BMC Neurology

CASE REPORT

Open Access

Unmasked acute intermittent porphyria in a patient with COVID-19-associated posterior reversible encephalopathy syndrome

Hideo Handa[1], Hiroki Masuda[1*], Satoki Hanayama[1], Amika Kajiyama[2,3], Sawako Suzuki[2,3], Atsuhiko Sugiyama[1], Koutaro Yokote[2,3] and Satoshi Kuwabara[1]

Abstract

Background Acute intermittent porphyria (AIP) is a rare but treatable disease. COVID-19 has various possible complications including posterior reversible encephalopathy syndrome (PRES). COVID-19 was reported to trigger an acute attack in patients with acute hepatic porphyria (AHP). The pathophysiology of AHP-associated PRES is not fully elucidated.

Case presentation A 31-year-old Vietnamese female initially presented with seizures, severe hyponatremia, and hypertension after COVID-19. Despite the initial treatment, she had recurrent seizures and developed PRES as confirmed by magnetic resonance imaging. Further investigations revealed a genetic mutation of c.517 C > T in *HMBS*, leading to a diagnosis of AHP. Treatment with hemin significantly improved her symptoms and corrected her electrolyte imbalance.

Conclusions This case highlights the potential for COVID-19 to trigger acute attacks in patients with underlying porphyria, potentially leading to complications such as PRES. Also, we observed elevated catecholamine levels during an acute porphyria attack and PRES, suggesting their involvement in the pathogenesis of AIP-associated PRES. Clinicians should consider the possibility of porphyria in patients with COVID-19-associated PRES, especially when they present with gastrointestinal and neuropsychiatric symptoms.

Background

After the COVID-19 pandemic, numerous neurologic complications have been reported, which include Guillain-Barre syndrome, acute disseminated encephalomyelitis, and posterior reversible encephalopathy syndrome (PRES); however, the pathophysiology of these complications is not fully understood [1].

Acute intermittent porphyria (AIP) is a subtype of acute hepatic porphyria (AHP). Patients with AHP could manifest clinically with abdominal pain, nausea, tachycardia, hyponatremia, mental status changes, hypertension, and urine color changes. Patients with AHP could also experience seizures and PRES [2].

*Correspondence:
Hiroki Masuda
hiroki_masuda@chiba-u.jp
[1]Department of Neurology, Graduate School of Medicine, Chiba University, 1-8-1 Inohana, Chuo-ku, Chiba 260-8677, Japan
[2]Department of Endocrinology, Hematology and Gerontology, Graduate School of Medicine, Chiba University, Chiba, Japan
[3]Department of Diabetes, Metabolism and Endocrinology, Chiba University Hospital, Chiba, Japan

Herein, we report the case of a patient with AHP whose first attack was incited by COVID-19 and who presented with PRES.

Case presentation

A 31-year-old Vietnamese female who presented with seizures was transported to our hospital by ambulance. The patient had been in her usual state until a week before the current presentation when she developed fever, vomiting, and abdominal pain. Two days before her first visit, a nasopharyngeal swab performed at a clinic returned a positive result for COVID-19. She had been vaccinated twice against COVID-19, and this was her first infection. On the day of the first visit, she experienced two episodes of generalized tonic-clonic seizures (GTCS) and was transported to our hospital in a coma. Her past medical history was unremarkable, and she had never experienced GTCS and severe gastrointestinal symptoms before. Her family history was marked by episodes of vomiting, seizures, and abdominal pain in her mother that lasted several months at the age of 31. This information was carefully collected at the time of admission. She had persistent hypertension and tachycardia. Her physical examination was unremarkable and she had no dermatologic abnormalities. Laboratory tests revealed severe hyponatremia (121 mEq/L) and mild hypomagnesemia (1.7 mg/dL). Her chest X-ray and head CT scans revealed no abnormalities. Despite her hyponatremia being resistant to hypertonic saline, she regained consciousness on the second day of hospitalization. On her 10th day of hospitalization, she had another episode of GTCS and transient mild left hemiparesis despite her hyponatremia having been corrected to 128 mEq/L (Table 1). She became mildly agitated and depressed after the GTCS episode, and she still had hypertension (177/99 mmHg), tachycardia (141 bpm), and generalized myalgia. Magnetic resonance imaging (MRI) revealed a T2 shine-through lesion in the bilateral parietal and right occipital lobes, encompassing both subcortical and cortical regions, indicative of PRES (Fig. 1). Her hypertension was

