

Acute intermittent porphyria: focus on possible mechanisms of acute and chronic manifestations

Yuelin Ma¹, Qing Teng¹, Yiran Zhang², Songyun Zhang^{1,*}

¹Department of Endocrinology, The second Hospital of Hebei Medical University, Shijiazhuang, Hebei, China;

²School of First Clinical Medical College, Southern Medical University, Guangzhou, Guangdong, China.

SUMMARY Porphyrias are a group of inherited metabolic diseases that include eight types, each of which is caused by a mutation that affects an enzyme of the heme biosynthetic pathway. When an enzyme defect has physiological significance, it leads to overproduction of pathway precursors prior to the defective step. The partial absence of the third enzyme in the heme biosynthetic pathway, porphobilinogen deaminase (PBGD) also known as hydroxymethylbilane synthase (HMBS), results in acute intermittent porphyria (AIP), which affects mainly women. Subjects who had AIP symptoms were deemed to have manifest AIP (MAIP). Clinical manifestations are usually diverse and non-specific. Acute AIP episodes may present with abdominal pain, nausea, and vomiting, and repeated episodes may result in a series of chronic injuries. Therefore, studying the mechanisms of acute and chronic manifestations of AIP is of great significance. This review aims to summarize the possible mechanisms of acute and chronic manifestations in patients with AIP.

Keywords acute intermittent porphyria, mechanisms, aminolevulinic acid (ALA), attack

1. Introduction

Porphyria is a rare metabolic disease caused by abnormal enzyme activity in the heme synthesis pathway (1,2). Acute intermittent porphyria (AIP) is due to a partial deficiency in porphobilinogen deaminase (PBGD), also known as hydroxymethylbilane synthase (HMBS) (3,4), which is autosomal dominant and has low clinical penetrance (5-7). A PBGD enzyme deficiency leads to the significant accumulation of certain porphyrin precursors, such as aminolevulinic acid (ALA) and porphobilinogen (PBG). Women are more susceptible (8). Most patients develop symptoms after puberty (6).

AIP has varied clinical manifestations, and its attacks can be induced by a number of factors, such as drugs, hormones, starving, infection, psychological stress, and other unknown factors (9). Porphyrin precursors may affect the automatic, central, and peripheral nervous systems. In addition, porphyrin precursor deposition in the liver, kidneys, and other organs can cause damage to these organs and cause metabolic disturbances.

2. Neurologic symptoms

Some patients with AIP may have neurological manifestations. The automatic, central, and peripheral nervous systems can all be involved (6,10-12).

2.1. Automatic nervous system symptoms

Most automatic nervous system symptoms are non-specific, including abdominal pain, vomiting, *etc.* (13).

More than 80% of patients have abdominal pain, which is intermittent and involves cramping (6,8). Abdominal pain usually lasts hours to days and does not respond well to narcotic pain medications (14). In addition, the degree of abdominal pain is often disproportionate to the physical examination findings (6,15). Evacuation disorders may also be seen, including constipation, abdominal distention, and intestinal obstruction. Cardiovascular symptoms such as arrhythmia and hypertension may also be observed in some patients. The condition can also manifest as bladder dysfunction, such as urinary retention, urinary incontinence, and dysuria (6).

There is a hypothesis that increased serotonergic activity is associated with autonomic neuropathy. Tryptophan dioxygenase (TDO) is a rate-limiting enzyme that catalyzes the degradation of tryptophan. Heme deficiency in the liver will lead to decreased TDO activity, which will cause an increase in tryptophan. Tryptophan is activated by tryptophan hydroxylase to produce serotonin (5-HT), so if tryptophan levels increase, the levels of 5-HT will also increase to some

extent. The following related studies further confirm this hypothesis. Puy *et al.* reported increased blood tryptophan and 5-HT levels, and the concentration of 5-hydroxy indoleacetic acid (5-HIAA) in urine also increased in patients with AIP. Injection of heme can correct these changes. The results of these studies add to the credibility of the hypothesis. 5-HT receptors are distributed in many tissues, such as the digestive tract, urinary bladder, adrenal glands, heart, and blood vessels. Several clinical manifestations of acute porphyrias, and autonomic neuropathy in particular, are similar to the effects of increased 5-HT activity (16).

2.2. Central nervous system damage

There are many clinical features associated with CNS damage, such as seizures, coma, syndrome of inappropriate antidiuretic hormone (SIADH), and porphyria-induced posterior reversible encephalopathy syndrome (PRES). The following will discuss possible mechanisms of three specific clinical manifestations.

