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Lesson of the month: carcinoid associated encephalopathy

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Here we present an unusual case of acute encephalopathy which could have been potentially prevented by simple supplementation of tryptophan in a patient with large metastatic carcinoid tumor in the liver.

An 80-year-old man presented to the Acute and Emergency Department with pyrexia (40 C degrees) and right upper abdominal pain radiating to back. Five days before he had undergone radiofrequency ablation (RFA) of 8cm liver lesion secondary to a neuroendocrine carcinoid, but multiple smaller liver lesions were also present. On admission he reported pain over the access site for RFA since the procedure and was associated with nausea and general malaise. However, there was an improvement in symptoms of diarrhoea since RFA. Clinical examination demonstrated that the patient was hypotensive, tachycardic and tachypnoic, with a normal abdominal examination. His initial blood results showed elevated CRP levels, leucopenia and anaemia. To rule out a post-RFA intrahepatic collection, an abdominal CT scan was performed, showing normal post-RFA changes and the patient was started on antibiotics, due to the initial impression of post-procedural sepsis. The blood cultures were positive for *E. coli* and the patient was started on Ertapenem and Metronidazole. He improved after five days and was afebrile, with reduced CRP levels. After 10 days, the patient started becoming confused and drowsy with clinical features of encephalopathy. However, there was no evidence of ongoing sepsis and blood cultures were negative, thus a brain MRI scan and an electroencephalogram (EEG) were performed. The EEG showed a diffuse mixture of theta and delta activities at 1.75-6.5Hz with absent alpha rhythm compatible with metabolic encephalopathy, while the MRI findings were essentially normal. Due to increased confusion and reduced GCS (GCS=9/15), a lumbar puncture was performed, showing no signs of encephalitis. Initially a diagnosis of paraneoplastic neurological syndrome was considered, which is described in patients with carcinoid. However Anti-Yo, Anti-Hu, Anti-Ri, Anti-Voltage gated K Channel, Anti-Glutamic Acid decarboxylase, Anti-NMDA Receptor antibodies were negative. Due to ongoing confusion and without any evidence of sepsis, a diagnosis of metabolic encephalopathy was made,

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Conflicts of Interest

Drs Femminella, Kenny, Sinha and Amlani have no disclosures to report.

based on clinical evidence of persistent encephalopathy, MRI findings (essentially normal), EEG features suggestive of metabolic encephalopathy and negative antineuronal antibodies. At this point, a diagnosis of encephalopathy secondary to low tryptophan was considered, and planned to replace tryptophan while waiting for laboratory results. Blood tryptophan level was low at 24 $\mu\text{mol/L}$ suggesting possible encephalopathy secondary to tryptophan deficiency. After ten days of oral supplementation levels reached normal range. The delay from the RFA to diagnosis of encephalopathy secondary to tryptophan was 7 weeks. Patients made initial improvement for few weeks, however eventually succumbed to death in the hospital due to pneumonia.

Even though paraneoplastic manifestations of malignant tumour and brain metastatic manifestations can occur in carcinoid patients [1, 2], encephalopathy due to tryptophan deficiency is extremely rare, thus diagnosis of tryptophan deficiency encephalopathy could be easily missed. In carcinoid syndrome with large tumor, there is a 70 fold increase in the utilization of tryptophan, which can cause deficiency over a period of time. Due to the insidious onset of symptoms, the levels of tryptophan are not routinely measured even in metastatic carcinoid disease with large tumors. If these patients are suffering from concurrent infection, usually a diagnosis of delirium secondary to infection is made. However, in this case, patient demonstrated the features of metabolic encephalopathy both clinically and in EEG without any evidence of derangement of usual metabolic parameters. This persistent metabolic encephalopathy prompted further investigation. Moreover, in our patient there was no evidence of metastatic tumor or paraneoplastic neurological syndrome. Previous case report has demonstrated that metabolic encephalopathy associated with carcinoid syndrome had responded to tryptophan replacement therapy [3]. Following tryptophan administration the patient's cognitive state improved significantly. Our patient could have been tryptophan deficient for several weeks before the definite diagnosis of the deficiency was made and the deficiency could have begun immediately after the RFA or might have been precipitated by the RFA. The longterm effect of tryptophan on neuronal function, and whether these effects are reversible needs further investigation. To date, none of the studies on the long-term results of laparoscopic RFA for treating unresectable liver metastases from neuroendocrine tumors has reported tryptophan-related encephalopathy among the possible contributing factor or complication [4, 5].

