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CASE REPORT

# Acute Intermittent Porphyria Presenting with Posterior Reversible Encephalopathy Syndrome, Reversible Cerebral Vasoconstriction Syndrome and Myocardial Ischemia: A Case Report and Review

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**Abstract:** Acute intermittent porphyria is a rare autosomal dominant metabolic disorder. It can affect the autonomic, peripheral, and central nervous system. The present study reports on the case of 28-year-old Chinese female patient with posterior reversible encephalopathy syndrome, reversible cerebral vasoconstriction syndrome and myocardial ischemia which have been very rarely reported in patients with acute intermittent porphyria.

**Keywords:** acute intermittent porphyria, epilepsy, posterior reversible encephalopathy syndrome, reversible cerebral vasoconstriction syndrome, myocardial ischemia

## Introduction

Porphyrias are a group of eight genetically inherited or acquired disorders that result from enzyme deficiencies within the pathway of heme biosynthesis. The disorder can be classified according to its clinical manifestations as acute hepatic porphyrias and the erythropoietic porphyrias. The group of acute hepatic porphyrias that can cause acute neurological symptoms includes four types of porphyria: acute intermittent porphyria (AIP), variegate porphyria (VP), hereditary coproporphyria (HCP) and aminolevulinic acid dehydratase porphyria (ADP).[1,2]

Acute intermittent porphyria (AIP) is a rare autosomal dominant metabolic disorder caused by deficient activity of the third enzyme of heme biosynthetic pathway, hydroxymethylbilane synthase (HMBS).[2] AIP is the most common and severe type of acute hepatic porphyria. It can show acute attacks manifesting as a combination of abdominal pain, hyponatremia, neurological disturbances, and psychiatric symptoms.[2,3] In this report, we describe a case of AIP presenting abdominal pain, seizures, hyponatremia, posterior reversible encephalopathy syndrome (PRES), reversible cerebral vasoconstriction syndrome (RCVS), vertebral aneurysmal dilation, and myocardial ischemia.

## Case Description

A 28 -year-old Chinese woman was admitted to the department of gastroenterology of our hospital in February 2019 for fever and severe abdominal pain that occurred intermittently over a 5-day period. Three days ago, she experienced

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nausea, vomiting. She had undergone cesarean section three months ago. On the admission, her blood pressure was 122/70mmHg, her pulse was 80 beats/min, physical examination revealed that slight tenderness below the xiphoid process, no rebound tenderness, suspicious positive Murphy sign. There was no blistering, scarring, or erythema on the skin either. Detailed family history revealed no significant inherited disorders. On the night of admission and the 3rd day, she had two generalized tonic-clonic seizures for which she received diazepam. On the 2nd day after admission, brain magnetic resonance imaging (MRI) showed symmetric hypointense lesions on T1-weighted images, hyperintense lesions on T2-weighted images, and high-intensity lesions on fluid-attenuated inversion recovery (FLAIR) imaging in the frontal, parietal, and occipital lobes and cerebellar hemispheres. These lesions showed isointense or slight hypointense on diffusion-weighted imaging (DWI) (Figure 1A–L). Magnetic resonance angiography (MRA) provided right vertebral artery tortuosity and aneurysmal dilation in left vertebral artery (Figure 1M).

She was then transferred to neurology department for further investigation on the 3rd day. At the time of transfer, her blood pressure was 160/128mmHg, her pulse was 140 beats/min with regular rhythm, and her urine became dark colored. Neurological examination revealed mild disturbance of consciousness, weakness of four limbs and depressed deep tendon reflexes. Her electrocardiogram (ECG) showed sinus tachycardia and right ventricular hypertrophy, 10 hours later ECG showed dynamic evolution: pathological Q wave in II, III and aVF leads, ST/T-wave changes (Figure 2). Rapid examination of troponin I showed a significant elevation of 3.013ng/mL (normal range: 0–0.09ng/mL) favoring the diagnosis of myocardial impairment. Bedside echocardiography suggested myocardial segmental dyskinesia, left ventricular prosthetic tendon cord, left ventricular dysfunction, and ejection fraction (EF): 44%.

