The Canadian Journal of Neurological Sciences (2025), 1–7
doi:10.1017/cjn.2025.19

Canadian Journal of Neurological Sciences
Journal Canadien des Sciences Neurologiques

Clinical Neuropathological Conference

New Diagnosis of Ornithine Transcarbamylase Deficiency in a 71-Year-Old Man

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Keywords: hyperammonemia; neurocritical care; ornithine transcarbamylase deficiency; seizures

Clinical presentation: Part 1

A 71-year-old male, diagnosed with a 2-month history of giant cell arteritis (GCA) (biopsy proven) and undergoing steroid therapy, presented to a community hospital with confusion, bilateral tremulousness, a wide-based gait and fatigue. Past medical history included GCA, dyslipidemia, cardiac septal thickening on echocardiogram with diastolic dysfunction, right retinal tear, bilateral cataract surgery and sudden left hearing loss of undetermined etiology (1 year ago). Comprehensive investigations, including complete blood count, liver and renal profiles, electrolytes, thyroid-stimulating hormone and cerebrospinal fluid cell count, protein and cultures, were normal. The only exception was elevated leukocytes (17.3 × 10*9/L), which was attributed to steroid use. A CT head with angiogram revealed no parenchymal abnormality or angiographic evidence of vasculopathy. He was discharged on day 3 of hospitalization after clinical stabilization. The differential diagnosis at that time included steroid-induced encephalopathy or possibly a GCA flare secondary to a recent reduction of the prednisone dose.

Two weeks later, his condition worsened, prompting a return to the community hospital. A CT head and blood work, including a complete blood count, serum electrolytes, blood glucose, basic autoimmune profile and HIV serology, were normal. A venous blood gas showed evidence of respiratory alkalosis. Initially, he was disoriented but able to follow commands. However, the next day, he had an unwitnessed decline and was found with decreased responsiveness, was unable to follow commands and was not responding to pain with a Glasgow Coma Score of 4–5/15. A repeat non-contrast CT head was within normal limits for age. He was intubated for airway protection and transferred to the critical care unit at our tertiary care center.

Upon reaching our center, he was not sedated and did not respond to voice or painful stimuli. Pupillary reactivity was intact, albeit with a right relative afferent pupillary defect. There was a weak corneal reflex bilaterally, along with non-localizing and variably disconjugate gaze, bilaterally absent vestibulo-ocular reflexes and weakened cough and gag reflexes. Involuntary twitching of the mouth was seen after stimulation and characterized as rhythmic but slow and not sustained. Examination of the extremities revealed uniformly flaccid tone, areflexia and mute plantar responses. Sustained subtle clonus was noted at the right ankle.

Given the 2-month history of intermittent delirium and prednisone exposure as well as the recent rapid progression from delirium to coma, the main differential diagnosis considered at this time comprised basilar artery thrombosis, meningitis or an opportunistic central nervous system (CNS) infections (cryptococcus, progressive multifocal leukoencephalopathy, toxoplasmosis), autoimmune encephalitis or an exacerbation of GCA. Infection of the CNS was considered less likely given the lack of leukocytosis, fever, headache or an infectious prodrome. Non-convulsive status epilepticus was considered to be less likely because there were no identified high-risk predisposing factors such as recent witnessed convulsive seizure, subtle potentially ictal movements or history of epilepsy or anti-seizure medication use.[1] Initially, the involuntary mouth twitching was only seen after stimulation. Despite infection being lower on the differential, empirical antimicrobial agents, including acyclovir, were initiated at meningitic doses. A CT head and neck angiogram revealed no evidence of basilar artery occlusion or vasculopathy. Lumbar puncture results were nonspecific and potentially suggestive of inflammation (cell count: 8×10^6/L, protein: 132 mg/dL, negative gram stain). Autoimmune and paraneoplastic panels were sent for both cerebrospinal fluid and serum. Enteric nutrition was initiated with 122.9 g of protein daily target, starting at 20 mL/h and increasing every 12 h from the time of admission until at target (0.44 g/kg/d for 1st 12 h, 0.88 g/kg/d for 2nd 12 h, 1.76 g/kg/d at 24 h and beyond).

