Dear Sir,

A 55-year-old gentleman with a history of a single episode seizure during his adolescent years, presented with non-specific symptoms of paresthesia of extremities and diffuse headache since a month. He was started on vitamin B complex tablets and low-dose pregabalin for the same. One week before the presentation, he also developed subtle memory impairment and altered behavior with aggressive traits. He was admitted to a local hospital and was given a haloperidol injection following which he developed drowsiness that persisted

Acute Fulminant Encephalopathy in an Adult due to Ornithine Transcarbamylase Deficiency

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through the day and was referred to our institution for further management.

In the emergency, the patient was unresponsive and was not localized to painful stimuli, but had preserved brainstem reflexes. There was no history of prior alcohol use or recreational drug use, consumption of pesticides, or other unknown substances. He was admitted for further evaluation of encephalopathy and the initial differentials included a subacute progressive encephalopathy, possibly of a metabolic autoimmune or infectious etiology. Initial magnetic resonance imaging (MRI) of the brain with contrast did not show any abnormality. His laboratory tests showed hyperammonemia (168 mmol/L), but the liver function tests (serum glutamic-oxaloacetic transaminase (SGOT) 42 IU/L, serum glutamic pyruvic transaminase (SGPT) 37 IU/L) and ultrasound abdomen showed normal findings.

His ambulatory electroencephalogram (EEG) showed a moderate degree of generalized slowing [Supplementary Figure 1]. He was started with anti-hepatic coma measures including lactulose retention enema with antibiotics metronidazole and rifaximin despite normal liver function tests with gastroenterology opinion aiming reduction in gut ammonia production. He was put on a protein-restricted diet. A cerebrospinal fluid (CSF) analysis was done which showed normal findings for routine CSF, culture, viral polymerase chain reaction (PCR), and autoimmune encephalitis panel. Blood cultures were negative. His viral markers including hepatitis B total core antigen, surface antigen, and hepatitis C were negative. In the subsequent 12 h, there was an exponential rise in ammonia levels (457 mmol/L) despite the best hepatic coma measures.

Hemodialysis was initiated on the third day and three sessions were given on consecutive days. However, sensorium remained poor and there was a relentless rise in the ammonia levels (997.1 mmol/L). At this stage, his liver function tests showed mild elevation with SGOT 99.4 and SGPT 53.5 IU/L, respectively. He developed hemodynamic instability and the following computed tomography (CT) of the brain imaging showed diffuse cerebral edema. He developed herniation and succumbed within the next 24 h. The rapid progression of encephalopathy with hyperammonemia in the absence of a decompensated liver disease suggested a possible metabolic pathway disorder. His plasma amino acid level estimates by high-performance liquid chromatography (HPLC) revealed mildly elevated glutamate and low citrulline levels [Supplementary Table 1] along with significantly elevated urinary orotic acid [Supplementary Table 2], suggestive of a proximal urea cycle defect. Genetic testing could not be done for the patient due to his early death. The patient’s relatives were counseled regarding the need for genetic counseling and testing. His daughter was detected to have heterozygous c.848G >T (P.Gly283val) mutation in exon 8 of the ornithine transcarbamylase (OTC) gene but was asymptomatic at the time of testing.

This is a case of subacute progressive encephalopathy due to high ammonia in adults in a patient with no pre-existing liver disease. The causes of this type of rapid encephalopathy due to liver injury include viral infection, medications like valproate, steroids, and chemotherapy. But extremely high levels of ammonia without obvious other causes lead to suspicion of urea cycle disorders (UCDs). They are rare inborn errors of metabolism, due to mutations resulting in the deficiency of one of the six enzymes in the urea cycle. Out of these, ornithine transcarbamylase deficiency (OTCD) is one of the most common enzyme defects worldwide with an incidence of 1 per 42,000 live births.[1] The disorder commonly presents in neonates and children but rarely, in adults as well. All of them are autosomal recessive, except OTCD, which has an X-linked pattern of inheritance [Table 1]. The defective gene lies on the short arm of the X chromosome on band Xp21.12. As OTCD has an X-linked pattern of inheritance, males are more severely affected, but 15% of the female carriers can also be affected.[2,3] In adults, it can present with rapid and fatal hyperammonemia.[4]

Except for a single episode of seizure during his adolescent years, our case remained asymptomatic till he was 55 years of age. None of his family members except his single daughter who is apparently healthy but genetic mutation positive. The trigger which caused hyperammonemia is not clear, which could be minor infections or medications or Atkins diet or weight loss.

Urea cycle deficits present with a variable clinical spectrum across age groups depending on the residual urea cycle activity in the liver.[5] Older children and adults present with hyperammonemia and episodic encephalopathy under stress conditions like infection, anesthesia, certain drugs, diet, or pregnancy. Other features may include recurrent vomiting, seizures, protein avoidance, behavioral changes, ataxia, progressive spasticity, and mental retardation. Compared to children, an adult will present with more psychiatric symptoms including hallucinations, and disorientation.[6] If there is a

| Urea Cycle Disorder | Gene | Inheritance | Plasma amino acids | Urine organic acids |
|---------------------|------|-------------|--------------------|---------------------|
| 1-Carbamyl phosphate synthetase I deficiency | CPS 1 | AR | ↑Arginine, ↓Citrulline | ↓Normal urine orotic acid |
| 2-Ornithine transcarbamylase | OTC | X-linked | ↑Arginine, ↓Citrulline | ↑Urine orotic acid |
| 3-Arginosuccinic acid synthase deficiency or citrullinemia type I | ASS | AR | ↑Arginine, ↓Citrulline | | |
| 4-Arginosuccinic acid lyase deficiency or arginosuccinic aciduria | ASL | AR | ↑Arginine, ↓Citrulline | |
| 5-Arginase deficiency | ARG1 | AR | ↑Arginine | |
| N-acetyl glutamate synthase deficiency | NAGS | AR | ↑Arginine, ↓Citrulline | ↓Normal urine orotic acid |
minor deficiency of an enzyme of the urea cycle, the symptoms
may present later in life, as was in our case.