Her blood test revealed increased levels on the 4th day as follows: white blood cells, $16.10\times10^9$/L (normal range: $3.5–9.5\times10^9$/L); red blood cells, $6.40\times10^{12}$/L (normal range: $3.8–5.10\times10^{12}$/L); hemoglobin, 167g/L (normal range: 115–150g/L); platelets, $387\times10^9$/L (normal range: $125–350\times10^9$/L); aspartate transaminase, 52U/L (normal range: 13–35 U/L); alanine transaminase, 49U/L (normal range: 7–40U/L); creatine kinase, 245U/L (normal range: 40–200U/L); creatine kinase MB, 26 IU/L (normal range: 0–25U/L); lactic dehydrogenase (LDH), 286U/L (normal range: 120–250U/L); α-hydroxybutyrate dehydrogenase (HBDH), 208IU/L (normal range: 72–182U/L); lactic acid, 8.37mmol/L (normal range: 0.5–2.22mmol/L), except for hyponatremia of 131.5mmol/L (normal range: 137–147mmol/L) and hypokalemia of 3.28 mmol/L (normal range: 3.5–5.3mmol/L). The results of a urinalysis showed epithelial cell 80.0/μL (normal range: 0–8.84/μL), occult blood (+-), protein (-),

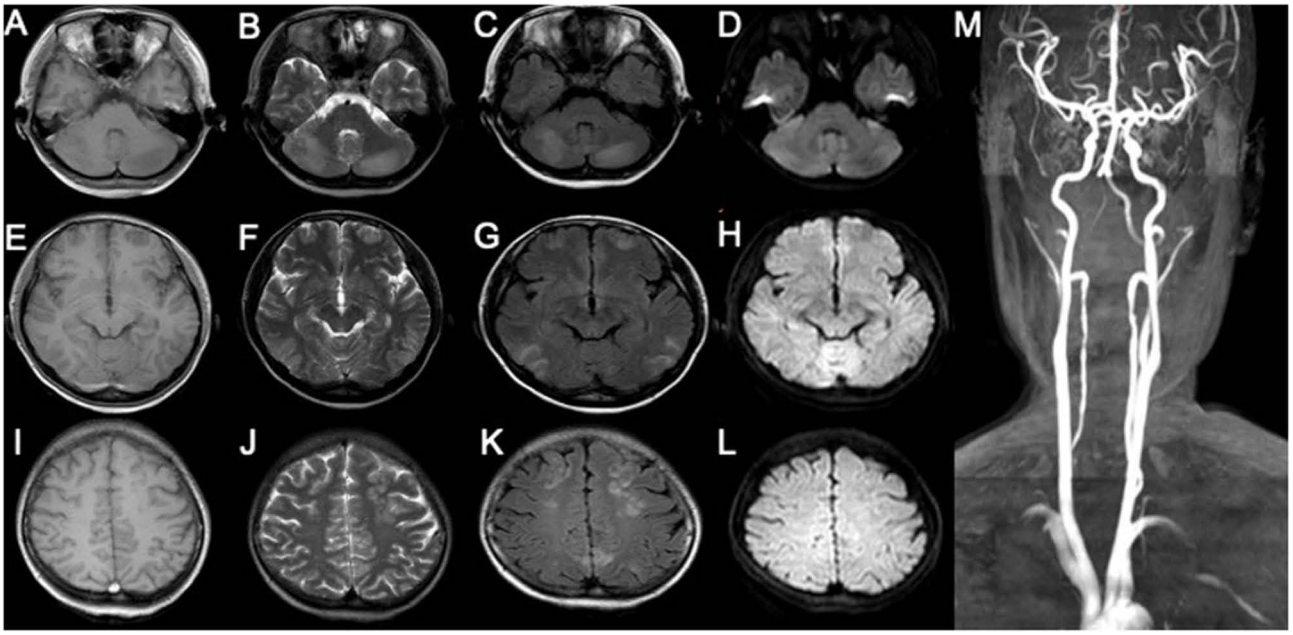


**Figure 1** MRI and MRA findings obtained on the 2nd day. Symmetric lesions in the frontal, parietal, and occipital lobes and cerebellar hemispheres showed hypointense on T1-weighted images (**A, E** and **I**), hyperintense on T2-weighted images (**B, F** and **J**) and FLAIR images (**C, G** and **K**), isointense or slight hypointense (**D**, **H** and **L**), on DWI. The distal portion of right vertebral artery was visualized ambiguously, and the left vertebral artery presented one aneurysmal dilation (**M**).