A routine 30-min electroencephalogram (EEG) on day 2 exhibited ictal and interictal epileptiform activity arising from the

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Cite this article: Daghreeri S, Bosma KJ, Hammond R, Rupar T, Pope V, Talal A, and Gofton TE. New Diagnosis of Ornithine Transcarbamylase Deficiency in a 71-Year-Old Man. *The Canadian Journal of Neurological Sciences*, https://doi.org/10.1017/cjn.2025.19

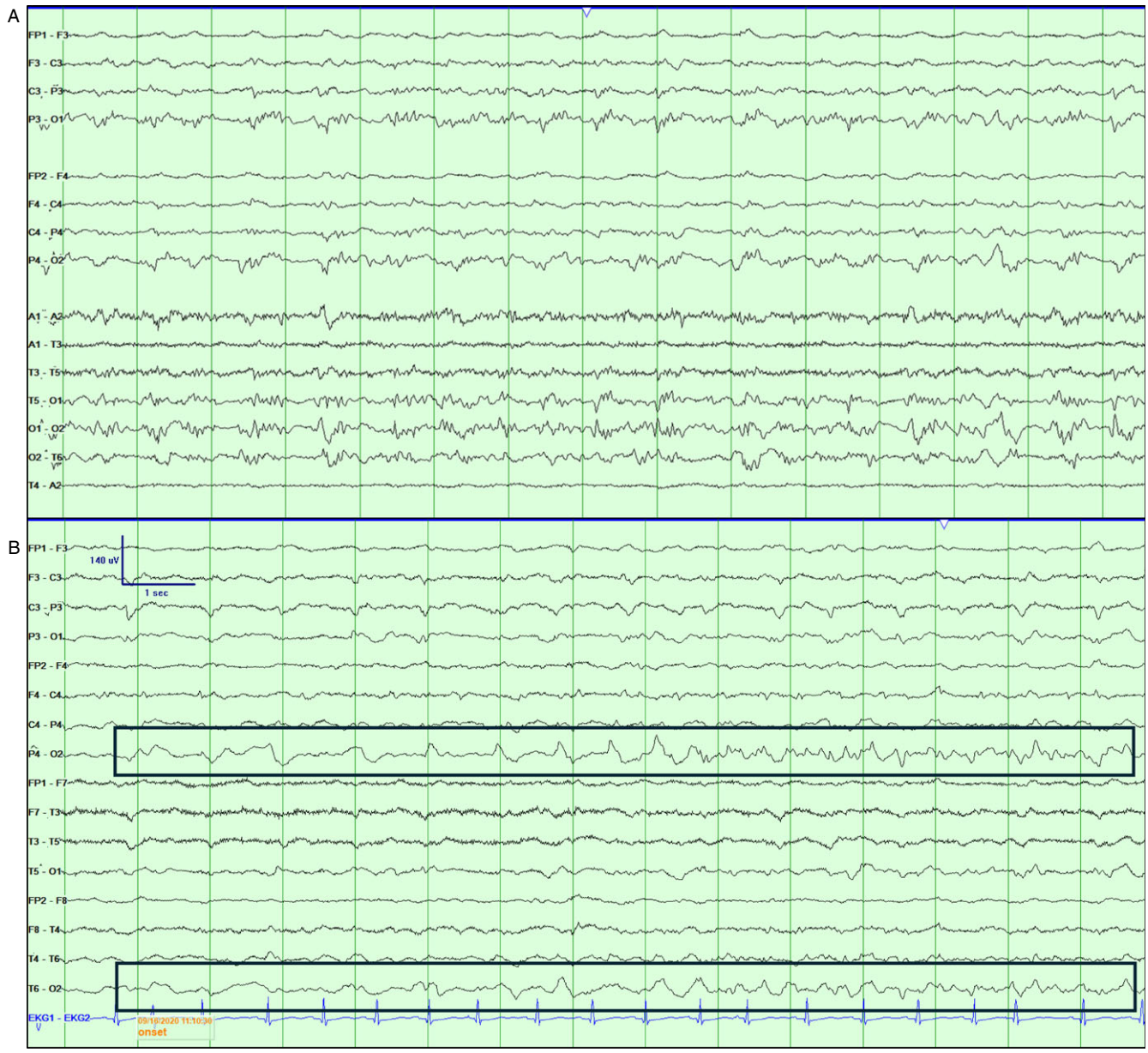

Figure 1. The 10–20 system electroencephalogram (EEG) using bipolar longitudinal montage at the time EEG was started. (A) An occipital coronal montage showing interictal epileptiform discharges originating from the occipital regions, maximum at O1. (B) The rectangles show rhythmic sharply contoured delta with evolution of both frequency and amplitude, consistent with a focal electrographic seizure (continuing into the subsequent epoch, not shown). *L* = left; *R* = right.

bi-occipital region, maximum on the right (Figure 1), and generalized slowing. Levetiracetam was administered (1000 mg IV BID). An MRI with gadolinium showed extensive restricted diffusion in a cortical distribution, sparing the basal ganglia, white matter, brainstem and cerebellum, with no abnormal enhancement (Figure 2). Although these findings were in keeping with known MRI changes associated with status epilepticus, the possibility of hypoxic-ischemic injury could not be ruled out. The cerebrospinal fluid culture returned negative on the second day of admission, leading to the discontinuation of antibiotics.

