

# Acute Intermittent Porphyria Presenting as Acute Pancreatitis and Posterior Reversible Encephalopathy Syndrome

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**Abstract-** Acute intermittent porphyria (AIP) is an inherited metabolic disease that can affect the autonomic, peripheral and central nervous systems. Pancreatic diseases associated with AIP is rarely reported. We report here a 60-year-old non-alcoholic male who had typical manifestations of AIP, including abdominal pain, constipation, tachycardia, hypertension, mental disturbances, psychiatric manifestations, seizures, peripheral neuropathy, and excessive excretion of porphyrin precursors in urine. Increases of serum amylase and lipase, as well as mild pancreatic edema on ultrasonography, were noted during the acute attack of AIP, suggesting concomitant acute pancreatitis. In this patient, brain magnetic resonance imaging revealed reversible multifocal cerebral lesions resembling a posterior reversible encephalopathy syndrome (PRES) during the acute attack of AIP. Because the clinical manifestations of acute pancreatitis could be present with an acute attack of AIP, early confirmation of diagnosis is mandatory to effectively manage the attack and avoid inappropriate treatment.

**Key Words:** Acute intermittent porphyria, Acute pancreatitis, Encephalopathy

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## INTRODUCTION

Acute intermittent porphyria (AIP) is an inherited metabolic disease with an autosomal dominant pattern, and could affect the autonomic, peripheral, as well as central nervous systems<sup>(1)</sup>. This disease is caused by a partial deficiency of the third enzyme, porphobilinogen deaminase, in heme biosynthesis<sup>(1)</sup>. Clinically, AIP is

characterised by neurovisceral crises, including abdominal pain, constipation, nausea and vomiting, tachycardia and hypertension, most of which are related to autonomic dysfunction<sup>(1,2)</sup>. The autonomic nervous system controls many of the functions of the body, including those of the pancreas, and is one of the important factors that regulate pancreatic regeneration and stimulate the carcinogenesis<sup>(3)</sup>.

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However, pancreatic diseases associated with AIP are infrequently reported in medical literatures. The exact mechanism of pancreatic involvement during an acute attack of AIP is uncertain. Few cases of AIP complicated by acute or chronic pancreatitis have been reported<sup>(4-7)</sup>. Herein, we report a case of AIP associated with both biochemical and morphological manifestations of acute pancreatitis. Moreover, brain magnetic resonance imaging (MRI) revealed reversible multifocal cerebral lesions resembling a posterior reversible encephalopathy syndrome (PRES) during the acute attack of AIP with pancreatic involvement.

### CASE REPORT

A 60-year-old non-alcoholic male was admitted to a local hospital in April 2005 because of colicky abdominal pain, nausea, and vomiting for 5 days. Three days later, he experienced two generalized motor seizures. After intravenous phenytoin therapy, he was transferred to our emergency room on April 22.

At the time of transfer, the patient appeared to be in an acute confusional state that included disorientation, psychosis, and agitation. The blood pressure was 164/98 mmHg and heart rate 123 beats/min. Biochemical studies revealed: serum amylase 385 U/L (normal, 27-137 U/L), serum lipase 845 U/L (normal, <190 U/L), aspartate transaminase 136 U/L, alanine transaminase 39 U/L, blood urea nitrogen 17 mg/dL, and serum creatinine 1.2 mg/dL. The cerebrospinal fluid examination was normal. Tests for drug screens, blood lead level, syphilis, antinuclear antibody, viral markers (herpes simplex virus, human immunodeficiency virus, hepatitis B, hepatitis C, cytomegalovirus and Epstein-Barr virus), tumor markers, serum electrophoresis, and thyroid function were all unremarkable. There was no family history of porphyria.

Abdominal roentgenogram showed ileus and ultrasound examination demonstrated a homogeneously enlarged pancreas (Fig. 1). There was neither dilatation nor stones in the common bile duct and gallbladder. No phlegmon, pseudocyst or extra-pancreatic fluid was found on abdominal computed tomography scans. Brain MRI revealed multiple cortical and subcortical hyperin-