Table 1 Laboratory results on the 10th and 11th days of hospitalization

Laboratory test	Value	Reference
Albumin (g/dL)	3.8	4.1–5.1
Blood urea nitrogen (mg/dL)	16	8–20
Creatinine (mg/dL)	0.44	0.46–0.79
Sodium (mEq/L)	128	138–145
Potassium (mEq/L)	3.5	3.6–4.8
Chloride (mEq/L)	94	101–108
Magnesium (mEq/L)	1.4	1.8–2.4
C-reactive protein (mg/dL)	0.01	< 0.15
Glucose (mg/dL)	116	73–109
Serum osmolality (mOsm/kg)	264	275–290
Vasopressin (pg/mL)	1.8	N.A.
Epinephrine (pg/mL)	196	< 100
Norepinephrine (pg/mL)	823	100–450
Dopamine (pg/mL)	48	< 20
Random cortisol (ug/dL)	28.8	7.1–28.8
Random ACTH (pg/mL)	22.2	< 63.3
TSH (uIU/mL)	0.990	0.350–4.940
Free T4 (ng/dL)	1.44	0.70–1.48
Antinuclear antibodies	1:160	< 1:40
Anti-dsDNA antibodies	Negative	Negative
Anti-Sm antibodies	Negative	Negative
Urine sodium (mEq/L)	152	N.A.
Urine osmolality (mOsm/kg)	542	50–1,300
Urine delta-aminolaevulinic acid (mg/gCre)	158.4	0.7–2.5
Urine coproporphyrin (μg/gCre)	1,170	< 170
Urine uroporphyrin (μg/gCre)	10,168	< 36
Urine epinephrine (μg/day)	25.3	3.4–26.9
Urine norepinephrine (μg/day)	227.5	48.6–168.4
Urine dopamine (μg/day)	258.5	365–961.5
Urine metanephrine (mg/day)	0.66	0.04–0.19
Urine normetanephrine (mg/day)	0.48	0.09–0.33

ACTH: adrenocorticotropic hormone, N.A.: not applicable, TSH: thyroid-stimulating hormone