Case discussion

The patient presented with recurrent acute encephalopathy, but there was insufficient information to identify a specific cause. Initially, the delirium was attributed to GCA, possibly from a flare or recent reduction of steroid medication. After readjustment, the patient's condition improved, but delirium returned soon after.

Unfortunately, the patient's level of consciousness deteriorated, requiring transfer to a tertiary care center for further assessment. A bedside neurological examination revealed non-lateralizing findings, except for a relative afferent pupillary defect indicating optic nerve pathway asymmetry (history of left retinal tear).

Early after presentation, a broad differential diagnosis should be considered, and potential causes for the reduced level of consciousness with diffuse CNS involvement outside of GCA should be considered. Vascular etiologies, such as ischemic stroke or intracerebral hemorrhage, and mass lesions were ruled out with the unremarkable non-contrast CT head done before transfer. A CT head with angiogram is required to assess for basilar artery

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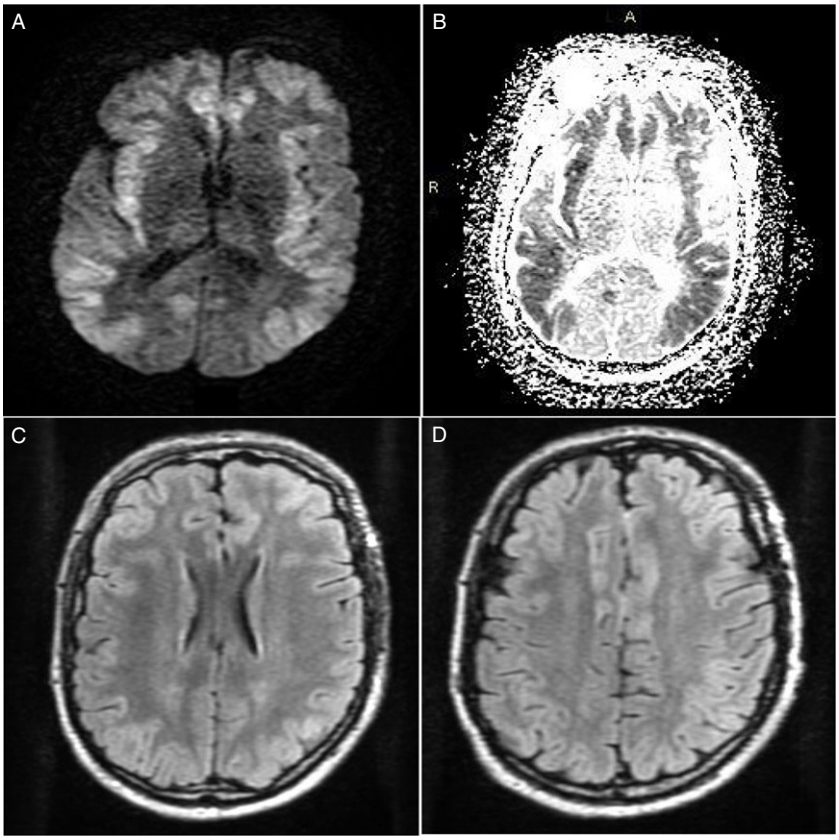

Figure 2. MRI images of the brain. (A) Diffusion-weighted image at the level of the thalamus showing cortical gyral diffusion restriction with relative sparing of the occipital cortex and deep gray structures. (B) Corresponding apparent diffusion coefficient imaging changes at the level of the thalamus showing abnormal signal in the cortical gyri with relative sparing of the occipital cortex and deep gray structures. (C) Fluid-attenuated inversion recovery image at the level of the superior aspect of the lateral ventricles and caudate showing cortical gyral high signal. (D) Fluid-attenuated inversion recovery image at the level of the superior cerebral hemispheres showing cortical gyral high signal with relative sparing of the parietal cortex.

occlusion or a more subtle vasculopathy. Infectious etiologies should be considered but are less likely given the lack of leukocytosis, fever or preceding headache. However, the lumbar puncture should be repeated, and empirical antimicrobial coverage should be initiated until infection can be excluded. Opportunistic infections should be investigated, given the 2-month history of exposure to prednisone. Inflammatory and autoimmune etiologies should be excluded, but test results take days or more to be received. Non-convulsive seizures should also be considered and require EEG to rule in or out.