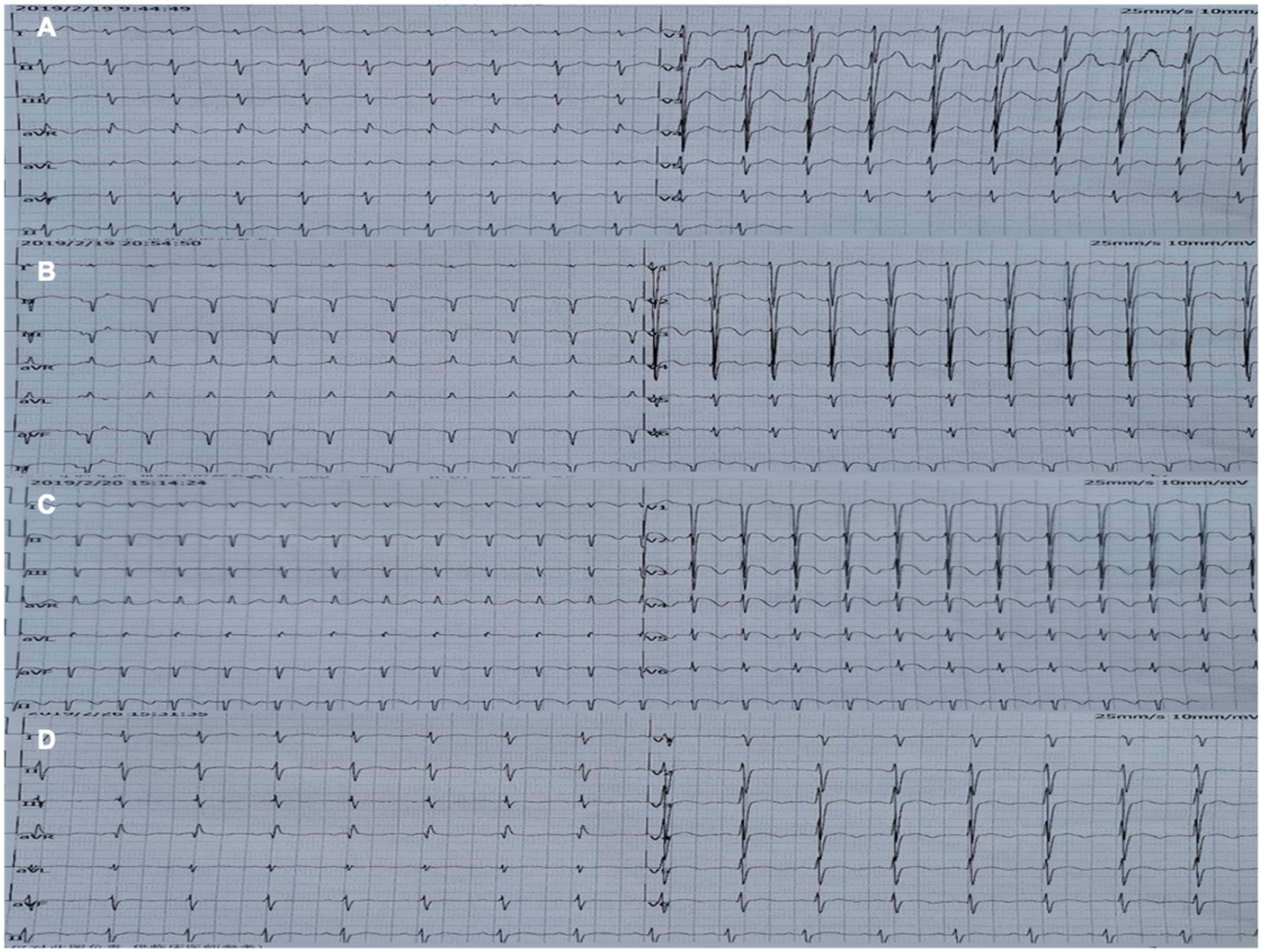


**Figure 2** Dynamic evolution of ECG ECG findings obtained on the 4th day (**A** and **B**), 5th day (**C**), 11th day (**D**). (**A**) showed slight ST-segment depression in limb leads and bidirectional change in the chest leads. (**B** and **C**) showed pathological Q wave in II, III and aVF leads and ST-segment arch like elevation in the chest leads. On the 11th day, all these changes improved (**D**).

urine bilirubin (++), ketone (++), besides discoloration of the urine. Her cerebrospinal fluid examination was normal. Electroencephalography revealed generalized slowing in both hemispheres but no epileptiform discharges. Nerve conduction studies showed normal findings except for a low incidence of F waves on the median nerves.

Although she had no family history of porphyria, AIP was considered because of the combination of central nervous system (CNS) abnormalities, dysautonomia, abdominal pain and the dark-colored urine, and the urinary porphyrinogen sun exposure detection was made which showing her urine turned darker and red (Figure 3), although urinary porphobilinogen (PBG) and delta-aminolevulinic acid (δ-ALA) could not be tested due to the limited conditions in our hospital. The patient