Neurological Manifestations and Neuroimaging Findings of Acute Intermittent Porphyria Patients

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Research

Keywords: acute intermittent porphyria, neuroimage, hyponatremia

DOI: https://doi.org/10.21203/rs.3.rs-77039/v1

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Abstract

Background: Acute intermittent porphyria (AIP) is an inherited disorder of heme biosynthesis, a porphric attack can affect the autonomic, peripheral, and central nervous systems. The neurological clinical manifestations of which are incompletely understood. The neuroimaging findings of AIP could be reversible.

Methods: In this report, we describe 29 cases of AIP, focusing on neurological clinical features and neuro-imaging.

Results: In this study, we showed two cases of PRES, two cases of ODS, two cases of porphyrnic encephalopathy (cortical laminar necrosis), one case of RESLES. We divided 29 cases into 2 groups, the blood sodium levels of who with MRI/CT abnormality were significantly lower than which with normal MRI/CT (110±43.15 mmol/L and 117±57.02 mmol/L, p=0.01).

Conclusions: To the best of our knowledge, these are the biggest series of MRI in AIP in China, and the only published cases of ODS associated with AIP in China. Hyponatremia may be an important mechanism in porphyrnic encephalopathy.

Background

Acute intermittent porphyria (AIP) is a rare autosomal dominant inherited disorder characterized by a partial deficiency of porphobilinogen deaminase (PBGD), the third enzyme in the heme biosynthetic pathway. Most AIP patients are no symptoms except for acute intermittent attacks. Such attacks are characterized by diverse symptoms including abdomen pain, tachycardia, hypertension, unawareness, seizures and psychiatric symptoms[1, 2]. There are just a few reports of the neuroimaging findings in AIP patients with acute neurologic manifestations including seizures. The performance of brain MRI of AIP is diverse. Posterior reversible encephalopathy syndrome (PRES) is associated with potentially reversible neuroradiological abnormalities predominantly in the parieto-occipital lobes. Osmotic demyelination syndrome (ODS) refers to central pontine myelinolysis and extrapontine myelinolysis. Reversible splenial lesion syndrome (RESLES) is a clinico-radiological syndrome characterized by the presence of reversible lesions specifically involving the splenium of the corpus callosum (SCC). Many of these studies have suggested that MRI changes were related to PRES[3–5]. The relationship of the neurological manifestations and neuroimaging findings of AIP is not well understood. Here, we describe 29 cases of neuroimaging findings of AIP with neurological symptoms.

Patients And Methods

From January 2013 to July 2019, a total of 69 patients were diagnosed with AIP in the emergency center of our hospital. The following diagnostic criteria were used: 1) acute attack symptoms and 2) positive for urine porphobilinogen (PBG). We conducted a retrospective analysis of these patients. 29 of 69 had neurological symptoms (convulsion, confusion, difficulty swallowing etc). We collected information about ethnicity, past medical history, clinical features, neuro-imaging, medications, treatment, investigations and outcome of these 29 patients. Among 29 patients 26 agreed to have genetic testing for porphobilinogen deaminase (PBGD) gene mutations. We did the genetic screening tests of AIP in these families.

Qualitative screening tests of urinary PBG (Watson-Schwartz method)

Urine porphobilinogen (PBG) was quantitatively screened using the Watson-Schwartz method. Briefly, urine was added to Ehrlich's reagent (0.7 g dimethylamine broane dissolved in 150 mL concentrated hydrochloric acid and 100 mL water). After 1–2 min, a saturated sodium acetate solution was added, and the non-specific colors were removed by extraction with chloroform and n-butanol. A positive PBG result was indicated by a distinct pink color in the lower layer[6].
CNS Studies

During porphyric attack, brain CT and/or MRI was performed on most (25/29) patients with CNS symptoms or headache, while electroencephalography (EEG) was performed on some (5/29) patients, CSF test was performed on (7/29) patients.