At the time of transfer to our tertiary hospital, potential etiologies remaining on the differential should include:

1. vascular causes such as large vessel occlusion or basilar artery thrombosis (already ruled out with CT head with angiogram).
2. infectious causes, especially given the patient's immunocompromised state (normal cerebrospinal fluid cell counts and negative culture).
3. autoimmune/paraneoplastic encephalitis, given the rapid deterioration of consciousness despite initial investigations (panels pending).
4. Non-convulsive seizures or non-convulsive status epilepticus (EEG was not available until day 2 of admission).

A lumbar puncture was repeated. There was no evidence to indicate CNS infection, and antimicrobial agents were subsequently stopped. The autoimmune panel results were negative. Neuroimaging revealed cortical ribboning on diffusion-weighted imaging, sparing the occipital region, potentially consistent with an anoxic brain injury or post-ictal changes. However, there was no documented hypoxic event, no signal change in the deep gray structures, and the epileptiform activity noted on EEG was maximal in regions of the brain without cortical signal change. Despite extensive investigations, a specific etiological explanation remained elusive.

The most likely cause of the imaging findings at this time includes status epilepticus with associated cortical changes on MRI or less likely an unwitnessed hypoxic event leading to cortical signal changes on MRI and epileptiform activity on EEG. Only a routine EEG was available, so the extent and persistence of epileptiform activity were not well understood. The timeline is not suggestive of intoxication. Recurrent encephalopathy with associated cortical changes on MRI can be seen with hyperammonemia. However, at 71 years of age and without laboratory evidence of hepatic dysfunction or administration of medications known to cause hyperammonemia, this would be unlikely. While hyperammonemia may be unlikely, a serum ammonia level should be ordered early on (arguably at the time of presentation) for any patient with unexplained impairment of level of consciousness.

Clinical presentation: Part 2

A continuous EEG (cEEG) was placed on day 3 of critical care admission and revealed non-convulsive status epilepticus with multifocal spikes and occipital seizures. A clinical seizure was witnessed with clonic right facial movements. The levetiracetam dose was increased (1500 mg IV BID), and valproic acid was introduced as a loading dose (30 mg/kg IV) and maintained at (500 mg IV BID).

On the fourth day of critical care admission, he continued to have abundant spikes on the EEG, and a clinical left arm seizure was noted with regular rhythmic clonic movements. Propofol was increased (3 mg/kg/h), an additional bolus of levetiracetam was administered (20 mg/kg) and a midazolam infusion (2 mg/h) was initiated. The cEEG changed with a more suppressed background