was started on administration of glucose, and a high carbohydrate diet as hematin was not available in our hospital. She responded well and made a gradual recovery. On the 5th day, her abdominal pain was relieved. From the 11th day of admission, her elevated liver enzymes, hypertension, and tachycardia gradually returned to normal levels. On the 21th day, the patient had recovered and discharged from the hospital.

Repeated MRI and MRA finding were as follows (Figure 4): On the 14th day, those lesions had nearly disappeared but MRA revealed vasoconstriction in the proximal portion of right vertebral artery, bilateral anterior cerebral artery (ACA), middle cerebral artery (MCA) and posterior cerebral artery (PCA), aneurysmal dilation in left vertebral artery. On the 36th day, the vasoconstriction of ACA, MCA and PCA returned to nearly normal, except the exacerbating of aneurysmal dilation in the left vertebral artery. On 1 year of onset, the dilation in the left vertebral artery had improved.

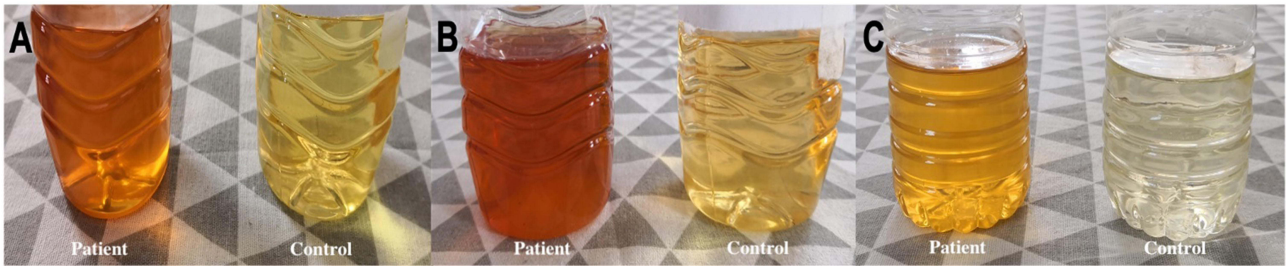


**Figure 3** Urine samples before (**A**) and after (**B**) exposure to sunlight. Her urine turned darker and redder upon exposure to light, and improved after 1 day of high-glucose administration (**C**).

