Case Report

Adult Onset Episodic Encephalopathy Due to Citrin Deficiency—A Case Report

Dipti Baskar, Vathsala Lakshmi, Atchayaram Nalini, Gautham Arunachal[1], Maya Dhattatraya Bhat[2], Nandakumar Dalavaikodihalli Nanjaiah[3], Ravi Yadav, Ravindranadh Chowdary, Pritam Raja, Ambati Mounika, Sharath PS, Seena Vengalil

Departments of Neurology, [1]Human Genetics, [2]Neuroradiology, [3]Neurochemistry, National Institute of Mental Health and Neuro Sciences (NIMHANS), Bengaluru, Karnataka, India

Abstract

Hyperammonemia is a rare cause of adult episodic encephalopathy. Citrin deficiency resulting in citrullinemia type 2 (CTLN2) can lead to recurrent delirium in adults. Here we report a case of adult onset episodic encephalopathy due to citrin deficiency. A 40 years old male presented with one-year history of episodic encephalopathy triggered by high protein and fat diet. He also had chronic pancreatitis and subacute intestinal obstruction which is a novel manifestation of CTLN2. Evaluation showed elevated blood liver enzymes, ammonia, and citrulline. MRI brain showed frontal hyperintensities and bulky basal ganglia which have not been reported. Diagnosis was confirmed by next-generation sequencing which showed a novel variant c. 1591G > A in exon15 of *SLC25A13.* Hyperammonemic syndromes should be considered in differential diagnosis of episodic encephalopathy in adults. This report shows novel features of subacute intestinal obstruction and MRI findings in CTLN2 expanding spectrum of manifestation.

Keywords: Citrullinemia, episodic encephalopathy, hyperammonemia

What is Known

- Citrin deficiency resulting in citrullinemia type 2 (CTLN2) can lead to recurrent delirium in adults.
- Typical clinical features include episodic hyperammonemia with nocturnal delirium, behavioral abnormalities, seizures, and coma.
- Common complications are pancreatitis, hyperlipidemia, and fatty liver.
- MRI brain findings include hyperintensities in insula and cingulate cortex.

What is New

- We report novel manifestation of subacute intestinal obstruction in CTLN2.
- MRI brain findings of frontal subcortical hyperintensities and bulky basal ganglia which has not been reported in CTLN2.
- Variant c.1591 G>A in exon 15 of SLC25A13 is novel and has not been reported.

Introduction

Adult onset hyperammonemia is a rare cause of late onset episodic encephalopathy. It is most commonly caused by decompensated hepatic disease. However, non-hepatic hyperammonemia has varied etiologies including inherited, metabolic, drug-induced, and hematological causes.[1] Among the inherited causes, the most important are urea cycle defects and citrin deficiency. Early identification of the etiology is vital to prevent further hyperammonemic episodes which can be fatal. Here we report a case of adult onset episodic encephalopathy due to citrin deficiency.

Case Report

A 40 years old male, born of third degree consanguineous parentage, presented with episodic altered sensorium for the last one year. Each episode was characterized by unresponsiveness and staring look with rolling on the floor/bed and lasted for 7–8 hours [Supplementary Video 1]. Occasional urinary incontinence was also noticed. This was followed by postictal lethargy which lasted for 24 hours. All these episodes were nocturnal and followed few hours of consumption of high protein diet such as chicken. There was no history of preceding fever, headache, or associated tonic-clonic limb movements. He had undergone multiple abdominal surgeries in the past

Address for correspondence: Dr. Seena Vengalil, National Institute of Mental Health and Neuro Sciences, Bengaluru, Karnataka, India.
E-mail: seenavengalil@gmail.com

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including cholecystectomy with pancreaticojejunostomy for chronic calcific pancreatitis and mesenteric adhesiolysis for subacute intestinal obstruction. He had specific preference for eating meat and had aversion to alcohol.