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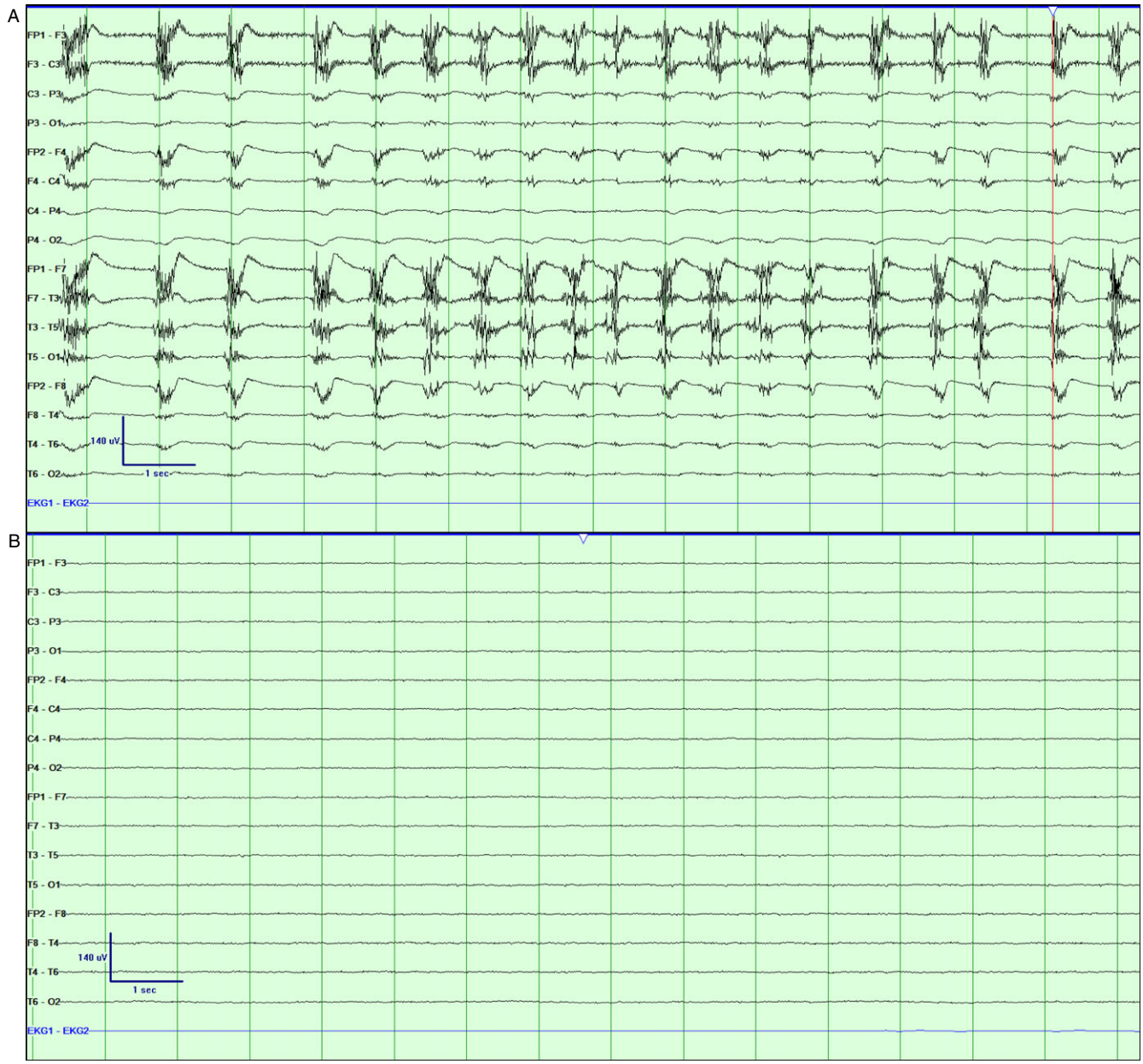

Figure 3. (A) The 10–20 system electroencephalogram (EEG) using bipolar longitudinal montage on day 4 of admission demonstrates a suppressed background with periodic likely polyspikes intermixed with myogenic artifact that were more prominent in the left frontotemporal region. (B) Complete suppression of EEG.

and regular polyspikes, most prominent in the left frontotemporal region, compared to the previous recording (Figure 3A).

Shortly after the change in EEG, pupillary responses became absent, with no response to central or peripheral stimuli, flaccid tone all over, a negative Hoffman sign bilaterally and mute plantar responses. This led to the discontinuation of propofol. Blood work showed a subtherapeutic serum valproate level (215 mmol/L; reference range 350–700 mmol/L; valproic acid serum levels and serum ammonia ordered routinely after intravenous loading doses) and a critically high ammonia, which peaked at 674 mmol/L (normal range: 15–55 mmol/L). Continuous EEG showed complete suppression (Figure 3B), and a stat CT head with angiogram showed diffuse cerebral edema with loss of gray-white differentiation. There was no opacification of the distal internal carotid arteries in the neck and the cavernous or petrous internal carotid arteries or anterior circulation arteries. There was no opacification of the vertebral arteries above the level of C1, and the basilar artery and its branches were not seen, all consistent with an absence of cerebral perfusion. Blood work was sent to investigate whether a urea cycle disorder (UCD) could have contributed to the unexpected and catastrophic elevation of ammonia after the administration of valproic acid. Death by neurological criteria was declared after the discontinuation of sedation for 24 h. The family stated that organ donation was consistent with the patient's wishes.