The core feature of hyperammonemia-inducedencephalopathy
is an increase in astrocyte glutamine synthesis, and swelling
of astrocytes in response to the osmotic effect of glutamine
accumulation, causing raised intracranial pressure.\(^7\)

Various therapies have been tried for the treatment of
hyperammonemia in cases of UCD including the following:
1. Nitrogen scavenging therapy
2. Replacement of deficient urea cycle intermediates
3. Reduction of protein catabolism
4. Therapy for rapid reduction of plasma ammonia levels
   by extracorporeal techniques
5. Liver transplantation.

Alternative pathway treatment diverts nitrogen from the urea
cycle to various other routes of excretion. Sodium phenylacetate
combines with glutamine, producing phenylacetylglutamine.
Phenylacetylglutamine is excreted by the kidneys and
sodium benzoate conjugates with glycine, producing sodium
hippurate, which is also excreted by the kidneys. Arginine
(urea cycle intermediate) can also be administered in the patient
with OTCD as low plasma arginine levels are associated with
OTCD. Protein intake should be restricted for at least the
first 24–48 h and the caloric requirement should be met with
carbohydrates and fats during this period, especially in patients
on hemodialysis, to prevent excess catabolic state. Currently,
the treatment of choice for hyperammonemia due to UCDs is
hemodialysis or renal replacement therapy or both as early as
possible.\(^8\)–\(^12\) We initiated hemodialysis for our patient early
during the course of the hospital stay, but despite repeated
sessions of hemodialysis, the patient did not respond. Liver
transplantation is the treatment option for patients having
recurrent hyperammonemia and for those patients who do not
respond well to pharmacological and dietary measures alone.

Plasma citrulline levels aid in distinguishing proximal from
distal UCDs. Plasma citrulline is absent or in trace amounts
in carbamyl phosphate synthetase 1 (CPS-1) deficiency
and low or normal in late-onset OTCD, both of which are
proximal UCDs. In the distal UCDs, like arginine succinic acid
synthetase deficiency, plasma citrulline levels are significantly
elevated (ten-fold), and in arginosuccinic acid lyase
deficiency, there is a moderate elevation of plasma citrulline
levels accompanied by elevation of arginosuccinic acid in
plasma and urine. Plasma arginine levels are reduced in all UCDs
except for arginase deficiency (five- to seven-fold elevation).
Urinary orotic acid levels help to differentiate CPS-1 deficiency
from OTCD as they are significantly elevated in OTCD, as
in our case as well. Urinary orotic aciduria is also present in
arginase deficiency and citrullinemia type. Genetic testing
would give a definitive diagnosis.

**Conclusion**

The current case shows that urea cycle defects can be a cause
of hyperammonemia with rapidly progressive encephalopathy
in the absence of evidence for pre-existing liver disease.

Early aggressive therapies with dialysis followed by liver
transplantation may be an option in severe cases of OTC
deficiency. Episodic high ammonia levels without obvious
liver disease should prompt the clinician to think about these
rare metabolic diseases.

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**Conflicts of interest**

There are no conflicts of interest.

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### Supplementary Table 1: Serum levels of amino acids by HPLC

| Test              | Plasma mmol/L | Reference range Umol/L |
|-------------------|---------------|------------------------|
| Aspartic Acid     | 26            | 34-94                  |
| Glutamic acid     | 21            | 17-69                  |
| Asparagine        | 17            | 28-65                  |
| Serine            | 35            | 92-196                 |
| Glutamine         | 907           | 457-857                |
| Histidine         | 84            | 68-108                 |
| Glycine           | 274           | 166-330                |
| Threonine         | 62            | 102-246                |
| Citrulline        | 5             | 19-52                  |
| Alanine           | 172           | 242-594                |
| Arginine          | 10            | 1-81                   |
| Tyrosine          | 25            | 35-107                 |
| Cystine           | 26            | 36-58                  |
| Valine            | 81            | 155-343                |
| Methionine        | 34            | 13-60                  |
| Tryptophan        | 9             | 10-140                 |
| Phenylalanine     | 41            | 34-86                  |
| Iso-leucine       | 47            | 34-106                 |
| Ornithine         | 18            | 47-195                 |
| Leucine           | 72            | 86-206                 |
| Lysine            | 365           | 116-276                |
| Hydroxy proline   | -             | 0-53                   |
| Proline           | 158           | 58-324                 |
| Total amino acids | 2489          | 3000-5000              |
| Total BCAA        | 200           | <600                   |
| Gly/BCAA          | 1.37          |                        |
| Ala/BCAA          | 0.85          |                        |
| Gly/Total         | 9%            | <10%                   |
| Ala/Total         | 6%            | <10%                   |

**BCAA**: Branched chain amino acids

### Supplementary Table 2: Urine orotic acid and creatinine

| Amino acids                  | Value          | Reference                  |
|------------------------------|----------------|----------------------------|
| 1 Urinary orotic acid        | 2,264.4 Umol/L | Reference 0.5-3.3          |
| 2 Oroditine                  | ND             |                            |
| 3 Urinary creatinine         | 5.74 mmol/L    | 4-17 mmol/L                |
| 4 Ratio of urinary           | 394.4 Umol/mmol| 0-30 Umol/mmol              |
| orotic acid/creatinine       |                |                            |

### Supplementary Figure 1: Generalized delta slow wave intermixed with frontal triphasic sharp waves