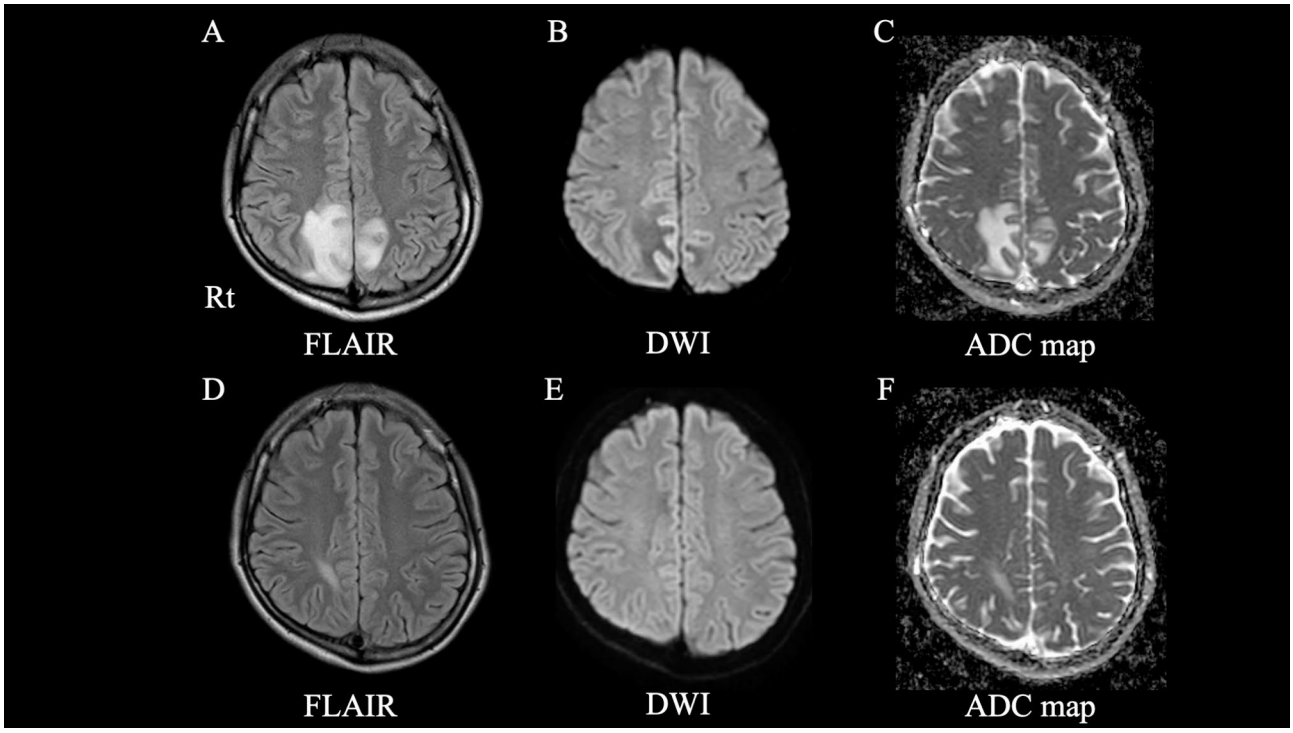

Fig. 1 MRI findings of the patient. After an episode of generalized tonic-clonic seizures, fluid-attenuated inversion recovery imaging demonstrated high-signal lesions in her bilateral parietal and right occipital lobes on the 10th day of hospitalization (**A**). The diffusion-weighted image (DWI) (**B**) and apparent diffusion coefficient (ADC) map (**C**) showed high ADC lesions in her bilateral parietal and right occipital lobes, suggesting T2 shine-through lesions and small-sized diffusion-restricted lesions in her parietal lobes. Follow-up MRI revealed shrinkage of the lesions on the 25th day of hospitalization (**D**, **E**, **F**)

successfully managed with a maximum dosage of 10 mg of amlodipine, and the follow-up MRI showed improvements in the abnormal findings. Given her female sex, young age, high blood pressure, tachycardia, and prior COVID-19 infection, we considered COVID-19-associated PRES, AHP, systemic lupus erythematosus, and pheochromocytoma as possible etiologies of PRES [1, 2]. Among these, we considered AHP the most likely diagnosis based on a constellation of characteristic manifestations including PRES, neuropsychiatric symptoms (agitation, depression), and gastrointestinal symptoms (vomiting, abdominal pain) [3]. First, we exposed the patient's urine to sunlight and observed its discoloration (Fig. 2). Second, urinalysis demonstrated elevated delta-aminolaevulinic acid (158.4 mg/g·Cre), coproporphyrin (1,170 mcg/g·Cre), and uroporphyrin (10,168 mcg/g·Cre). Her antinuclear antibody titer was 1:160; however, both anti-dsDNA antibodies and anti-Sm antibodies tested negative. Plasma epinephrine (196 pg/mL [< 100]), norepinephrine (823 pg/mL [100–450]), and dopamine (48 pg/mL [< 20]) levels were elevated. Catecholamine levels were measured using a standard protocol after 30 min of supine rest. The 24-hour urinary excretion assay revealed that her metanephrine (0.66 mg/day [0.04–0.19]) level was markedly elevated. The patient had not consumed any foods, beverages, or medications known to elevate catecholamine or its metabolite levels in plasma and urine samples. However, a torso CT scan did not reveal pheochromocytoma or extraadrenal paraganglioma. Furthermore, genetic analyses demonstrated a heterozygous missense mutation of c.517 C > T in *HMBS*, confirming the diagnosis of AIP [4]. She received hemin from day 30 to day 33 of hospitalization. Following hemin administration, all her symptoms (e.g., depression, agitation, myalgia, and tachycardia), as well as electrolyte disturbances including hyponatremia, showed significant improvement. Simultaneously, her amlodipine was tapered off without any recurrence of hypertension.

Discussion and conclusions

This case highlights two important clinical issues. First, COVID-19-associated PRES was caused by the first attack of AHP. Second, AHP-associated PRES was linked to abnormally high blood pressure and increased catecholamine levels.

First, in this case, COVID-19-associated PRES was caused by AHP, a metabolic disorder induced by a genetic defect in the heme synthesis enzyme. AIP, the most common form of AHP, is caused by a deficiency in porphobilinogen deaminase [3, 5]. Previous case reports have demonstrated that COVID-19 can trigger an acute attack in patients with AHP [6, 7]. Other researchers