It was not until after the time of organ procurement that the blood work results became available. Urine orotic acids were significantly elevated, and nonspecific plasma amino acid elevations were measured, particularly alanine and glutamine (Table 1). Single gene sequencing was performed and found to be consistent with a late-onset ornithine transcarbamylase (OTC) deficiency OTC: c.622G>A (p. Ala208Thr) (rs72558416), American College of Medical Genetics and Genomics (ACMG 1 – pathogenic).[2]

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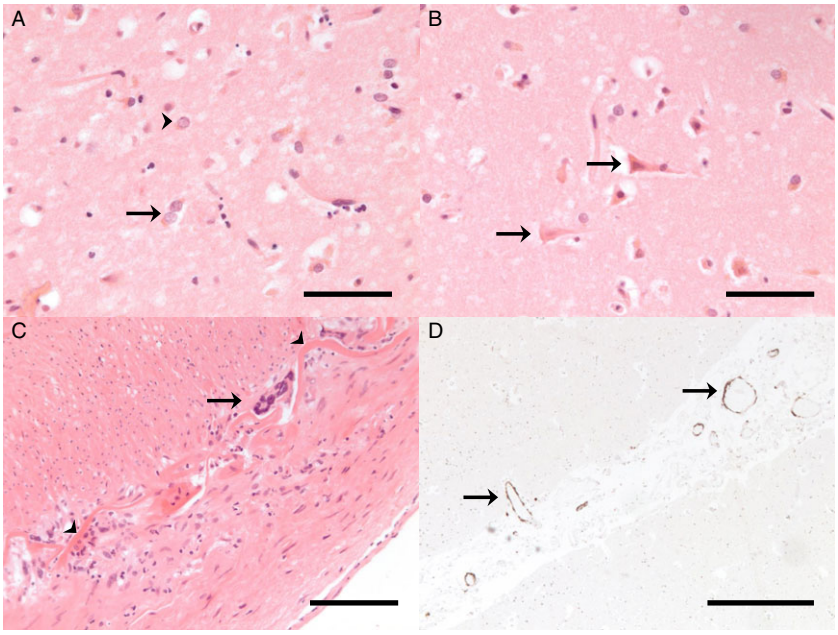

Figure 4. Pathology photomicrographs. (A) Abundant Alzheimer type II astrocytes (arrowhead), including doublets (arrow), indicate a metabolic encephalopathy hematoxylin and eosin (H&E, bar = 50 µm). (B) Shrunken, hypereosinophilic neurons (arrows) confirm a hypoxic-ischemic injury (H&E, bar = 50 µm). (C) Vertebral artery lymphohistiocytic infiltrates including giant cells (arrow) in the vicinity of the internal elastic lamina constitute giant cell arteritis (H&E, bar = 50 µm). (D) Select leptomeningeal and superficial cortical vessels contained beta-amyloid deposits, indicating cerebral amyloid angiopathy (anti-bA4 immunohistochemistry, bar = 500 µm).

Table 1. Amino acid testing results consistent with the diagnosis of a non-hepatic genetic cause of hyperammonemia. Abnormal results more than double the upper limit of normal are bolded and underlined. ND = not detected

Amino acid (normal range)	Result
Alanine, plasma (175–530 mmol/L)	**1232**
Arginine (43–140 mmol/L)	103
Argininosuccinic acid	ND
Citrulline (10–50 mmol/L)	43
Cystathionine, plasma (0–3 mmol/L)	4
Cystine, plasma (1–50 mmol/L)	74
Glutamine, plasma (109–750 mmol/L)	**2244**
Glycine, plasma (138–427 mmol/L)	446
Isoleucine (28–98 mmol/L)	85
Leucine, (70–170 mmol/L)	166
Lysine, plasma (96–230 mmol/L)	**786**
Methionine, plasma (16-44 mmol/L)	96
Ornithine (21–115 mmol/L)	95
Proline (84–330 mmol/L)	488
Threonine (41–198 mmol/L)	291
Tyrosine (35–90 mmol/L)	140
Valine (110–312 mmol/L)	266
Other (normal range)	
Acylcarnitine, plasma (5–20 mmol/L)	26
Free carnitine, plasma (20–53 mmol/L)	55
Total carnitine, plasma (25–73 mmol)	81
Orotic acid, urine (0–5.6 mmol/L)	**130.8**

Case discussion

This patient experienced a pronounced and prolonged deterioration of consciousness. Whether or not there are truly clinical seizures can be difficult to determine at the bedside in a critically ill patient with metabolic disturbances such as hyperammonemia. Low amplitude myoclonus may be difficult to differentiate from true clonic movements. An EEG correlate will help to make this differentiation. However, smaller clonic movements may be associated with smaller epileptic foci. Very small epileptic foci may be missed with conventional 10–20 scalp EEG. In this case, there were other epileptiform abnormalities seen on the EEG and cortical abnormalities on MRI, so clinical judgment was used to generate a hypothesis regarding the most likely cause of the rhythmic clonic perioral movements. Furthermore, myoclonus associated with metabolic disturbances is generally irregular and multifocal. In this case, the movements were not multifocal, and they were rhythmic. A routine EEG revealed epileptiform activity, prompting the use of cEEG, which showed electrographic status epilepticus. This necessitated readjustment of anti-seizure medications and an increase in sedation to achieve burst suppression. Unfortunately, the patient's condition deteriorated further after the administration of valproic acid with cerebral edema and herniation.