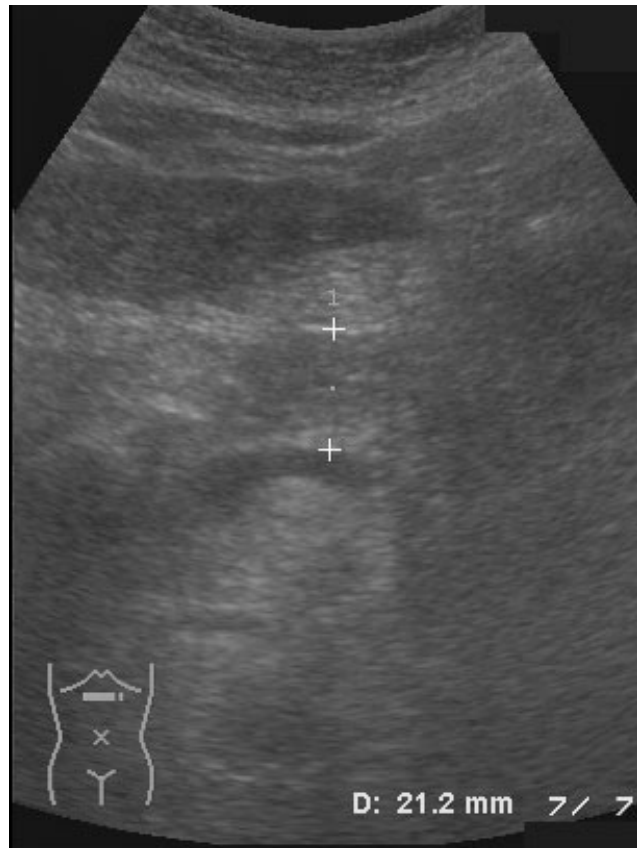
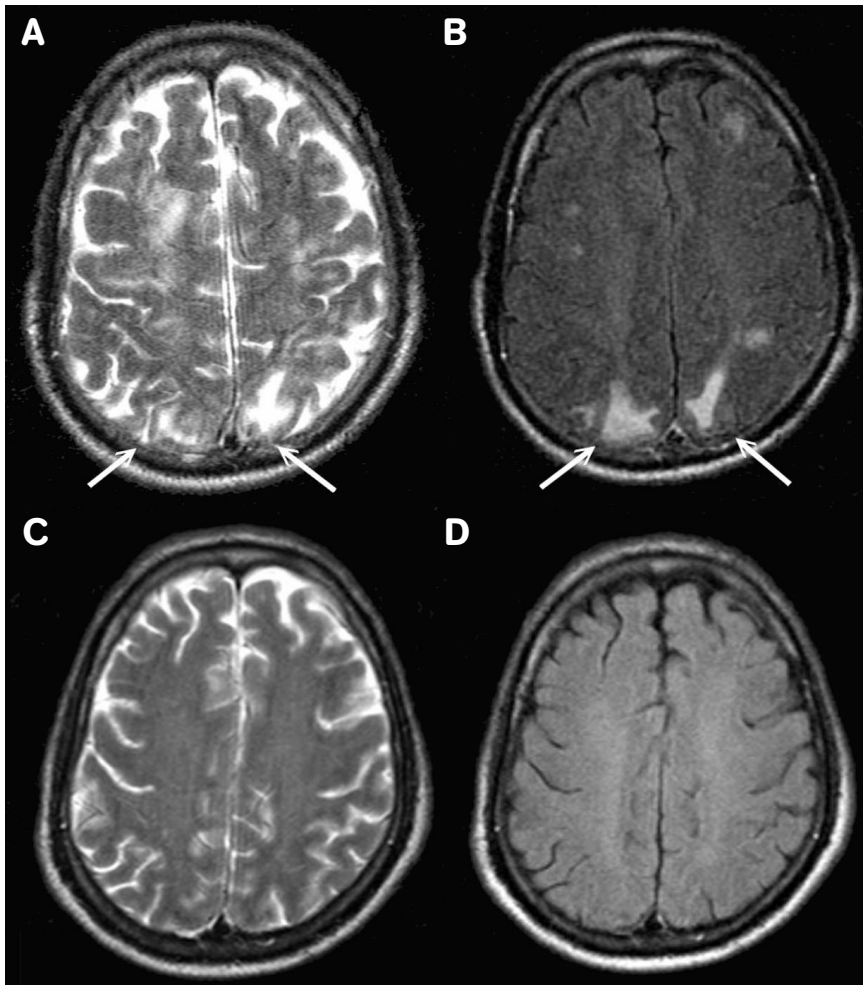


Figure 1. Ultrasonogram shows mild edema of pancreas during the acute attack of acute intermittent porphyria.

tensity lesions on T2-weighted images in the bilateral frontoparietal and occipital areas (Fig. 2A). These signal alterations were predominantly located in the posterior regions of the brain and were detected best by fluid-attenuated inversion recovery (FLAIR) sequences (Fig. 2B). The T1-weighted images, diffusing-weighted images and MR spectroscopy of lesions were unremarkable and there was no contrast enhancement. MR angiography and venography showed normal results.