2.2.1. Epileptic seizures

Seizures have been reported in patients with AIP suffering an acute attack (17-22). Types of seizures include myoclonic jerks, tonic-clonic seizures, partial seizures followed by secondarily generalized seizures, and generalized seizures (23-26). The actual mechanisms are poorly understood, though the following are the major hypotheses for those mechanisms. First, hyponatremia may be a pathogenic factor (6,14,27). Corroborating the hypothesis is the fact that seizures have been reported to be associated with hyponatremia in some cases (23,28-30). Second, the pathogenesis of seizures may be related to ALA and PBG (12). One study has indicated that injections of ALA and PBG into the brain of mice, respectively, cause seizures (31). In addition, ALA is known to be toxic to neuronal and glial cells in culture (32). Third, sympathetic excitation results in increased production of catecholamine, which can cause vasoconstriction (6). Constriction of blood vessels in certain parts of the CNS may lead to seizures. Fourth, the loss of normal gamma-aminobutyric acid (GABA) function is thought to cause epilepsy. GABA is thought to suppress the CNS. ALA is structurally similar to GABA. One study has shown that ALA can inhibit the release of K^+ -stimulated GABA from preloaded synaptosomes (33). Thus, ALA accumulation is assumed to impair normal GABA function, causing damage to the CNS (34). Finally, PRES may be a possible cause of seizures in patients with AIP because some patients with PRES present with seizures (12,35-38).

2.2.2. SIADH

An important characteristic of SIADH is hyponatremia,

and SIADH can manifest as varying degrees of loss of appetite, nausea, vomiting, convulsions, and coma. There is a theory that excess PBG and ALA might cause SIADH through neurotoxic mechanisms (6). Suarez *et al.* reported such a case, and a histopathological examination of that patient revealed a marked decrease in the number of hypothalamic cells. Those results indicate that hypothalamic-hypophyseal tracts may be damaged, leading to SIADH (39).

2.2.3. PRES

PRES can present as headaches, nausea, seizures, visual disturbances, *etc.* (12,21,40,41). Recently Jaramillo-Calle *et al.* reviewed previous cases to describe several features of PRES and discuss possible pathogenesis. Neuroimaging often reveals bilateral vasogenic edema characterized by asymmetry and major involvement of the parieto-occipital regions, and these imaging changes usually disappear during reexamination (10).

Endothelial dysfunction is considered to be a major pathogenic process. Many factors contribute to endothelial dysfunction. First, if the blood pressure rises significantly beyond the upper limit of autoregulation (mean arterial pressure \sim 150 mmHg), endothelial damage may occur. Second, a theory contends that toxic damage can cause endothelial dysfunction. This theory may explain the pathogenesis of PRES in patients with normal blood pressure and patients with hypertension within the range of autoregulation. Finally, a primary inflammatory injury might lead to endothelial dysfunction. One study showed that the concentrations of several proinflammatory cytokines and vascular endothelial growth factor (VEGF) were higher in symptomatic patients with AIP than control groups (10). This result further validates the hypothesis.

2.3. Peripheral neuropathy

Peripheral neuropathy is a common neurological manifestation of AIP (42). Patients may present with pain, muscle weakness, paresis, sensory neuropathy, *etc.* (23,43-46). Pain may involve the limbs, chest, back, *etc.* (6). Paresis usually begins at the proximal end of the upper limb (46,47). Sensory neuropathy may include paresthesia, hypoesthesia, numbness, and neuropathic pain (5,47). If bulbar paralysis is present with cranial nerve involvement, the symptoms are usually severe, including dysphagia, dysarthria, and dysphonia. Severe cases may require intubation and mechanical ventilation (6). Paralysis usually can be completely reversed with proper treatment and months of recovery (5).

Electrophysiological findings in patients who have acute porphyric neuropathy reveal primary axonal motor neuropathy (26,48-50). An autopsy study of patients with AIP conducted by Cavanagh and Mellick

found that axonal motor fibers were affected more significantly than sensory fibers (34,51).

Fast axonal transport depends on energy. Therefore, a reduction in heme production may disrupt this process and result in axonal degeneration (52,53). Heme is required for aerobic metabolism and the production of adenosine triphosphate (ATP) (52,54,55). Therefore, a heme deficiency may lead to axonal damage, causing peripheral neuropathy.

3. Psychiatric symptoms

Some patients with AIP may also experience a variety of psychiatric symptoms, such as depression, anxiety, and insomnia (56-61). Severe cases can even manifest as schizophrenia and hallucinations (25,62-64). Psychiatric symptoms may occur during an acute episode or as a chronic complication.