The possibility of acute metabolic derangement secondary to valproic acid was considered. Valproic acid is contraindicated in OTC deficiencies and other UCDs.[3] The ammonia level was significantly elevated. This raised concerns of a UCD as the cause for hyperammonemia.[3] However, as previously discussed, it would be uncommon to have a first presentation of a UCD in a person over 70 years old. Investigations showed significantly elevated urine orotic acid (131 mmol/mol of creatinine, reference range 0–5.6), and urine organic acid analysis identified significant amounts of orotic acid and uracil, which are present in OTC deficiency. Valproic acid metabolites were also present, and genetic testing was consistent with a late-onset OTC deficiency.

Early detection of hyperammonemia in acute encephalopathy requires a high degree of suspicion and is paramount to the identification of OTC deficiency. Once identified, hyperammonemia could be treated with intravenous hydration, reversal of the catabolic state through glucose supplementation, the use of ammonia scavengers, administration of L-arginine and restriction of natural protein intake.[4,5] Long-term management involves

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adhering to a low-protein diet with a maximum of 0.6–0.8 g/kg/d of protein (surpassed in this case).[6] While liver transplantation is the only curative option, it does not reverse sustained brain damage.[7] Liver transplantation is reserved for patients with severe OTC or recurrent metabolic decompensation despite medical management.[8] For an in-depth review of OTC deficiency, its clinical presentation and management, see Stepian *et al.* (2019)[8] and Redant *et al.* (2021).[9]

Pathology

At autopsy, the brain was symmetrically swollen and soft, with flattened gyri, narrowed sulci and evidence of bilateral uncal herniation, accompanied by ventral midline brainstem hemorrhages.

Microscopic examination (Figure 4) of the cerebral cortex and deep gray structures revealed acute neuronal injury and Alzheimer type II astrocytosis. Further, neuronal necrosis and type II astrocytosis were widespread in the cerebellum and brainstem. The vertebral arteries were noteworthy for the finding of GCA, whereby the vessel wall (including the internal elastic lamina) was focally disrupted by granulomatous inflammatory infiltrates.

The neuronal necrosis is presumed to be on the basis of status epilepticus (in the absence of documented severe hypotensive episodes). The finding of Alzheimer type II astrocytosis (metabolic encephalopathy) correlates with the patient's hyperammonemia. Both insults likely contributed to the cerebral swelling. The diagnosis of GCA was also confirmed.

Because of findings consistent with OTC deficiency, the liver was also examined, showing steatosis but no other abnormality.

Discussion

Ammonia is ordinarily metabolized by the liver through the urea cycle pathway. This intricate process, facilitated by multiple enzymes,[10,11] transforms nitrogen – a byproduct of protein metabolism – into urea, which is subsequently excreted in the urine. Genetic anomalies in these biochemical steps give rise to UCD, leading to hyperammonemia.[10] The most prevalent genetic UCD is OTC deficiency, classically presenting as neonatal encephalopathy. On occasion, it may manifest partially, leading to a late-onset appearance. Inherited in an X-linked manner, OTC deficiency is considered the most common UCD, accounting for nearly two-thirds of all patients.[12] OTC is one of the six enzymes within the urea cycle responsible for breaking down and eliminating nitrogen. Among individuals with OTC deficiency, 30% exhibit a neonatal-onset type, while 70% manifest a late-onset type.[4] Neonatal-onset OTC deficiencies present with hyperammonemia, anorexia, encephalopathy and respiratory alkalosis, progressing to coma and seizures. Late-onset OTC deficiency occurs in men with partial OTC deficiency or heterozygous women, emerging from 2 months after birth to adulthood. This form is triggered by stressors such as acute infections, menstruation, corticosteroid administration, starvation, surgery or increased protein intake.[13]

The clinical manifestations of hyperammonemia exhibit variability and encompass symptoms resulting from ammonia's toxic impact on the brain.[8] These symptoms include personality changes, lethargy, vomiting, irritability, confusion and, in severe instances, seizures, stupor, coma and even death.[14] In acute hyperammonemic encephalopathy, brain MRI reveals distinctive changes characterized by diffuse gyriform restricted diffusion across the cerebral hemispheres, particularly affecting the insula and cingulate gyrus bilaterally,[15] which was present in our patient. Additionally, our patient exhibited respiratory alkalosis, which is typically seen with urea cycle defects.[16]