On April 30, the patient was floridly confusional and developed facial diplegia, hoarseness and quadriplegia. The findings of serial nerve conduction studies were listed in the Table. The initial study showed a reduction in amplitude of compound muscle action potentials (CMAPs) in bilateral median nerves. His sensory nerve conduction findings including sensory nerve action potentials (SNAPs) were within the reference limits.



**Figure 2.** During the acute attack of acute intermittent porphyria, axial views of brain magnetic resonance imaging (MRI) T2-weighted image (A) and Fluid-attenuated inversion recovery (FLAIR) image (B) show sub-cortical hyperintensity lesions, more obvious in the occipital region (arrows). T2-weighted image (C) and FLAIR image (D) are followed-up 6 weeks later, showing complete regression of the lesions.

There was no evoked response in the sympathetic skin response test. At this point, dark tea-colored urine was noted. The diagnosis of porphyria was confirmed by increased urinary  $\delta$ -aminolevulinic acid (ALA) of 57.83 mg/24 h (normal, 1.3-7 mg/24 h) and porphobilinogen (PBG) of 139.8 mg/24 h (normal, 0-2 mg/24 h). Urinary coproporphyrinogen was negative and porphyrin was positive. Serum amylase and lipase were 263 and 573 U/L, respectively, and remained elevated for the next five weeks. He received intravenous glucose therapy at a rate of 10 g/h for 2 days. Progressive reduction in the amplitude of CMAPs and SNAPs in all tested nerves was noted 4, 5 and 6 weeks after the porphyric attack (Table). Antiepileptic therapy was changed to

gabapentin.

After glucose treatment, the patient still developed respiratory failure, and hematin (4 mg/kg/day) was administered for another 14 days. On June 9, serum amylase and lipase returned to normal limits. Abdominal pain resolved and the conscious level was improved to clear and alert. A repeat MRI showed that the lesions were completely resolving (Fig. 2C and 2D). Series of nerve conduction studies (Table) showed gradual improvement in CMAPs and SNAPs of all tested nerves (except for the peroneal nerve) at the interval of 3, 8 and 36 weeks after hematin. The patient was followed at the out-patient department, and only mild residual polyneuropathy was noted during his last visit in August 2006.

**Table.** Serial nerve conduction studies in our patient with porphyric neuropathy

Time	Motor NCS												Sensory NCS		
	Median			Ulnar			Peroneal			T	ibial	Sensory NCS			
	DL (ms)	Amp (mV)	CV (m/s)	DL (ms)	Amp (mV)	CV (m/s)	DL (ms)	Amp (mV)	CV (m/s)	DL (ms)	Amp (mV)	CV (m/s)	Amp ( $\mu$ V)	Amp ( $\mu$ V)	Amp ( $\mu$ V)
3rd week															
R	4.0	3.3	49	3.3	8.3	47	4.2	8.1	42	6.0	8.3	46	22	31	13
L	4.1	6.1	48	3.1	8.3	51	4.7	5.9	42	6.1	6.6	42	35	34	28
4th week															
R	2.8	2.2	51	2.1	5.4	54	3.0	2.9	47	2.8	6.9	49	25	19	3
L	2.8	2.1	51	2.2	6.9	56	2.9	3.1	46	3.1	10.3	49	18	18	6
5th week															
R	3.0	1.7	53	2.3	5.6	53	3.0	2.6	44	3.3	6.3	45	16	20	10
L	3.4	1.5	51	2.3	5.9	55	2.8	3.6	44	3.5	9.1	47	18	18	6
6th week															
R	3.1	1.2	53	2.7	4.7	52	3.2	2.3	44	3.8	4.6	49	14	18	7
L	3.4	1.6	51	2.4	4.6	53	3.0	2.1	42	4.9	4.1	45	21	13	6
12th week (3 weeks after hematin therapy)															
R	3.2	1.8	47	2.7	4.4	48	4.3	0.6	27	5.5	5.1	43	16	14	12
L	3.5	2.2	46	2.4	5.5	50	3.9	2.1	36	4.9	3.1	38	22	25	5
17th week (8 weeks after hematin therapy)															
R	4.0	2.0	45	3.7	4.4	45	NR	NR	NR	6.1	5.8	37	14	18	6
L	3.9	2.1	45	2.9	4.5	51	5.4	0.3	30	6.2	7.0	37	20	13	7
45th week (38 weeks after hematin therapy)															
R	4.5	6.3	52	3.6	10.5	54	NR	NR	NR	5.3	10.2	32	32	32	15
L	4.4	8.4	49	3.4	11.0	54	6.8	1.1	40	5.0	13.9	38	28	34	16
Reference	4.3	6.0	50	3.5	5.5	50	5.5	2.0	40	6.5	4.0	40	12	9	5