Several studies have been conducted to observe the incidence of psychiatric symptoms in patients with AIP (64-67). Other studies were done to screen psychiatric patients for acute intermittent porphyria (68,69). First, genetics may play a role. One study showed that patients with AIP and their first-degree relatives were at varying degrees of increased risk of being diagnosed with schizophrenia and bipolar disorder. The results suggest that there may be a genetic link between AIP and psychiatric symptoms (64). Another study examined the association between the PBGD genetic variation and schizophrenia, and it found that the PBGD *MspI* 2.2-kb allele is significantly associated with schizophrenia. However, subsequent studies failed to replicate this finding (70,71). Second, the activity of the disease may be associated with psychiatric symptoms. Two studies have shown that psychiatric symptoms are more common in patients with manifest AIP (MAIP) (65,66). Finally, rare homozygous mutations may cause depression-like mental behavior. Most HMBS mutations are known to be heterozygous mutations. Berger *et al.* conducted an animal study which found that severe HMBS deficiency led to depression-like behavior in a mouse model of homozygous dominant AIP (72).

4. Hepatic impairment

An association between AIP and hepatocellular carcinoma (HCC) was reported for the first time in 1984 (73). Since then, several studies have estimated the relative risk (RR) or standardized incidence ratio (SIR) for HCC in patients with AIP. In a Finnish study, the RR was 61 (74). A French study reported an SIR of 36 (75). A Swedish study reported an SIR of 64 in 2011 and 86 in 2013 (76,77). The risk of HCC in patients with AIP may be underestimated because better diagnostic methods have been developed in recent years, some patients could not be traced, or for

other reasons (73,74,78). In conclusion, the results of different studies have varied greatly, but these results still indicate that the risk of developing HCC may be greater in patients with AIP.

The exact mechanism by which HCC develops in patients with AIP is not completely known. The following are several possible risk factors.

4.1. Cirrhosis may be a possible risk factor

Some patients with AIP have both HCC and liver cirrhosis (73,75,77-79). In some samples, the number of patients with non-neoplastic parenchyma was too small to adequately assess possible liver cirrhosis. Thus, the number of patients with known liver cirrhosis may be underestimated (74). These findings suggest that cirrhosis may play a significant role in the development of HCC in patients with AIP.

4.2. Elderly patients with AIP may have an increased risk of developing HCC

The mean age at diagnosis of HCC was over 60 in numerous studies (1,73,76,77,79,80). However, a French study reported that 50 years was the mean age at diagnosis. Two patients with hepatitis were included in the French study, which may account for the slightly younger age at diagnosis of HCC, because hepatitis may contribute to the development of HCC to some extent (75,76). These results suggest that HCC develops more often in patients over 60 years of age, which may be related to the physical condition of the elderly patients and the course of AIP.

4.3. The frequency of AIP attacks may affect the development of HCC

In several previous studies, the ratio of the number of patients with HCC who had a history of AIP symptoms to the total number of patients with AIP and HCC was 6/9, 16/22, 3/5, or 3/23 (75-78). Although the ratios vary, HCC seems to be more common in symptomatic patients with AIP.

4.4. An HMBS enzyme deficiency may diminish the inhibition of tumor growth

One study excluded several key genes associated with HCC, including KRAS, TP53, BRAF, and CTNNB1 (80). However, the study found a somatic mutation in the HMBS gene, L220X, which was present only in cancer tissues, and the study did not find that somatic mutation in the liver tissues of ten patients with non-porphyrria-related HCC. These results strongly suggest that the HMBS gene defect may play a role in tumor growth in the AIP patient studied. Although it is only a single study, the hypothesis it generated cannot be ignored.

4.5. ALA may be carcinogenic

Since ALA is the main cause of AIP episodes, numerous studies have hypothesized that ALA itself may be carcinogenic (78,81,82). Further research is needed to explore the carcinogenicity of ALA and the mechanism by which ALA induces HCC.

4.6. Decreased heme production may influence the development of HCC

Recent studies have shown that hemein has obvious antigenotoxic and anti-inflammatory effects (83-86). Unfortunately, these studies used non-HCC cells, so there is no conclusive evidence that heme inhibits the development of HCC.

In summary, patients with AIP are at risk of developing HCC, so patients with AIP over 50 years of age can be screened for HCC annually to detect HCC early (87-91).