From a pathophysiological perspective, the hyperammonemic state is associated with astrocyte swelling and increased extracellular glutamate, which leads to mitochondrial dysfunction and oxidative stress.[17] Increased glutamate results in neuronal hyperexcitability.[18] Neurons themselves are relatively spared until the cerebral edema reaches the point where intracranial pressure exceeds mean arterial pressure. At this point, cerebral blood flow is compromised, and cerebral ischemia ensues. The EEG will become progressively slower as ammonia rises with eventual suppression,[10] even before cerebral herniation. With appropriate management, recovery is possible, even with a suppressed EEG, up until cerebral ischemia develops.

Reflecting on this patient's presentation, there are likely triggers for decompensation of a UCD, leading to hyperammonemia even before the administration of valproic acid. He was likely in a catabolic state from the administration of corticosteroids, which increases protein metabolism, and from the critical illness.[19,20] He also received protein-enriched enteral feeding following usual protocols in critical care, leading to an increased nitrogen burden. It is noteworthy that the patient had already experienced seizures and cortical changes on MRI before the administration of valproic acid, indicating that ammonia levels were already likely to have been neurotoxic but went unrecognized.

Patients with late-onset OTC deficiency are often initially misdiagnosed with other conditions, such as encephalitis, poisoning, psychiatric disorders or epilepsy. A thorough investigation into the patient's personal and family history, along with identifying any possible triggers, is crucial for accurate diagnosis.[21] In retrospect, an extensive family history revealed that the patient's nephew died several decades earlier from what was thought to be Reye's syndrome. When faced with a patient displaying acute psychiatric symptoms or alterations in level of consciousness due to hyperammonemia, it is imperative to consider UCDs and gather a comprehensive history, including recent and historical dietary changes that might have triggered hyperammonemia episodes.[22] Recent increases in dietary protein intake and corticosteroid administration are increasingly recognized as a potential trigger for hyperammonemia in undiagnosed individuals with partial OTC deficiency. Further, it is well known that valproic acid can induce hyperammonemia in patients with a urea cycle defect, even at therapeutic dosages, through the inhibition of carbamoyl phosphate synthase 1.

To date, there have been documented instances of at least five cases where OTC deficiency has been genetically confirmed, with symptoms emerging in individuals aged 50 and above.[10,20,23–25] Our case represents the oldest reported age at diagnosis documented in the literature. These reports highlight the importance of monitoring ammonia levels and considering the possibility of UCDs in older individuals presenting with encephalopathy. Diagnosing this condition is crucial as it is treatable, and early intervention can significantly impact patient outcomes. Additionally, it's imperative to conduct familial screening to identify other potentially affected individuals in subsequent generations. This proactive approach can help prevent and promptly address life-threatening episodes of encephalopathy or neonatal coma in newborns, thereby improving overall patient care and management. In this case, an adult daughter was identified as being heterozygous for the mutation. She has been asymptomatic for OTC deficiency. Plasma ammonia and amino

https://doi.org/10.1017/cjn.2025.19

acids are monitored, and she has been counseled on the risks of having an affected child.

In conclusion, it is essential to check ammonia levels in individuals facing unexplained coma, seizures or cerebral edema, regardless of age. This is especially important for critically ill patients and for those experiencing a catabolic state. While late-onset OTC deficiency is infrequent, it should be considered when evaluating unexplained delirium or coma, particularly in cases where hepatic enzymes and synthetic function seem relatively normal. Early identification of an OTC deficiency and initiation of therapy have the potential to be lifesaving.

Acknowledgments. No funding was received for this manuscript. The authors would like to extend their gratitude to the family of the patient.

Author contributions. KB and TG participated in conception, drafting and revising the manuscript. SD, VP and AT participated in drafting and revising the manuscript. RH and TR provided clinical expertise and revisions for the manuscript.

Competing interests. TG, KB, RH, TR, SD, VP and AT have no competing interest to declare. TG has received grant funding to the institution from the Canadian Institutes of Health Research, Lawson Health Research Fund, Academic Medical Organization of Southwestern Ontario and the Robert N. Kohn NORSE Family Registry Memorial Research Fund for unrelated research. TG is a medical advisory board member of the NORSE Institute.

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