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CASE REPORT

Fibrolamellar Hepatocellular Carcinoma Mimicking Ornithine Transcarbamylase Deficiency

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Abstract We report an unusual case of recurrent non-hepatic hyperammonaemic encephalopathy in an adult patient. She had a previous history of treated fibrolamellar hepatocellular carcinoma (FLC). This posed a diagnostic challenge, as she had normal liver function tests and normal looking liver on imaging but with extra hepatic metastases. This case highlights the importance of measuring plasma ammonia levels in all patients presenting with unexplained acute confusion. Clinical awareness of non-hepatic hyperammonaemic encephalopathy can contribute to early diagnosis and timely initiation of life-saving treatment. Delay in treatment results in irreversible brain damage, deep coma and death. Treatment of hyperammonaemia must begin prior to confirmation of aetiology, for a favourable outcome. This case also highlights the need for further research to understand the exact mechanism of hyperammonaemia in hepatocellular carcinoma.

Introduction

Non-hepatic hyperammonaemic encephalopathy in an adult is a diagnostic challenge for the clinician. Its aetiology includes both inherited and acquired causes. Late onset ornithine transcarbamylase (OTC) deficiency is one of the most common inherited urea cycle defects presenting in adult life as hyperammonaemia. Our patient presented with biochemical features of OTC deficiency though this was not confirmed on genetic testing. Rapidly growing hepatic tumours are known to cause hyperammonaemia, however, the exact mechanism remains to be elucidated. Physicians should be aware of this rare complication in order to provide early diagnosis and treatment.

Case Report

A 20-year-old woman was admitted to hospital with an acute onset of confusion and agitation following repeated vomiting. She had an underlying history of fibrolamellar hepatocellular carcinoma(FLC), diagnosed at the age of 14, and initially treated by left lateral hepatectomy. At age 17 she had developed extra hepatic disease recurrence (abdominal lymphadenopathy) but with no recurrent tumour in the liver. She was treated by chemotherapy, which was well tolerated and she remained in partial remission for the succeeding three years. She last received chemotherapy ten months before this admission. Blood tests on admission including liver function, renal function, serum urate, full blood count and coagulation screen were normal. Computed tomography (CT) of head, including CT venogram, and magnetic resonance imaging (MRI) of brain were also normal. Lumbar puncture revealed normal cerebrospinal fluid. No bacterial infection was detected. Toxicology, viral and autoimmune disease screen were negative. A working diagnosis of hepatic encephalopathy was made and she was initially treated with oral lactulose and phosphate enema with resolution of her symptoms. However, she was re-admitted within few weeks of discharge, with similar symptoms. She then had electroencephalography which suggested metabolic encephalopathy with diffuse slowing and high incidence of triphasic waves

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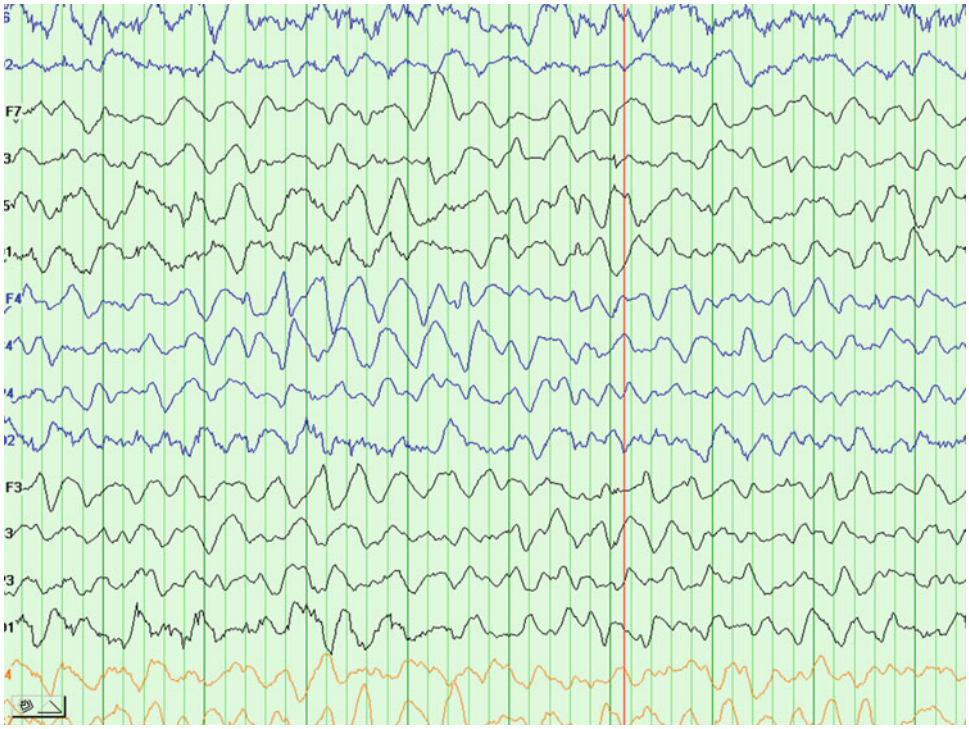

Fig. 1 Electroencephalography showing a diffuse slowing and high incidence of triphasic waves

(Fig. 1). A subsequent plasma ammonia level was 281 μmol/L (<50 μmol/L) with peak ammonia level of 410 μmol/L. CT scan of abdomen (Fig. 2) showed widespread intra-abdominal lymphadenopathy, consistent with progression of her recurrent cancer, encasing blood vessels, but there were no focal hepatic lesions and no portosystemic shunting was evident. Further metabolic investigations revealed high plasma glutamine levels 825 μmol/L (413–690 μmol/L), low ornithine 11 μmol/L (29–125 μmol/L), low citrulline18 μmol/L, arginine113 μmol/L and grossly elevated urinary orotic acid levels 420.3 μmol/mmol creatinine (<3 μmol/mmol creatinine), suggesting an inherited urea cycle disorder namely, ornithine transcarbamylase (OTC) deficiency. Genetic testing, however, did not reveal a pathogenic sequence, variant, or exon deletions/duplication in OTC gene. In addition, there was no relevant family history. She was treated with intravenous sodium phenyl butyrate, sodium benzoate and arginine with good response.

