (thyroid stimulating hormone 49  $\mu\text{U/mL}$  [0.5–4.7  $\mu\text{U/mL}$ ] and free T4 <2.57 pmol/L [10.3–35 pmol/L]). Antithyroid peroxidase and antithyroglobulin antibody were negative. Ultrasound examination displayed an enlarged thyroid gland with multiple ill-defined nodules characteristic of Hashimoto’s Thyroiditis. Treatment with intravenous levothyroxine 100  $\mu\text{g}$  was commenced and resulted in a rapid (within 24 hours) regain of consciousness and a drop in serum ammonia level to 64  $\mu\text{g/dL}$ . Soon thereafter the EEG pattern normalized, CK and liver function test results returned to baseline. After regaining full consciousness, the patient reported that she had discontinued levothyroxine therapy 4 months before admission.

## DISCUSSION

We present a patient with hypothyroidism, adrenal insufficiency, suspected autoimmune hepatitis and atrophic gastritis—a combination that is consistent with autoimmune polyglandular syndrome type 2. Discontinuation of levothyroxine therapy resulted in hyperammonemic coma with severe hypothyroidism that was unresponsive to lactulose and neomycin, but which was resolved after thyroid hormone replacement.

In this patient hyperammonemic coma may represent an atypical case of myxedema coma in the setting of liver disease. An alternative explanation may be that hypothyroidism was a precipitant for decompensation of liver disease and thus

hyperammonemic coma was the manifestation of hepatic encephalopathy.

Myxedema coma and hepatic encephalopathy share many clinical features: coma, ascites, pleural effusion, peripheral edema, clubbing, anemia, hypercholesterolemia, hyponatremia, hypoglycemia, elevated liver enzymes level including lactate dehydrogenase and metabolic pattern on EEG.

An EEG pattern of triphasic waves, elevated liver enzymes, and hyperammonemia are rare and unfamiliar features of myxedema coma, which may divert the clinical judgment from the correct diagnosis and be confused with hepatic encephalopathy.

An EEG pattern of triphasic waves was first described in hepatic encephalopathy by Bickford and Butt in 1955 and became synonymous with hepatic encephalopathy (HE).<sup>2</sup> Nevertheless, triphasic waves are not pathognomonic for hepatic encephalopathy and have been reported in other metabolic encephalopathies, the most common of which are renal failure and anoxic injury.<sup>3</sup> To the best of our knowledge, only 1 report in the literature describes triphasic waves during hypothyroidism.<sup>4</sup>

Elevated liver enzymes may reflect the effect of hypothyroidism on the liver or be related to a concomitant liver disease. The association of hypothyroidism and liver diseases including autoimmune hepatitis, primary biliary cirrhosis, and chronic hepatitis C is not uncommon (6–13%).<sup>5–7</sup>

The liver is not considered a hormonally regulated organ. Nevertheless, hypothyroidism has a vast effect on liver function and structure. Thyroid hormones regulate hepatic mitochondrial catabolism. An increase in liver enzymes concentration, AST more than ALT, is often found.<sup>8</sup> An animal study in hypothyroid rats has, however, shown that, whereas ALT function (production of pyruvate) increases, AST function (production of oxaloacetate) decreases.<sup>9</sup> Microscopic changes including central congestive fibrosis have been described in myxedema ascites.<sup>10</sup> In our patient, elevated liver enzymes, AST more than ALT, may have been a consequence of either hypothyroidism or autoimmune hepatitis. A high titer of antinuclear antibody (ANA) and hypergammaglobulinemia in the setting of autoimmune polyglandular syndrome type 2 are suggestive of autoimmune hepatitis, yet a definite diagnosis was not reached, as the patient declined a liver biopsy.

A retrospective review of the medical history of the patient confirmed that increased plasma levels of liver enzymes in the presence of normal TSH had repeatedly been recorded several years before admission. Hence, in the presence of euthyroidism, it is reasonable that some other smoldering chronic liver disease, most probably autoimmune hepatitis, was present before the occurrence of hypothyroidism.

The most common cause of hyperammonemia in adults is liver cirrhosis. Rare causes of hyperammonemia include drug toxicity (e.g., valproic acid, salicylates, and 5 fluorouracil), and urinary tract infection with a urease-producing organism, such as *Klebsiella pneumoniae*, *Proteus mirabilis*, *Corynebacterium* species, or *Staphylococcus* species.<sup>11–13</sup> Hyperammonemia in our patient was at first attributed by us to decompensation of a chronic liver disease. Common precipitants of hyperammonemia in patients with liver cirrhosis are delineated in the table. Evaluation of our patient identified constipation and exacerbation of autoimmune hepatitis to be possible inciting events for hyperammonemia. However, lack of response to lactulose, neomycin and steroids did not support this assumption. Prompt response to thyroid hormone replacement suggested that hyper-

ammonemia was either an atypical manifestation of severe hypothyroidism or that hypothyroidism was the inciting event for liver decompensation and hepatic encephalopathy in the setting of a chronic liver disease.