Tryptophan is a branch chained amino acid that serves as the rate limiting substrate for the production of serotonin [6]; acute tryptophan depletion in healthy volunteers specifically impairs long-term memory performance [7], while long-lasting tryptophan depletion has been described in patients suffering from a metastatic carcinoid tumor [8], resulting in reduced peripheral tryptophan levels and decreased bioavailability for the brain synthesis of serotonin. Approximately 90% of tryptophan catabolism occurs via the kynurenine pathway with subsequent production of kynurenic and quinolinic acids. Both these metabolites affect neurotransmission as glutamate receptor antagonist and agonist, respectively, further suggesting that tryptophan imbalance is strictly linked to neuronal function [9]. Quinolinic acid is also a precursor of niacin (vitamin B3) and the shift of tryptophan metabolism towards serotonin synthesis in carcinoid patients might also result in niacin deficiency, which might contribute to impairment of neuronal function in these patients [10]. We did not

evaluate niacin levels in our patient, which could have helped in further elucidating the aetiology of encephalopathy.

This case highlights the importance of considering tryptophan deficiency in carcinoid syndrome where large carcinoid tumors are present. We recommend routine measurement of tryptophan in patients with large carcinoid tumors, as this could be easily treated by high dose tryptophan orally, which is not expensive preventing unnecessary morbidity and mortality of these patients.

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References

1. Lapeire LD, Tansens A, Lemmens GM, et al. Carcinoid encephalopathy: A single entity or a spectrum of different disorders? *Acta Oncol.* 2010; 49:268–270. [PubMed: 20001498]
2. Tschernatsch M, Dierkes C, Gerriets T, et al. Paraneoplastic neurological syndromes in patients with carcinoid. *Eur J Neurol.* 2008; 15:1390–1394. [PubMed: 19049559]
3. Rosenthal MA. Carcinoid associated encephalitis successfully treated with tryptophan. *J Clin Neurosci.* 2004; 11:66–67. [PubMed: 14642370]
4. Akyildiz HY, Mitchell J, Milas M, et al. Laparoscopic radiofrequency thermal ablation of neuroendocrine hepatic metastases: long-term follow-up. *Surgery.* 2010; 148:1288–1293. discussion 1293. [PubMed: 21134563]
5. Norlen O, Stalberg P, Zedenius J, et al. Outcome after resection and radiofrequency ablation of liver metastases from small intestinal neuroendocrine tumours. *Br J Surg.* 2013; 100:1505–1514. [PubMed: 24037573]
6. Fernstrom JD, Wurtman RJ. Brain serotonin content: physiological dependence on plasma tryptophan levels. *Science.* 1971; 173:149–152. [PubMed: 5581909]
7. Riedel WJ, Klaassen T, Deutz NE, et al. Tryptophan depletion in normal volunteers produces selective impairment in memory consolidation. *Psychopharmacology.* 1999; 141:362–369. (Berl). [PubMed: 10090643]
8. Swain CP, Tavill AS, Neale G. Studies of tryptophan and albumin metabolism in a patient with carcinoid syndrome, pellagra, and hypoproteinemia. *Gastroenterology.* 1976; 71:484–489. [PubMed: 133045]
9. Richard DM, Dawes MA, Mathias CW, et al. L-Tryptophan: Basic Metabolic Functions, Behavioral Research and Therapeutic Indications. *Int J Tryptophan Res.* 2009; 2:45–60. [PubMed: 20651948]
10. Shah GM, Shah RG, Veillette H, et al. Biochemical assessment of niacin deficiency among carcinoid cancer patients. *Am J Gastroenterol.* 2005; 100:2307–2314. [PubMed: 16181385]