Genetic testing

The molecular genetic analysis of the HMBS gene was performed by direct sequencing of peripheral blood sample. All 14 exons of the PBGD gene and a minimum of 20 base pairs of flanking intronic DNA for each exon were amplified by polymerase chain reaction (PCR) (Tiangen Biotech, Beijing, China) and subsequently sequenced using the BigDye Terminator Cycle sequencing kit version 3.1 (ABI Biosystems) on an ABI PRISM 3730 Sequence Analyzer according to the manufacturer's instructions. We aligned the sequences by Chromas software and ncbi website (http://blast.ncbi.nlm.nih.gov/Blast.cgi) to identify variations. We also annotated the filtered variants as "known" or "novel", depending on whether they had been previously reported in the 1000 Genomes Project (http://www.1000genomes.org/data)

All methods were performed in accordance with the relevant guidelines and regulations.

Results

The demographics, disease course, clinical features and of these 29 AIP patients are summarized in table I. The patients had a disease history ranging from 4 days to 6 years. Acute attacks were accompanied by gastrointestinal symptoms in 28 patients. 29 patients all exhibited neurological manifestations, including consciousness disturbance (n = 25), convulsion or seizure (n = 21), and muscle weakness (n = 7). 3 of the 29 patients exhibited impairment of bulbar and respiratory function. 29 patients all had a documented history of hyponatremia (97–127 mmol/l). 12 patients had MRI/CT abnormality.

Results for electrophysiology and radiological studies, and molecular genetic analysis are summarized in table II.

We divided 29 patients into 2 groups, group 1(MRI/CT abnormality), group 2(MRI/CT normal), there are significant differences in blood sodium levels between the two groups, [Na] of group 1(110 ± 43.15 mmol/L) lower than group 2(117 ± 57.02 mmol/L, p = 0.01).

MRI scans of Case 8 (14th day after onset) showed abnormal signals in the cerebral cortex, which were isointensity on T1W1 images, hyper-intensity on T2W2. (Fig. 1A and B). The cranial MRI performed 11 days later revealed that the lesions determined on the first MRI were enhanced on contrast-enhanced axial T1-weighted MRI (Fig. 1C, D and E), repeated brain MRI at 10 months showing that the gyriform cortical lesions larger than before (Fig. 1F and G). Case 6 also had the same abnormal signals located in the cerebral cortex as case 3, but case 6 wasn't followed up.

The initial brain MRI of Case 20 revealed hyperintense gyriform lesions on fluid-attenuated inversion recovery (FLAIR) images (Fig. 3A and B). The cranial MRI performed 40 days later revealed that the lesions determined on the first MRI were significantly regressed (Fig. 3C and D, respectively). MRI findings of Case 9 just like Case 6.

Brain MRI of Case 16 revealed central pontine and extra pontine myelinolysis on FLAIR images (Fig. 2A and B). The cranial MRI five months later revealed that the lesions determined on the first MRI were significantly regressed (Fig. 2C and D, respectively). MRI findings of case 2,16 and 27 all diagnoses as ODS, but case 2 wasn't followed up, case 27 aggravated after 18 days.
Due to the lack of hemin in China, only supportive treatments could be administered, including high carbohydrate intake (250–300 g of glucose per day), fluid restriction (< 2000 ml per day), and avoiding suspicious drugs.

Sequence analysis of the PBGD gene identified 25 mutations in 25 patients are summarized in table 2 (3 patient didn't make detection). There were nine missense, four nonsense, seven splicing mutations, two aberrant splice site mutations. More details of case 9 and case 28 have been previously published.

**Discussion**

Porphyria is a collective name of seven different diseases that are caused by an enzyme deficiency that inhibits the synthesis of heme. AIP is one of four forms of acute porphyria, which is caused by an inherited deficiency of PBGD. Symptoms of AIP occur during intermittent attacks are caused by the excess production of porphyrin precursors in the visceral, peripheral, autonomic, and central nervous systems, and may be life threatening.

Neurological manifestations of AIP include epileptic seizures, impaired consciousness, behavioral changes and hyponatremia maybe caused by inappropriate antidiuretic hormone syndrome [7, 8]. Peking union medical college hospital reported the characteristics of 36 Chinese patients with acute porphyria in 2016; 12 patients experienced neurological symptoms involving the CNS (12/36 confusion, 10/36 convulsion, 2/36 rapid progression to acute respiratory insufficiency)[7]. The prodromal symptoms in these cases included abdominal pain, muscle weakness. The weakness in case 9 and 15 progressed rapidly to quadriplegia and acute respiratory insufficiency, resulting in the delayed diagnosis.