Examination showed poor built male with generalized wasting of muscles with a body mass index (BMI) of 18 Kg/m^2. At the baseline, he was concious with increased response time and poor attention. Cranial nerve examination was normal. There was spasticity of upper and lower limbs with brisk tendon reflexes. Muscle power was normal with mild upper limb incoordination. Clinically, the possibilities of episodic encephalopathy or seizures were considered including hyperammonemic delirium such as urea cycle disorders.

On evaluation, liver function tests showed elevated AST (75 U/L) and ALT (71 U/L). Plasma ammonia was also elevated (111 umol/L) which was checked in two occasions. His lipid profile showed elevate triglyceride levels (210 mg/dl) with mildly reduced high-density lipoprotein (38 mg/dl). Tandem mass spectrometry showed high citrulline, elevated five times above the upper limit. Magnetic resonance imaging (MRI) brain showed subcortical white matter hyperintensities and bulky basal ganglia with MR spectroscopy (MRS) showing glutamine peak [Figure 1]. Cerebrospinal fluid analysis was normal. Electroencephalography showed right frontotemporal spikes. Clinical exome sequencing showed homozygous mutation in exon 15 of Solute Carrier family 25A13 (SLC25A13) with a novel variant of c. 1591 G>A (pGly531Ser), confirming the diagnosis of citrullinemia type 2. Patient was started on oral sodium benzoate (8g/day) along with calorie restricted medium triglyceride-rich diet and Tab. Levetiracetam 500mg twice daily as anticonvulsant. He did not have further episodes.

Discussion

Citrin is an aspartate–glutamate transporter across mitochondrial membrane. Citrin deficiency is an autosomal recessive disorder involving the gene *SLC25A13* on chromosome 7q21.3. It leads to decrease in cytoplasmic aspartate, limiting the activity of the enzyme argininosuccinic acid synthase in the liver