NCS: nerve conduction study; DL: distal latency; Amp: amplitude; CV: conduction velocity; R: right; L: left; NR: no response.

## DISCUSSION

The diagnosis of acute porphyria should always be considered in patients with unexplained recurrent abdominal pain, especially those with neuropsychiatric features, despite its rarity and even in the absence of a family history<sup>(1,2)</sup>. Our patient had typical manifestations of AIP, which included abdominal pain, paralytic ileus, constipation, tachycardia, hypertension, mental disturbances, peripheral neuropathy, and seizures. The confirmed diagnosis of an acute attack of AIP was established by the excessive urinary excretion of ALA and PGB. The patient might have the first attack with unknown precipitating factor. In addition, elevated serum pancreatic enzymes (amylase and lipase) and mild

pancreatic edema on ultrasonography were noted, suggesting concomitant acute pancreatitis. The clinical manifestation and a 24-hour urine PBG/ALA elevation in AIP would be similar to the ALA dehydratase porphyria (ADP)<sup>(2)</sup>. However, ADP is a rare disease characterized by markedly increased production of ALA, such that ALA production is 10-20 times higher than PBG<sup>(2)</sup>. Our patient had increased production of both ALA and PBG that suggested the diagnosis of AIP rather than ADP.

Pancreatic involvement in AIP is infrequent. Although the pancreatitis and porphyria might have been coincidental in our patient, the elevated pancreatic enzymes continued for more than 6 weeks and recovered following the treatment for porphyria. The clinical course again suggests a true association between the two

conditions. Moreover, there are a few reported cases of AIP complicated by pancreatic disease in support of our argument<sup>(4,6,8-11)</sup>. The reported pancreatic diseases associated with porphyria include acute pancreatitis<sup>(4,6,9,11)</sup>, chronic pancreatitis<sup>(7)</sup>, chronic pancreatitis with cystadenocarcinoma<sup>(8)</sup> and transient macroamylasemia<sup>(9)</sup>. More recently, Maramattom et al.<sup>(12)</sup> reported a case of AIP with diffuse porphyric encephalopathy, whose blood amylase levels also increased during the acute attack like in our patient.

The pathophysiologic mechanism of acute pancreatitis in AIP remains unclear. Kobza et al.<sup>(4)</sup> suggested that the spastic contraction of the sphincter of Oddi caused by AIP is a possible mechanism of acute pancreatitis. Another study<sup>(5)</sup> indicated that an acute porphyric attack is precipitated by prior pancreatitis, e.g. by a diminished caloric intake. In our patient, pancreatitis developed together with mental disturbance and the neurovisceral crises, pointing to a possible etiologic relationship. The slow and gradual recovery from pancreatitis was consistent with the usual course of improvement in AIP, indicating that porphyric neurotoxicity probably plays a major role.

Despite the increased understanding of the molecular and cellular biology of AIP, the nature of AIP-related autonomic dysfunction remains unknown. Pathologic examination revealed demyelination and axonal loss of the vagus nerve and chromatolysis in the sympathetic and celiac ganglia<sup>(13)</sup>. Direct neurotoxicity of porphyrin precursors or heme deficiency in neural tissue may be responsible for the biochemical changes that result in neuronal dysfunction<sup>(14)</sup>. In our patient, the clinical and electrophysiological features revealed dysautonomia. We postulate that an autonomic nervous system injury during the acute attack of AIP will cause spasms and dysfunction of the sphincter of Oddi, and thus lead to acute pancreatitis. However, other possible causes of pancreatic damage, such as free radical formation as well as mitochondrial and nuclear DNA damage induced by toxic effects of ALA and PBG<sup>(14,15)</sup> and vasospastic mechanisms leading to pancreatic ischemia can not be excluded. Further studies are needed to confirm the underlying pathophysiological mechanism in this context.