5. Renal impairment

Renal impairment is more common in AIP, and particularly in patients with frequent porphyric attacks (92). Kidney damage in patients with AIP is mainly reflected in laboratory results, such as elevated creatinine and urea nitrogen (93,94).

Pallet *et al.* conducted a follow-up study from 2003 to 2013, and their experimental data showed that more than 50% of patients with AIP are diagnosed with chronic kidney disease (CKD), compared with about 10% of asymptomatic patients (95). In addition, the kidney function of asymptomatic patients is analogous to that of the general population, indicating that repeated attacks can exacerbate kidney damage. Multiple regression analysis revealed that AIP may independently induce estimated glomerular filtration (eGFR) damage. Histological findings from renal biopsies of patients with AIP revealed varying degrees of glomerulosclerotic and interstitial changes (95,96).

Current research has yet to reveal the exact mechanism underlying renal impairment.

5.1. Porphyrin precursors may have a negative effect on the kidney

5.1.1. Porphyrin precursors promote tubular injury

In a previous study, human renal epithelial cells (HRECs) were cultured using ALA and PBG, and results showed that ALA and PBG can cause cell death and endoplasmic reticulum stress. DNA damage is thought to induce apoptotic cell death. Consistent with this finding, a marker of tubular damage, urinary neutrophil gelatinase-associated lipocalin (NGAL), was found to be at higher levels in patients with AIP during attacks than levels in

asymptomatic carriers (95). In one study, nine patients with AIP in clinical remission underwent an isotopic renography, which revealed tubular damage (97). These findings may explain the interstitial changes in renal biopsy results from patients with AIP (95,96).

5.1.2. Porphyrin precursors promote severe arteriolar lesions

ALA is an effective vasoconstrictor that can promote injury in target organs. Studies have shown that the presence of excessive ALA may cause vasospastic renal vascular lesions, leading to chronic vasculopathy with a narrowed lumen and tissue ischemia that contribute to CKD (92,98,99). Other cardiac and ophthalmic symptoms were reported during the onset of AIP, suggesting arterial spasms (100,101). These findings may correspond to glomerular sclerosis as revealed by renal biopsies (95,96).

5.1.3. Porphyria-related nephropathy is due to genetic variations in renal ALA transporters

The reabsorption of ALA occurs in the S2 and S3 segments of the proximal tubule, and the transporter of its reabsorption is the human peptide transporter 2 (PEPT2). Tchernitchko *et al.* conducted an observational study to explore the relationship between PEPT2 genotypes and porphyria-associated kidney disease (PAKD). Notably, immunohistochemistry revealed PEPT2 expression in the renal proximal tubules of both patients with porphyria-associated kidney disease (PAKD) and individuals without PAKD. According to haplotype analysis, PEPT2*1 and PEPT2*2 are the two main variants of PEPT2. The Km values for different PEPT2 genotypes indicated that the PEPT2*1 genotype features a stronger ability to bind to the substrate than the PEPT2*2 genotype. Experimental data revealed that patients with PEPT2*2 had less severe PAKD and slower progression. In addition, PEPT2*1/*1 independently predicts PAKD severity, and the PEPT2 genotype is an independent risk factor for eGFR degradation over time (102).

Although the aforementioned study described the effect of different genotypes of PEPT2 on the kidneys, there is no histological evidence of increased ALA in the kidney. This finding leads to the question of whether the ALA level in the kidney can be measured using immunohistochemistry or other methods.

In contrast to previous studies, a study by Unzu *et al.* found no significant renal dysfunction or histologic changes other than a few small inflammatory infiltrates. The model used in that study was an HMBS-deficient mouse, and the accumulation of porphyrin precursors was induced via a phenobarbital challenge over 14 weeks to produce acute AIP episodes (92). A number of factors can account for the experiment's results. First,

only if 30% of the HMBS activity was retained could the mice survive. Second, the duration of the experiment (14 weeks) may not have been long enough for kidney damage to occur. Finally, germ-line differences in mice may have affected the results (95).

5.2. Hypertension

High blood pressure (HHP) occurs frequently in patients with AIP, and especially in patients with recurrent attacks (96,99). A population-based study on the clinical aspects of AIP in northern Sweden involving 356 gene carriers suggested that hypertension was significantly associated with MAIP, adjusted for age and sex (66). First, excessive porphyrin metabolites lead to cytotoxic or vasospastic renal vascular lesions, which may lead

to HHP (96). Second, sympathetic excitation may occur during an acute episode, leading to increased release of catecholamines (96,99). Other factors, like vasopressin and angiotensin, may also play a significant role (96).