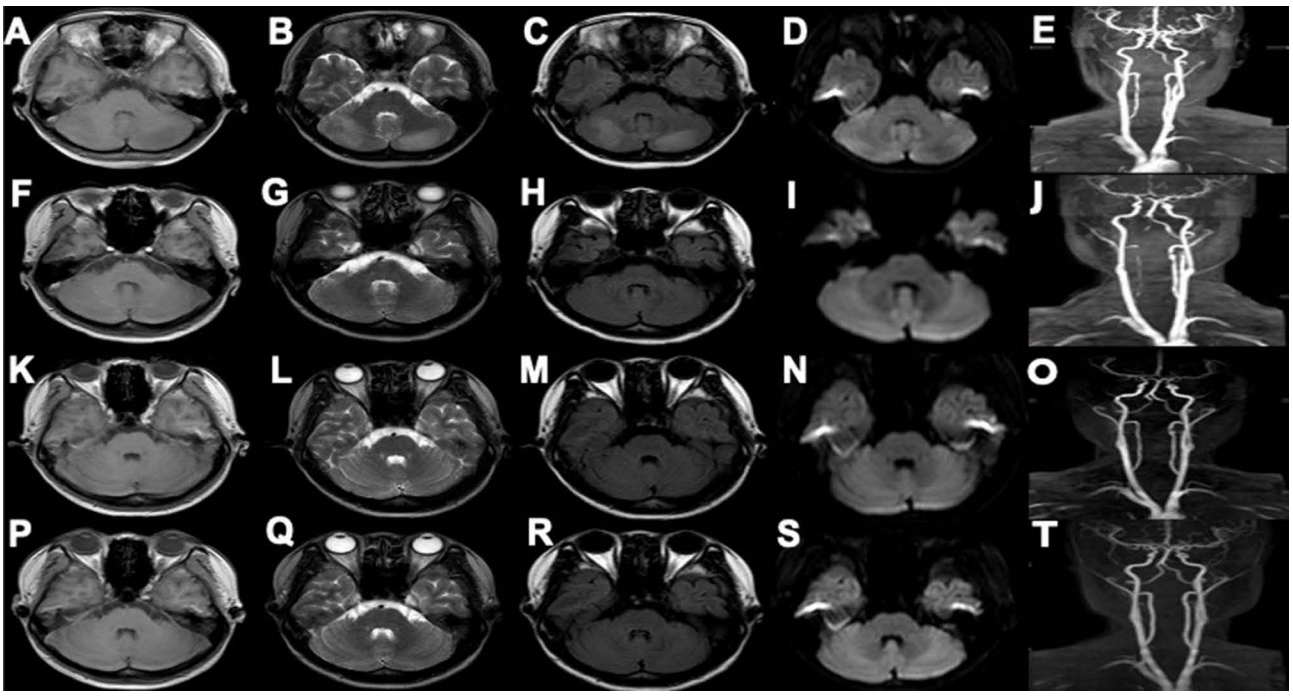


**Figure 4** Dynamic evolution of MRI and MRA. The lesions observed on the 2nd day (**A–D**) were improved on the 14th day (**F–I**). The vasoconstriction observed on the 2nd day (**E**) spreads to the whole right vertebral artery, ACA, MCA and PCA on the 14th day (**J**). As with the improvement in the MRI findings, the constriction of right vertebral artery, ACA, MCA, and PCA was nearly normalized on the 36th day (**K–O**), except the exacerbating of the aneurysmal dilation in left vertebral artery which improved on the 1 year of onset (**P–T**).

