Can *Klebsiella* sepsis lead to hyperammonemic encephalopathy with normal liver function?

Sir,

Hyperammonemia as a cause of encephalopathy in a patient with normal liver enzyme levels is unusual.[1,2] Hence, it remains undiagnosed especially in intensive care (ICU) settings.[3] We recently had a patient with *Klebsiella* sepsis and hyperammonemic encephalopathy (HE) with normal liver function tests. We report this unique case after taking informed consent from patient's kin.

A 63-yr-old house-wife presented to our ICU with fever and dysuria for 10 days and impaired level of consciousness with hypotension for 1 day. She was having adequately controlled type-2 diabetes mellitus for last 10 years and hypothyroidism for 3 years.

On examination, her best Glasgow coma score was 9 ($E_3V_2M_4$) with no signs of meningeal irritation. In view of hemodynamic instability trachea was intubated. She was treated with broad spectrum (initially empirical β-lactamase and β-lactamase inhibitor then culture-based carbapenems) antibiotics, mechanical ventilation, enteral nutrition, fluids, and vasoactive agents. On admission liver function test revealed: Albumin 2.8 g/dl, total bilirubin 0.5 mg/dl, AST 37 U/L, ALT 26 U/L, normal INR (maximum1.4), alkaline phosphatase 152 U/l. Her urine culture sent on admission showed growth of *Klebsiella pneumoniae*. Other cultures were sterile. Within 7 days, her urosepsis resolved but her sensorium did not recover. Her renal function, serum electrolytes, arterial blood gases, random blood sugar, perfusion parameters (lactate), thyroid profile were all within normal limits. Repeat liver function tests revealed high alkaline phosphatase (2000 U/l) and γ-glutamyl transferase (670 U/l) levels only with negative viral hepatitis markers (initially hepatitis A, B, C, D, and subsequently hepatitis E also). The patient had neither gastrointestinal bleeding nor on intravenous steroids. Abdominal ultrasonography was not suggestive of chronic liver disease. We did brain magnetic resonance imaging (MRI), which suggested (T1 and T2 axial view) age unrelated cerebral atrophy and empty sella [Figures 1 and 2]. Cerebro-spinal fluid (CSF) showed a normal study (repeated twice). An electroencephalogram showed continuous generalized slowing suggestive of metabolic encephalopathy. In view of raised alkaline phosphatase and glutamyl transferase with MRI picture (suggesting astrocyte loss) gastroenterologist opined for arterial ammonia level. Her arterial ammonia level (sent on ice and processed within 30 minutes) came extremely high [265 μmol/L (normal range 9-33 μmol/L)]. Interestingly, there was no history of any drug intake (like valproate, 5-fluorouracil, salicylate) before and during this hospitalization. Serum M-protein level was also normal. In view of old age and short history, underlying urea cycle enzyme abnormality was not evaluated. We restricted protein intake (0.8 g/kg), initiated dialysis, and started L-carnitine therapy. Her sensorium improved with decreased arterial ammonia level (148 μmol/L). During this period she developed new onset blood stream infection by multi-drug-resistant *K. pneumoniae*. We escalated broad-spectrum antibiotics. Patient, however, developed refractory septic shock and succumbed to her illness. Post-mortem liver biopsy could not be done.

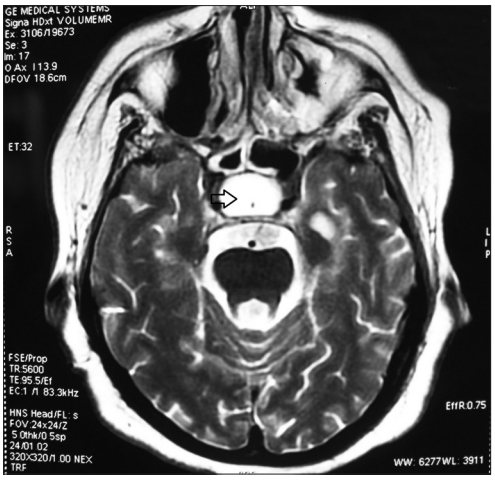

Figure 1: Magnetic resonance imaging (MRI) head T2-weighted axial view showing empty sella (arrowed)

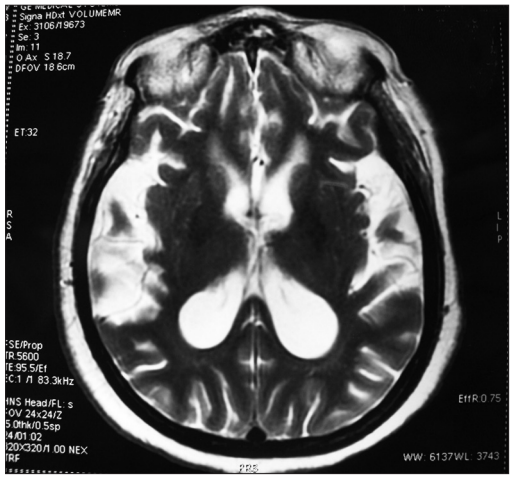

Figure 2: Magnetic resonance imaging (MRI) head T1-weighted axial view showing cerebral atrophy

Normally ammonia produced in body is metabolized and eliminated from body by liver. When ammonia

production is excessive, portal blood-carrying ammonia can bypass liver leads to hyperammonemia.[2] As ammonia is freely permeable through blood-brain barrier, astrocytes metabolize excess ammonia to glutamine with the help of enzyme glutamine synthetase.[2,3] Thus, osmotically active glutamine concentrations increase in brain, leading to astrocytic swelling and destruction. Importantly, astrocytes release inflammatory cytokines (like tumor necrosis factor and interleukins) causing apoptotic astrocyte loss. In HE, neuropathological findings like ventriculomegaly, cerebral cortical atrophy, especially increase in the sulcal depth of the frontal, parietal, regions, and intracranial bleed indicate astrocyte loss.[4] MRI scans in our case were also suggesting astrocyte loss.

HE is usually related with liver dysfunction,[3] drugs (like valproate, salicylate)[5] or malignancies (like multiple myeloma).[2] Due to her old age and short history (as proximal urea cycle disorder is unlikely), we attribute *Klebsiella* sepsis as the most probable reason for HE in our case. *Klebsiella* is a urease-splitting organism. Hyperammonemic coma was described with such urease-splitting organism with anatomical abnormality of lower urinary tract.[2] *Klebsiella* can cause excessive ammonia production and absorption of ammonia in urinary tract leading to hyperammonemia.[6] Hence, we suggest early blood ammonia testing in cases of *Klebsiella* sepsis with encephalopathy in intensive care settings.

Tanmoy Ghatak, Afzal Azim, Sameer Mahindra[1], Armin Ahmed

Departments of Critical Care Medicine and [1]Gastroenterology, Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow, Uttar Pradesh, India

Address for correspondence: Dr. Tanmoy Ghatak, Rammohan Pally, Arambagh, Hooghly-712 601, West Bengal, India.
E-mail: tanmoyghatak@gmail.com

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