We also cannot exclude the possibility that the acute attack of AIP was precipitated by existent pancreatitis. However, we could not find any established etiologic factors of pancreatitis, such as trauma, drugs, alcohol, hypercalcemia, hypertriglyceridemia, and viral infections in our patient. In addition, the gallbladder and extra-hepatic biliary ducts appeared normal, with no gallbladder stone noted. Thus, pancreatitis due to biliary tract diseases was unlikely in this patient.

In instances where the central nervous system is affected, transient or permanent MRI abnormalities during the acute attack of AIP have been described<sup>(12,16-20)</sup>. In our patient, brain MRI demonstrated multifocal cerebral lesions which particularly involved the parietal and occipital lobes and resolved during follow-up. The pattern of MRI abnormalities showed similarity to those described as PRES<sup>(17,21)</sup>. Disorders that could lead to PRES include immunosuppressive therapy, eclampsia, and hypertensive encephalopathy<sup>(21)</sup>. Since our patient had only mild increases of blood pressure, hypertensive encephalopathy probably was not the cause of PRES. The pathophysiology of these reversible lesions is not fully clear, but reversible cerebral vasospasm and loss of autoregulation are thought to be the most likely pathogenic mechanisms underlying acute porphyric encephalopathy<sup>(16)</sup>. Other possible mechanisms include neurotoxic effects of excessive porphyrin precursors and deficit substrate cofactors from a heme biosynthetic defect<sup>(14,18)</sup>. However, patchy white matter signal abnormalities on MRI could also be seen in patients with pancreatic encephalopathy<sup>(22)</sup>. It remains a possibility that the PRES in our patient is related to the coexistence of acute porphyric encephalopathy and pancreatic encephalopathy.

A series of nerve conduction studies in this patient showed progressive reduction in amplitude of CMAPs and SNAPs in all tested nerves after the onset of AIP. The prominent motor symptoms as well as the electrophysiological finding were consistent with the motor predominant axonal polyneuropathy commonly reported in porphyric neuropathy. After hematin treatment, the porphyric neuropathy was gradually improved. Thus, early hematin therapy may be suggested in acute and

chronic porphyric neuropathy<sup>(23)</sup>.

The inappropriate antiepileptic drug therapy (phenytoin) might have aggravated AIP in this patient. Seizures affect 15-20% of patients with AIP and tend to occur during an acute attack<sup>(13,24)</sup>. In general, epileptic seizures in patients with acute porphyria are thought to be related to metabolic disturbance due to heme deficiency<sup>(24)</sup>. In addition, a potential direct epileptogenic effect of ALA has been proposed<sup>(25)</sup>. ALA at a low concentration has been shown to inhibit the release of  $\alpha$ -aminobutyric acid (GABA) from nerve endings by acting as an agonist at GABA autoreceptors<sup>(25)</sup>. It is also possible that ALA interacts with glutamate receptors<sup>(24,25)</sup> to play a crucial role in the epileptogenesis related to porphyric encephalopathy<sup>(24)</sup>. Because conventional antiepileptic drugs, including phenytoin, barbiturates, carbamazepine and valproate, may exacerbate the attacks of AIP<sup>(24)</sup>, seizures constitute an important problem in the management of patient with AIP. Control of seizures often require the use of new alternative anti-epileptic drugs, such as gabapentin and levetiracetam<sup>(24)</sup>.

In conclusion, the association of unexplained abdominal pain, neuropsychiatric features and acute pancreatitis combined with encephalopathy should arouse a clinical suspicion of AIP. Because manifestations of acute pancreatitis could be present or even predominate at an acute attack of AIP, the patient with a first attack of AIP may be misdiagnosed and treated as acute pancreatitis. It is necessary to reach the correct diagnosis as early as possible in order to effectively manage the attack and to avoid inappropriate treatment such as fasting, which is a standard therapeutic maneuver in acute pancreatitis but may exacerbate the crisis and result in a vicious circle in patients with AIP.

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