Repeated echocardiography on 18th day of onset showed improved EF: 55% besides the sustained myocardial segmental dyskinesia meanwhile her coronarography suggested normal.

The diagnosis of AIP was confirmed by the following genetic analysis: she carried a heterozygous mutation c.772–20A>C in intron 11 of the HMBS gene, family verification revealed that the patient's father carried the mutation. Due to differences in the mutation rate of the genetic variant, her father has not developed the disease temporarily. The patient's mother did not carry this mutation. The results of the mutation verification are shown in Figure 5. She was discharged after 3 weeks with weakness of limbs. After 1 year of onset, the patient showed anemia (red blood cells, $3.62\times10^{12}$/L; hemoglobin, 69g/L). No acute attacks have occurred to date.

## Discussion

Acute intermittent porphyria is a rare inherited disorder, which is caused by mutations in the HMBS gene, HMBS, an enzyme in the heme biosynthetic pathway, its deficiency leads to the accumulation of δ-ALA and PBG.[2,3] AIP can show

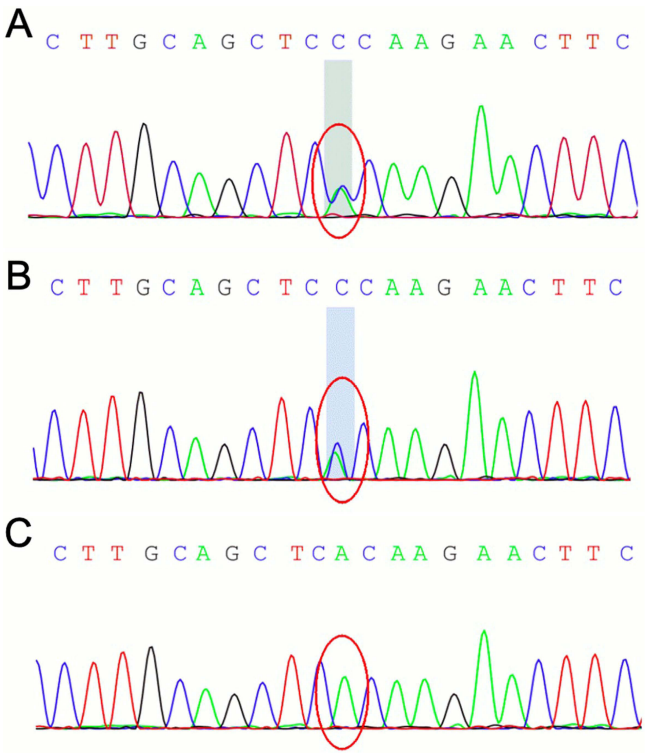


**Figure 5** Gene analysis revealed a heterozygous Mutation involving intron 11 (c.772–20A>C) of HMBS in the patient (**A**), the mutation was identified in the patient's father (**B**), but not in the patient's mother (**C**) (as shown in red circle).

acute attacks manifesting as a combination of abdominal pain, neurological disturbances, psychiatric and behavioural symptoms.[1–3]

Acute attacks can be provoked by certain drugs such as most antiepileptic drugs, alcoholic beverages, endocrine factors, calorie restriction, stress, pregnancy, infections (such as COVID-19) and so on.[4,5] Its diagnosis is usually missed and delayed because of its varied presentation. It is characterized by periodic acute attacks of neurovisceral symptoms such as abdominal pain, hyponatremia, neurologic dysfunction, and psychiatric symptoms and colored urine.[6] Our patient not only had these common symptoms but also had rare phenomena such as PRES, RCVS, myocardial damage and possible coronary spasm.