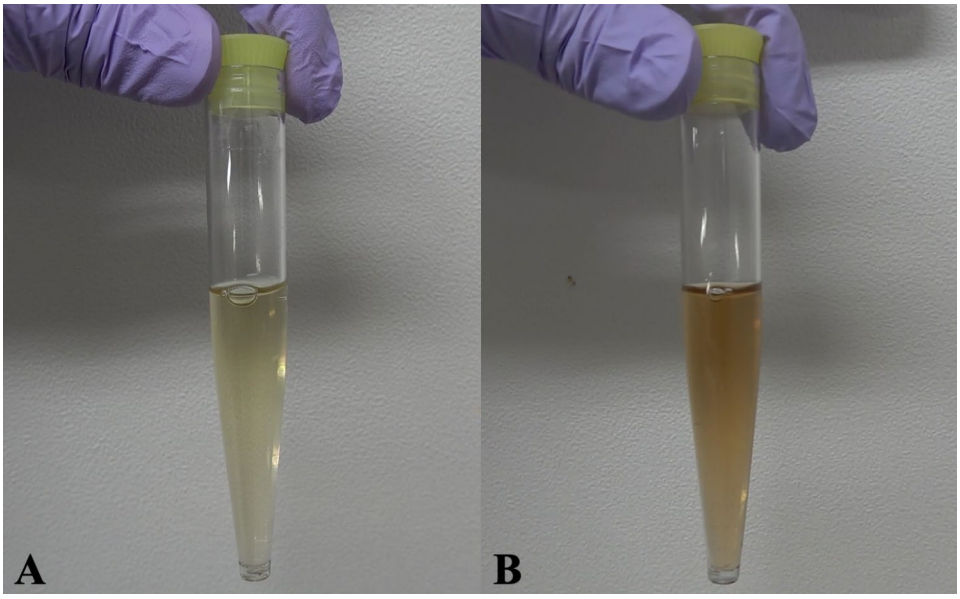

Fig. 2 Discolored urine after exposure to the sunlight. A day of sunlight exposure darkened the patient's urine, indicating urinary porphyrin accumulation

have reported that COVID-19 alters porphyrin metabolism, potentially accumulating uroporphyrin and coproporphyrin in the serum of infected patients [8]. Based on these studies and our case, COVID-19 has the potential to trigger an attack of AHP.

Porphyria might play a role in COVID-19-associated PRES, and there may have been undiagnosed AHP patients among those with COVID-19-associated PRES, for two main reasons. First, as described in this case, COVID-19-associated PRES can be caused by the first attack of AHP. Second, porphyrin can accumulate in the serum of patients with COVID-19. While the pathophysiology of COVID-19-associated PRES remains unclear and is often explained by hyperinflammation and endothelial cell damage caused by the SARS-CoV-2 spike protein [10, 11], some cases of COVID-19-associated PRES could be linked to porphyria. Clinicians should be aware that the penetrance of mutated *HMBS* gene is low (less than 1%), despite its prevalence is as high as 1 in 1,675–1,782 [9]. Therefore, to reduce false-positive results in *HMBS* gene testing, clinicians should consider porphyria as a potential underlying cause of COVID-19-associated PRES, particularly in patients presenting with concurrent PRES, gastrointestinal symptoms such as abdominal pain, and neuropsychiatric manifestations, including agitation or depression [5, 12]. Further studies are needed to determine the prevalence of mutated *HMBS* and to measure porphyrin levels in patients with COVID-19-associated PRES.

In our case, hypertension and increased catecholamine levels were observed simultaneously during the acute attack of AHP and PRES. While the pathophysiology of AHP-associated PRES is not well understood [13], three hypotheses have been suggested: (1) reduced levels of nitric oxide synthase, a heme-containing enzyme, during an acute attack causes decreased levels of nitric oxide, a key vasodilatory substance, leading to uncontrolled cerebrovascular vasoconstriction; (2) autonomic dysfunction during an acute attack causes high blood pressure and disrupts the cerebrovascular endothelium; (3) excessive porphyrin precursors may directly cause endothelial damage and vasoconstriction [13, 14]. Additionally, a previous report demonstrated that aminolaevulinic acid and porphobilinogen blocked catecholamine reuptake, leading to the accumulation of the catecholamines [15]. Our data and this previous report support the hypothesis that a porphyrin-induced catecholamine surge may contribute to high blood pressure beyond the upper limit of cerebral autoregulation, resulting in PRES. Further large-scale studies involving catecholamine tests during acute attacks should be conducted to probe into the pathophysiology of PRES in patients with AHP.

In conclusion, COVID-19-associated PRES can be caused by AHP, and AHP-associated PRES is linked to increased catecholamine levels. Clinicians should know that COVID-19 can trigger the first attack of AHP and that AHP can be an underlying mechanism of COVID-19-associated PRES. A constellation of gastrointestinal symptoms, neuropsychiatric symptoms, and urine discoloration is a key indicator for the diagnosis of AHP.

Abbreviations

PRES	Posterior reversible encephalopathy syndrome
AIP	Acute intermittent porphyria
AHP	Acute hepatic porphyria
GTCS	Generalized tonic-clonic seizures
MRI	Magnetic resonance imaging

Acknowledgements
None.