Over the next few months, she had multiple admissions with hyperammonaemic encephalopathy, each time responding well to intravenous sodium benzoate and phenyl butyrate infusion. She was then commenced on regular oral sodium benzoate, phenyl butyrate and arginine. During follow-up, a repeat plasma amino acid levels showed high glutamine 716 μmol/L, low citrulline 23 μmol/L and low arginine 16 μmol/L while urine orotic acid level was very high 687 μmol/mmol creatinine. However later, with improved compliance to ammonia scavenging medication she had no further episode of acute encephalopathy. She was also commenced on palliative chemotherapy with Sorafenib. She remained metabolically stable though her general condition gradually deteriorated due to her underlying malignancy and she passed away in 6 months.

Discussion

Hyperammonaemic encephalopathy is a well-known complication of advanced liver disease. Other causes include rare inherited metabolic disorders such as urea cycle defects and organic acidaemias. It has also been reported in association with drugs like Valproate, porto-systemic shunts, malignancies including multiple myeloma, hepatocellular carcinoma (HCC), following chemotherapy for haematological malignancies, bone marrow transplantation and reconstructive surgeries like bariatric surgery and ureterosigmoidoscopy. Fibrolamellar hepatocellular carcinoma (FLC) is a rare variant of hepatocellular carcinoma of unknown aetiology, arising almost exclusively in a non-cirrhotic liver of young adults and in the absence of chronic viral hepatitis. This patient received conventional treatment comprising liver

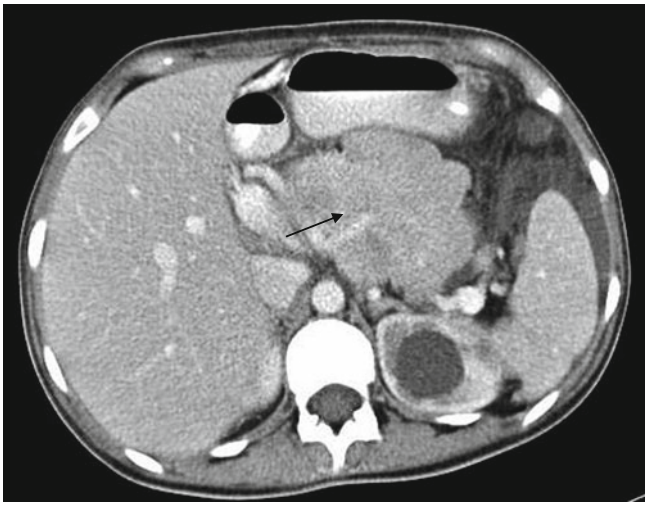

Fig. 2 CT of the abdomen showing epigastric neoplastic mass with encasement of major coeliac axis branches (*arrow*)

resection and upon disease recurrence cytotoxic chemotherapy neither of which precipitated encephalopathy, and she remained well for several years. It was unexpected of her to present with hyperammonaemic encephalopathy with normal liver function and no imaging evidence of hepatic lesion or porto-systemic shunt. Although initial metabolic investigations suggested inherited OTC deficiency, this was not confirmed by DNA analysis. Similar cases have been reported in the literature of patients with FLC (Jeffers et al. 1988; Sethi et al. 2009) presenting with hyperammonaemic encephalopathy, in some cases related to chemotherapy (Chan et al. 2008; Winter et al. 1997). A previous study on rats has shown an inverse relationship between ornithine carbamyl transferase activity and the rate of growth of hepatoma (Weber et al. 1972). It is possible that FLC may release a chemical inhibitor of OTC enzyme or there is increased activity of ornithine decarboxylase. There may be genetic alteration associated with under expression of OTC gene during the course of development of FLC leading to hyperammonaemia.

In view of her deteriorating condition, liver biopsy was not performed to assess OTC enzyme activity.

This case illustrates the diagnostic challenge posed by unexplained encephalopathy with normal routine biochemical, haematological and microbiological studies as well as brain imaging. Such patients should be evaluated thoroughly to identify any treatable cause, including measurement of blood ammonia levels and referral for specialist metabolic assessment. Although the precise mechanism of the development of hyperammonaemia in FLC remains unclear, treatment with ammonia scavenging medication resolves encephalopathy. Further studies are required both at a molecular and biochemical level to determine the cause for the lack of urea cycle expression in hepatic tumour cells causing significant hyperammonaemia.

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Synopsis

Patients with unexplained encephalopathy should also be investigated for hyperammonaemia for early initiation of potentially life-saving treatment.

Details of the Contributions of Individual Authors

Dr R A Sulaiman did the planning, literature search, and wrote the manuscript of this case report.
Dr T G Hiwot reviewed and edited the manuscript.
Guarantor of this article: Dr T G Hiwot

Compliance with Ethics Guidelines

Conflict of Interest

R A Sulaiman and T G Hiwot declare that they have no conflict of interest.

Informed Consent

Patient had signed an informed consent form, giving permission for the publication of this case report. This will be available on request.

Animal Rights

This report does not contain any study with human or animal subjects performed by any of the authors.

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