Complications such as PRES and RCVS have been very rarely reported in patients with AIP.[7,8] Although our patient did not show an acute severe headache, but the clinical findings were similar to the clinical presentation of RCVS in the following aspects: the reversibility of vasoconstriction within 3 months after onset; the coexistence of changes consistent with PRES.[9] Although the precise mechanism remains unclear, there are several hypotheses. Endothelial dysfunction is considered to be a major pathogenic process.[8–10] Hypertension might beyond the autoregulation limit, leading to breakdown of blood-brain barrier and subsequent vasogenic edema.[11,12] The lack of the heme protein nitric oxide synthase (NOS) can lead to decreased production of the major vascular dilator nitric oxide (NO), which is thought to cause vasoconstriction.[7,8] To clarify the theory, Tadayuki et al firstly measured the concentration of serum nitrate ion ($NO3^-$), which is an oxidized metabolite of NO, in a patient with AIP.[8] Meanwhile, porphyrin precursors such as ALA or PBG might cause direct endothelial cell damage and release of potent vasoconstrictors such as endothelin or thromboxane.[11,13,14]

Besides, our patient presented troponin I and ECG evolution and suffered heart failure; although the coronary CT angiography did not present obvious abnormalities after acute onset, we still considered the possible existence of coronary vasospasm during an attack of AIP. Three case reports presented cases with RCVS accompanied by coronary artery vasospasm.[15–17] There are also another three case reports for patients with Takotsubo Cardiomyopathy triggered by AIP, which is characterized by transient left ventricular dysfunction with mimicking acute myocardial infarction,[18] this

patient had similar presentations, and we think that this is the first report of reversible myocardial infarction in association with AIP accompanied by PRES and RCVS.

The diagnosis of porphyria can be challenging unless a high clinical suspicion is present. The presence of a family history of similar symptoms can be helpful, but often this is not present. The key differential diagnosis for this case includes CNS infection, cerebral vasculitis, mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS), methylmalonic acidemia (MMA), and lead poisoning.

The treatment of porphyria requires two phases: acute management and prophylactic management.[1,19,20] Intravenous hematin is an evidence-based effective therapy during acute attack. Antiepileptic therapy requires more care because many commonly used antiepileptic drugs like barbiturates, valproate, carbamazepine, and lamotrigine are porphyrinogenic.[6]

## Conclusion

PRES and RCVS have a wide range of possible causes, and physicians must be aware of those rare causes. Acute intermittent porphyria should be considered early and equal to other differential diagnoses in the patient with unexplained abdominal pain, hyponatremia, PRES, RCVS and /or acute myocardial infarction.

## Abbreviations

AIP, acute intermittent porphyria; VP, variegate porphyria; HCP, hereditary coproporphyria; ADP, aminolevulinic acid dehydratase porphyria; HMBS, hydroxymethylbilane synthase; PRES, posterior reversible encephalopathy syndrome; RCVS, reversible cerebral vasoconstriction syndrome; MRI, magnetic resonance imaging; FLAIR, fluid-attenuated inversion recovery; DWI, diffusion-weighted imaging; MRA, magnetic resonance angiography; EF, ejection fraction; LDH, lactic dehydrogenase; HBDH, α-hydroxybutyrate dehydrogenase; CNS, central nervous system; PBG, urinary porphobilinogen; δ-ALA, delta-aminolevulinic acid; ACA, anterior cerebral artery; MCA, middle cerebral artery; PCA, posterior cerebral artery; $NO3^{-}$, nitrate ion; NO, nitric oxide; NOS, nitric oxide synthase; MELAS, mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes; MMA, methylmalonic acidemia.

## Data Sharing Statement

The original contributions presented in the study are included in the article, and further inquiries can be directed to the corresponding author.

## Ethical Approval

The case details needed the institutional approval to publish, and it was approved by the Ethics Committee of Liaocheng People's Hospital, and written informed consents including the consent to publish were obtained from the patient. The study complied with the Declaration of Helsinki.

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## Disclosure

The authors declare that they have no conflicts of interest in this work.

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