Author contributions
All authors had roles in writing this manuscript. HH, HM, SH and SK wrote the main manuscript text and prepared figure 1; Table 1. HH, HM, and SH prepared figure 2. AK, SS, AS, and KY supervised the main manuscript. HH, HM, SH, AK, SS, AS, KY, and SK participated in the care of this patient. AS conducted the genomic counseling. All authors read and approved the final manuscript.

Funding
This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Data availability
The datasets used and/or analyzed during the current study is available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
No Institutional Review Board (IRB) approval was necessary because this article is a case report.

Consent for publication
Patient provided verbal and written informed consent for this work after her symptoms had improved.

Competing interests
The authors declare no competing interests.

Received: 30 September 2024 / Accepted: 26 March 2025
Published online: 04 April 2025

References

1. Sharifian-Dorche M, Huot P, Osherov M, et al. Neurological complications of coronavirus infection; a comparative review and lessons learned during the COVID-19 pandemic. J Neurol Sci. 2020;417:117085. https://doi.org/10.1016/j.jns.2020.117085.
2. Hinduja A. Posterior reversible encephalopathy syndrome: clinical features and outcome. Front Neurol. 2020;11:71. https://doi.org/10.3389/fneur.2020.00071.
3. Marcacci M, Ricci A, Cuoghi C, et al. Challenges in diagnosis and management of acute hepatic porphyrias: from an uncommon pediatric onset to innovative treatments and perspectives. Orphanet J Rare Dis. 2022;17(1):160. https://doi.org/10.1186/s13023-022-02314-9.
4. Lee JS, Anvret M. Identification of the most common mutation within the porphobilinogen deaminase gene in Swedish patients with acute intermittent porphyria. Proc Natl Acad Sci U S A. 1991;88(23):10912–5. https://doi.org/10.1073/pnas.88.23.10912.
5. Stein PE, Badminton MN, Rees DC. Update review of the acute porphyrias. Br J Haematol. 2017;176(4):527–38. https://doi.org/10.1111/bjh.14459.
6. Bardak AE, Alada MO, Senkal N, Alibeyoğlu A, Köse M. Acute intermittent porphyria attack triggered by COVID-19 infection. Cureus. 2023;15(4):e37412. https://doi.org/10.7759/cureus.37412.
7. Upchurch M, Donnelly JP, Deremiah E, et al. Hereditary coproporphyria mimicking Guillain-Barré syndrome after COVID-19 infection. Cureus. 2022;14(1):e21586. https://doi.org/10.7759/cureus.21586.
8. San Juan I, Bruzzone C, Bizkarguenaga M, et al. Abnormal concentration of porphyrins in serum from COVID-19 patients. Br J Haematol. 2020;190(5):e265–7. https://doi.org/10.1111/bjh.17060.
9. Chen B, Solis-Villa C, Hakenberg J, et al. Acute intermittent porphyria: predicted pathogenicity of HMBS variants indicates extremely low penetrance of the autosomal dominant disease. Hum Mutat. 2016;37(11):1215–22. https://doi.org/10.1002/humu.23067.
10. Bonura A, Iaccarino G, Rossi SS, et al. Posterior reversible encephalopathy syndrome and reversible cerebral vasoconstriction syndrome in patients with COVID-19 infection: is there a link? A systematic review and case report analysis. J Neurol. 2023;270(6):2826–52. https://doi.org/10.1007/s00415-023-11684-4.
11. Hixon AM, Thaker AA, Pelak VS. Persistent visual dysfunction following posterior reversible encephalopathy syndrome due to COVID-19: case series and literature review. Eur J Neurol. 2021;28(10):3289–302. https://doi.org/10.1111/ene.14965.
12. Ventura P, Cappellini MD, Biolcati G, et al. A challenging diagnosis for potential fatal diseases: recommendations for diagnosing acute porphyrias. Eur J Intern Med. 2014;25(6):497–505. https://doi.org/10.1016/j.ejim.2014.03.011.
13. Oliveira Santos M, Leal Rato M. Neurology of the acute hepatic porphyrias. J Neurol Sci. 2021;428:117605. https://doi.org/10.1016/j.jns.2021.117605.
14. Pischik E, Baumann K, Karpenko A, Kauppinen R. Pathogenesis of acute encephalopathy in acute hepatic porphyria. J Neurol. 2023;270(5):2613–30. https://doi.org/10.1007/s00415-023-11586-5.
15. Beal MF, Atuk NO, Westfall TC, Turner SM. Catecholamine uptake, accumulation, and release in acute porphyria. J Clin Invest. 1977;60(5):1141–8. https://doi.org/10.1172/JCI108866.

Publisher's note