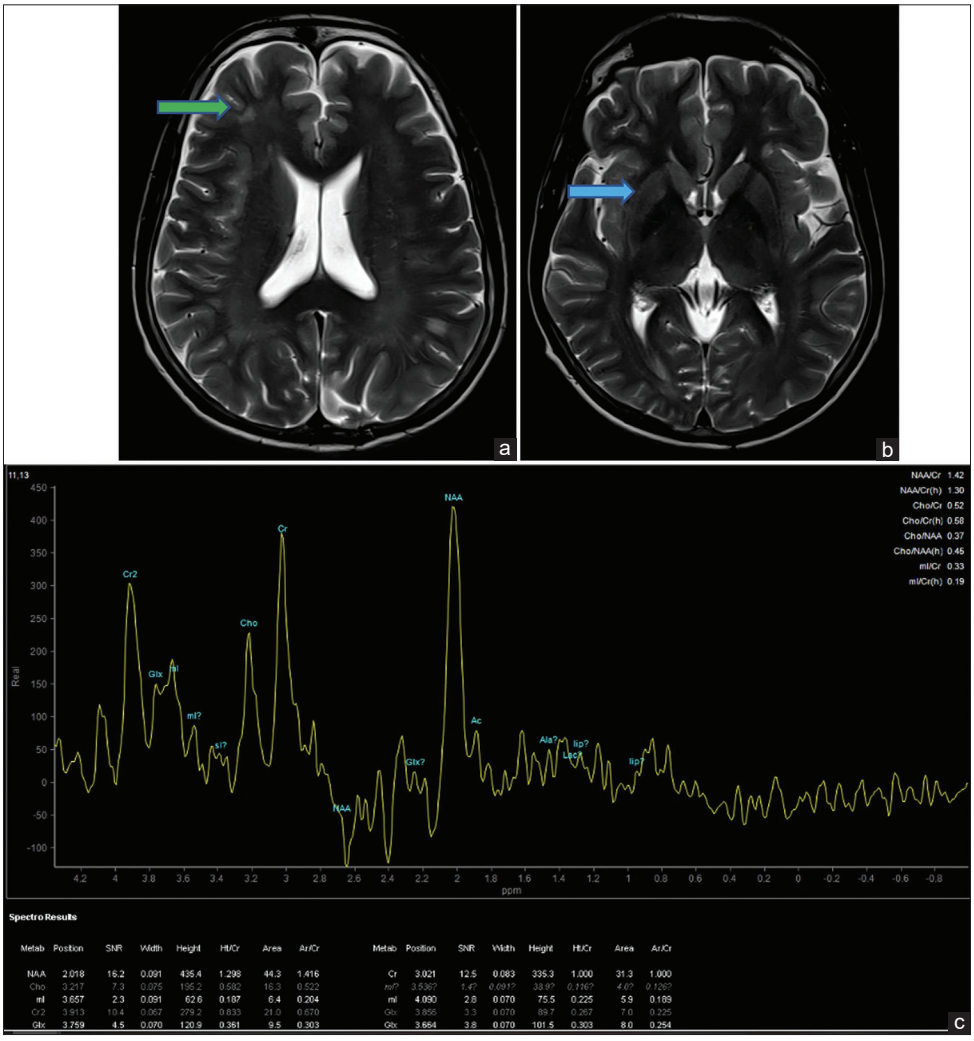

Figure 1: Magnetic resonance imaging and magnetic resonance spectroscopy of brain. (a) T2W MRI showing frontal subcortical hyperintensities (green arrow). (b) T2W MRI showing bulky basal ganglia (blue arrow). (c) MRS showing prominent elevation of glutamine and glutamate (Glx) levels. Choline (Cho) and myoinositol (Mi) levels are decreased

and elevated blood citrulline and ammonia levels.[2] Citrin deficiency has a spectrum of manifestations including neonatal intrahepatic cholestasis, failure to thrive and dyslipidemia in older children, and citrullinemia type 2 (CTLN2) in adults.[3] Though initially found only in Japanese population, it is now being reported in various other ethnic groups including cases reported from India.[4-6] All cases from India were adult onset with neuropsychiatric symptoms.[4-6] The mean age of onset is 34.4 ± 12.8 years ranging from 3rd to 6th decade[7] as seen in our patient. Onset of symptoms is usually precipitated by protein/fat-rich foods for which these patients have peculiar preference with aversion to alcohol.[2] Characteristic clinical features include episodic hyperammonemia with nocturnal delirium, behavioral abnormalities, seizures, and coma. Most of these patients are thin built with low BMI as noted in our patient.[8] The common complications noted are pancreatitis, hyperlipidemia, and fatty liver noted in 10% of patients.[9] Along with the above complications, our patient also had subacute intestinal obstruction requiring surgery which has not been reported previously. Laboratory findings include elevated blood ammonia and citrulline (5–10 times the normal) among others such as elevated arginine, plasma threonine-to-serine ratio, and serum pancreatic secretory trypsin inhibitor.[8] Previous reports have shown that the MRI brain findings in CTLN2 include hyperintensities in insula and cingulate cortex.[9] Elevated glutamine/glutamate peak (Glx) and decreased choline and myoinositol levels in MRS are well known in hepatic hyperammonemic encephalopathy.[10] Similar findings in adult CTLN2 were previously reported by Wong YC *et al*.[11] Our patient also had similar MRS findings but also had frontal subcortical hyperintensities and bulky basal ganglia which has not been reported in CTLN2. The variant c. 1591 G>A in exon 15 of *SLC25A13* is novel and has not been reported. Management of CTLN2 includes dietary restrictions of carbohydrates and alcohol, sodium pyruvate/benzoate and medium chain triglyceride oil. Though conventionally urea cycle disorders are treated with protein restriction, it may lead to inadvertent increase in carbohydrate intake which is detrimental in patients with CTLN2. Hence, this conventional protein-restricted diet with high carbohydrate has to be avoided in CTLN2.[12] However, the most successful ultimate treatment modality is liver transplantation which prevents further hyperammonemic crises.[13]

Conclusion

Hyperammonemic syndromes should be considered in the differential diagnosis of episodic encephalopathy in adults. Specific food preferences and aversions provide clues to diagnosis of CTLN2. Early diagnosis is imperative to initiate appropriate treatment and prevent further cerebral damage.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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