Not all Patients with Citrullinemia Require Liver Transplant

Urea cycle disorders are inborn errors of metabolism resulting from defective functioning of liver enzymes or transport protein involved in nitrogen metabolism.[1] Citrullinemia (CTLN) is one such UCD occurring due to deficiency of arginosuccinate synthase (enzyme) or citrin (transporter).[1] CTLN type I is common and has been reported from India.[2–4] However, there are only a few case reports on CTLN type II reported from India.[5] Here, we report a case of adult-onset CTLN-type II.

A 23-year-old man with a body mass index of 17.6 kg/m^2 presented with complaints of altered behavior after surgery for duodenal perforation (secondary to duodenal ulcer). The patient was initially suspected to be suffering from an intensive care unit-related psychosis and was referred to our tertiary care. On clinical examination, the patient was drowsy but arousable and had flaps. The liver was palpable three cms below the right coastal margin, and the spleen was nonpalpable. The sepsis workup was negative. The laboratory investigation showed high ammonia levels (185 μmol/L), while the rest of the laboratory investigations and etiological workup were inconclusive (Table 1). Magnetic resonance imaging of the brain was normal, and electroencephalogram was suggestive of diffuse slowing. The patient was treated with sodium benzoate, rifaximin, zinc, and other supportive medications. The patient transiently improved but worsened again with a low protein diet.

Tandem mass spectrometry for plasma amino acids was advised. The patient's citrulline levels were 411 (normal - 3.86–50) μmol/L with an elevated citrulline arginine ratio of 16.6. The urine for organic acids was normal. Blood DNA exome sequencing was suggestive of homozygous pathogenic variants C.1474C>T (p.Arg492Trp) on exon 15 in the *SLC25A13* gene, which led to arginine->tryptophan substitution at 492nd position of the SLC25A13 protein sequence. This variant is located on the mitochondrial carrier domain of the SLC25A13 protein. The phenotype, genotype, and biochemical parameters were consistent with the diagnosis of adult-onset CTLNII. The patient was then advised a low carbohydrate and high protein diet. The patient's symptoms improved, and the ammonia level normalized within one week of dietary management, oral sodium benzoate, and L-arginine supplementation. After twenty months of diagnosis, the patient has had no further encephalopathy episodes. The patient's current ammonia is 12 μmol/L, and citrulline is 97.4 μmol/L α-fetoprotein, and ultrasonography of the abdomen is normal.

The patient's family was screened for carrier status of SLC25A13 targeted variation by sanger sequencing. Parents are heterozygous carriers, and the elder brother (25-year-old) harbors a similar homozygous variant (C.1474C>T. p.Arg492Trp) like the proband but is asymptomatic with normal ammonia (19 μmol/L) and citrulline levels (23.2 μmol/L).

CTLN type II is associated with mutations in SLC25A13.[6] Citrin (aspartate glutamate carrier) is a transport protein involved in the transfer of aspartate from mitochondria to the cytosol for urea metabolism and is involved in the malate-aspartate cycle.[7] Citrin deficiency blocks the malate-aspartate shuttle. This leads to an increase in cytosolic nicotinamide adenine dinucleotide (NADH) to oxidized nicotinamide adenine dinucleotide ratio (NADH/NAD$^+$).[8] The increased NADH/NAD$^+$ ratio inhibits glycolysis and alcohol metabolism. Hence carbohydrates should be avoided. Thus, adult-onset CTLNII can be managed medically with regular screening for hepatocellular carcinoma. However, close social support and clinical follow-up are paramount for good long-term outcomes. As the risk of cerebral edema due to hyperammonemia cannot be disregarded, the decision not to transplant is cautioned in patients where compliance to therapeutic dietary specifications and HCC surveillance is uncertain.

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

Anand V Kulkarni: Conceptualization, Writing - original draft, approved the final draft. Vinu N: Conceptualization, Writing - original draft, approved the final draft. Madhusudhan R. Lingala: retrieved the data, approved the final draft. Srikanth Kulkarni: retrieved the data, approved the final draft. Mithun Sharma: critically assessed the manuscript, provided intellectual inputs, approved the final draft. Duvvuru N. Reddy: critically assessed the manuscript, provided intellectual inputs, approved the final draft. Padaki N. Rao: critically assessed the manuscript, intellectual inputs, approved the final draft.

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Table 1 Baseline Characteristics of the Proband.

Variables (units)	Patient's value	Normal range
Hemoglobin (g/dl)	13.8	13–17
White cell count (cells/mm$^{3)}$	5300	4000–11000
Platelets (lakhs/mm^3)	2.1	1.5–4.1
INR	1.17	<1.3
Total bilirubin (mg/dl)	1	0.3–1.2
Direct bilirubin (mg/dl)	0.2	0–0.2
Aspartate transaminase (U/L)	21	<50
Alanine transaminase (U/L)	14	<40
Alkaline phosphatase (U/L)	94	30–120
Total proteins (gm/dl)	6.8	6.6–8.3
Serum albumin (g/dl)	3.7	3.5–5.1
Blood urea (mg/dl)	21	13–43
Serum creatinine (mg/dl)	1.06	0.7–1.3
Sodium (mEq/L)	142	136–145
Potassium (mEq/L)	3.6	3.5–5.1
Arterial lactate (mmol/L)	0.9	<1.5
Creatinine phosphokinase (IU/L)	20	18–232
Serum ceruloplasmin (mg/dl)	22	20–24
24-h urinary copper (μg)	16	>40
Total cholesterol (mg/dl)	198	<200
HDL (mg/dl)	55	<40
VLDL (mg/dl)	30	2–30
LDL (mg/dl)	49	<100
Triglycerides (mg/dl)	151	<150
Procalcitonin (ng/ml)	0.3	<0.5
Ammonia (μmol/L)	185	0–54
ANA	negative	negative
Total IgG (mg/dl)	865	<1100
Gastroscopy	No evidence of portal hypertension	

INR - international normalized ratio; HDL - high-density lipoprotein; VLDV- very-low-density lipoprotein; LDL - low-density lipoprotein; ANA - antinuclear antibody.

CONFLICTS OF INTEREST

The authors have none to declare.

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Anand V. Kulkarni[#]
Department of Hepatology and Liver Transplantation, Asian Institute of Gastroenterology, Hyderabad, India

Narayan Vinu[#]
Department of Paediatrics and Genetics, Rainbow Children's Hospital, Marathahalli, Bangalore, India

Madhusudhan R. Lingala
Department of Internal Medicine, Asian Institute of Gastroenterology, Hyderabad, India

Srikanth Kulkarni
Division of Neonatology, Ovum Women and Child Hospital, Bangalore, India

Mithun Sharma, Duvvuru N. Reddy, Padaki N. Rao
Department of Hepatology and Liver Transplantation, Asian Institute of Gastroenterology, Hyderabad, India

Address for correspondence: Dr. Anand V Kulkarni, Department of Hepatology and Liver Transplantation, Asian Institute of Gastroenterology, Hyderabad, India.
E-mail: anandvk90@gmail.com

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[#] First coauthor.