To date, 4 cases of hyperammonemia and myxedema coma have been described in the literature.<sup>14-17</sup> All reported cases, including ours, describe patients with an undiagnosed or fully compensated liver disease. All cases presented a clinical picture of hyperammonemic coma, unresponsive to lactulose and neomycin therapy, which improved only after thyroid hormone replacement. Precipitants for hepatic encephalopathy were not evident.

Hyperammonemia has also been described in 3 patients with hypothyroid myopathy and no known previous liver disease, in whom a concomitant increase in transaminases, and hyperammonemia attributed to increased catabolism of muscle, completely resolved after gaining euthyroidism. Hyperammonemia in this setting did not result in any neurological impairment.<sup>18</sup>

Hyperammonemia in hypothyroidism may be explained by pathophysiological studies of the urea cycle in this condition. In a rat liver model, hypothyroidism was associated with an increased urea synthesis, attributed to an increase in urea cycle enzyme activity.<sup>9,19</sup> However, when studied in hypothyroid women, a decreased urea synthesis rate, in comparison with values measured in euthyroidism, was found.<sup>20</sup> Inefficient urea synthesis during hypothyroidism, as was demonstrated in vivo, is expected to result in an increased ammonia level. Moreover, an increased load of nitrogen products during hypothyroidism may aggravate the hyperammonemic state. Several mechanisms can explain the suspected increased nitrogen load: 1) Decreased protein synthesis and increased protein catabolism (attributed to a decrease in growth hormone and to hypothyroid myopathy)<sup>21,22</sup>; 2) Decreased intestinal motility that promotes bacterial production of ammonia and augments its absorption; and 3) decreased glutamine synthetase activity that may diminish utilization of glutamine by the urea cycle in the liver.<sup>9</sup>

Despite the available information on mechanisms by which hypothyroidism may impair liver functions, the exact role of hypothyroidism in hyperammonemic coma as a direct inciting event or a precipitant for decompensation of liver disease has not yet been resolved.

It is of utmost importance to bear in mind the possibility of combined hypothyroidism and liver disease in hyperammonemic coma and to carefully search for clues to each of these conditions in physical examination, laboratory results, and imaging studies. A careful physical examination may reveal findings typical of myxedema such as dry cool skin, coarse, sparse hair, and macroglossia, or findings suggestive of cirrhosis: jaundice, spider angiomas, caput medusa, Dupuytren's contracture, palmar erythema, fetor hepaticus, gynecomastia, hair loss, paper money skin, parotid enlargement, clubbing, and Terry's nails (white nails), all of which were missing in our patient. Peripheral edema is typically nonpitting in myxedema, in contrast to the typical pitting edema in liver disease. Tendon reflexes are delayed in myxedema coma as was noticed in our patient, whereas hyperreflexia, asterixis, and flapping tremor are characteristic of hepatic encephalopathy. Laboratory work-up may reveal pancytopenia caused by hypersplenism, a characteristic of cirrhosis or elevated CPK and macrocytic anemia more typical to myxedema. Finally, imaging studies

may help demonstrate pericardial effusion or an enlarged thyroid gland, characteristic of myxedema or a nonhomogenous liver with hepatofugal flow in hepatic veins, characteristic of cirrhosis.

In conclusion: in patients with an elevated ammonia level, altered mental status, and liver disease, who do not have a clear inciting event for decompensation of liver disease, overwhelming evidence of hepatic decompensation, or who do not respond to appropriate therapy for hepatic encephalopathy, hypothyroidism should be considered and evaluated.

## COMMON PRECIPITANTS OF HEPATIC ENCEPHALOPATHY

Increased nitrogen load:

Excess of dietary protein  
Azotemia  
Constipation

Electrolytes and metabolic imbalance:

Hypokalemia  
Alkalosis  
Hypoxia  
Hyponatremia  
Hypovolemia

Drugs:

Narcotics, tranquilizers, sedatives, diuretics

Miscellaneous:

Infection  
Surgery  
Superimposed acute liver disease  
Progressive liver disease  
Portal systemic shunt

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