Chronic hypertension can lead to thickening of the vessel wall and narrowing of the lumen, which can trigger damage to the kidneys and aggravate renal arteriosclerosis. These findings may explain the glomerular sclerosis observed in kidney biopsies (95,96).

5.3. Repeated heme therapy

Renal damage may be caused by repeated heme therapy. A case of renal injury following heme infusion has been reported (103). Whether the renal injury was caused by heme infusion is not known, but this factor

Table 1. Summary of possible mechanisms of acute and chronic manifestations

Acute and chronic manifestations	Symptoms	Possible mechanisms
Neurologic symptoms	<i>Automatic nervous system symptoms:</i> abdominal pain, vomiting, constipation, intestinal obstruction, arrhythmias, hypertension, etc.	The effects of increased 5-HT activity are similar to some symptoms of autonomic neuropathy
	<i>Central nervous system damage:</i> <i>Epileptic seizures:</i> myoclonic jerks, tonic-clonic seizures, partial seizures followed by secondarily generalized seizures, generalized seizures, etc.	1. Hyponatremia 2. ALA is toxic to neuronal and glial cells 3. Increased production of catecholamine can cause vasoconstriction 4. CNS suppression induced by GABA is diminished 5. PRES itself can trigger seizures
	<i>SIADH:</i> loss of appetite, nausea, vomiting, convulsions, coma, etc.	Excess PBG and ALA cause damage to hypothalamic-hypophyseal tracts
	<i>PRES:</i> headaches, nausea, seizures, visual disturbances, etc.	Endothelial dysfunction caused by HHP, toxic damage, and a primary inflammatory injury is a major pathogenic process
Psychiatric symptoms	<i>Peripheral neuropathy:</i> pain, muscle weakness, paresis, sensory neuropathy, etc.	A reduction in heme production disrupts fast axonal transport
	Depression, anxiety, insomnia, schizophrenia, hallucinations, etc.	1. Genetic factors 2. AIP attacks 3. Homozygous HMBS mutations (animal study)
Hepatocellular carcinoma	Elevated transaminases and hepatalgia	1. Liver cirrhosis 2. Elderly patients may have an increased risk 3. AIP attacks 4. HMBS enzyme deficiency may diminish the inhibition of tumor growth 5. The carcinogenicity of ALA 6. Decreased heme production reduces heme's antigenotoxic and anti-inflammatory effects
Renal impairment	Elevated creatinine and urea nitrogen	1. Porphyrin precursors can cause tubular injury and severe arteriolar lesions, and PEPT2, a transporter of ALA, plays an important role. 2. Hypertension may aggravate renal arteriosclerosis 3. Repeated heme therapy
Metabolically related changes	Elevated serum uric acid and hypercholesterolemia	The exact mechanism is unclear

cannot be ruled out.

Based on the above mechanism, corresponding treatment can be given to improve the state of the kidneys. Damage to the kidneys can be limited by reducing attacks, such as by avoiding predisposing factors and providing preventive treatment. In addition, PEPT2 may be an alternative therapeutic target. It works by inhibiting the tubular reabsorption of ALA, but it still needs to be tested.

6. Metabolically related changes

Few studies have examined elevated serum uric acid and hypercholesterolemia in patients with AIP. According to existing research, the exact mechanism is unclear (104). The factors associated with hypercholesterolemia are as follows. First, hypercholesterolemia may be related to porphyria itself and acute AIP attacks (105-109). Second, hypercholesterolemia is associated with an increase in low-density lipoprotein (LDL) (105,106). Studies have found that increases in cholesterol are sometimes accompanied by increases in LDL. LDL is known to be a transporter of human plasma cholesterol, which transports endogenous cholesterol to extrahepatic tissues. If LDL is elevated, more cholesterol is transported outside of the liver, causing hypercholesterolemia. Relevant studies need to be designed to explore the possible mechanism of these changes.

7. Conclusion

The possible mechanisms of acute and chronic manifestations of AIP are briefly summarized in Table 1. Although several studies have examined acute and chronic manifestations in patients with AIP, the specific mechanisms behind those manifestations are not fully understood. Therefore, future research on this disease should continue to explore the mechanisms of those manifestations. Understanding the relevant mechanisms can help us to better understand the disease and to take corresponding actions to delay its incidence and progression.

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**Address correspondence to:*

Songyun Zhang, Department of Endocrinology, The second Hospital of Hebei Medical University, Shijiazhuang 050000, Hebei, China.
E-mail: zsy2020@hebmh.edu.cn

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