The pathophysiology of the nervous system involvement of AIP patients is not very clear. Most reports of the neurological manifestations and brain imaging findings of AIP have been restricted to a single or small number of cases [8–10]. In vivo studies in mice have suggested that multiple mechanisms leading to the varied symptoms, including interactions between 5-Aminolevulinic acid (ALA) and gamma-Aminobutyric acid (GABA) receptors and possibly heme depletion in nerve cells [9]. However, some findings in AIP patients have suggested that the relationship between the severity of neurological manifestations and the ALA/PBG levels is little [10]. In mainland China, tests of ALA and PBG levels are unavailable, it had been found that the serum sodium concentration was significantly negatively correlated with convulsion in our clinical studies [7]. These findings may reveal many factors contributing to the neurological manifestations of AIP. In 2011, the Chang Gung Memorial Hospital in Taiwan reported 12 cases of AIP; 9 patients experienced neurological symptoms involving the CNS (8 consciousness disturbance, 4 convulsion/seizure, 1 behavioral change). Among 4 patients who underwent brain MRI, 3 showed normal results, and 1 showed PRES, and this lesion recovered after 1 year [10]. In our study, 29 patients experienced CNS neurological symptoms, among 20 patients who underwent MRI, 9 showed MRI abnormality (2 PRES, 4 ODS, 3 porphyrin encephalopathy, 1 RESLES).

The porphynic encephalopathy are believed to be most likely due to transient ischemic cerebral changes, although specific mechanism is unknown [11, 12]. These porphynic encephalopathy showed cortical and subcortical increased signal and gyriform diffuse enhancement [11–13]. Our case 6 and 8 (Fig. 1) had similar cerebral abnormalities, case 8 had been followed by 3 MRI though 10 mons, showed consistent cerebral abnormalities, case 6 wasn't followed up.

Even though there are only a handful of PRES has been reported in AIP patients, it is by far the most common MRI abnormalities in AIP [3, 4, 9, 10]. In these cases, transient changes were observed in the cerebral cortex on MRI. Usually, these lesions are partially or completely reversible, symmetrical cortical and subcortical involvements of the occipital and parietal lobes, without or with mild enhancement, as observed in case 20 (Fig. 3). The most widely accepted hypothesis of the pathophysiology of PRES is the hyperperfusion theory [14]. The mechanism of PRES in AIP has been suggested to be mediated by hypertension due to autonomic dysfunction [5]. Case 20 progressed to dysphoria, confusion...
and severe hyponatremia after being diagnosed with "pregnancy-induced hypertension." However, our first patient with PRES in AIP (case 9) remained normotensive throughout, but she also had severe hyponatremia. Cases of PRES secondary to hyponatremia are rare in the literature\[5, 15\], little is known about the influence of hyponatremia on cerebrovascular regulation.

ODS refers to central pontine myelinolysis and extrapontine myelinolysis. These disorders are characterized by insults to regions of the brain with anatomical features predisposing white matter tracts to myelin injury in the setting of osmotic disturbances and their attempted correction\[16\]. Although many AIP patients have hyponatremia\[7\], ODS in AIP has been rarely previously reported\[13\]. Case 2,5,16 and 27 are first reported cases of AIP with ODS in China. These two patients had severe hyponatremia, which was quickly corrected before she experienced confusion or frequent convulsion. After three weeks, MRI of case 5 showed typical central pontine myelinolysis and extrapontine myelinolysis, as shown in Fig. 2. The clinical outcome of ODS was thought to be universally devastating\[16\], but case 5 completely recovered, and the MRI lesions regressed (Fig. 2). The MRI lesions of case 2 after 2 weeks no changed to the first time.

All 29 cases we reported showed severe hyponatremia, and it was found that the serum sodium concentration was significantly negatively correlated with convulsion before\[7\]. Blood sodium levels of who with MRI/CT abnormality were significantly lower than which with normal MRI/CT (110 ± 43.15 mmol/L and 117 ± 57.02 mmol/L, p = 0.01). We suggest that hyponatremia may be not only a clinical feature of AIP but also an important mechanism in porphyric encephalopathy. An increase in vasopressin levels occurs in hyponatremia\[5\]. Vasopressin facilitates the movement of water molecules into cerebral cells independently of hyponatremia by reducing the use of cerebral oxygen. Hyponatremia therefore plays an important role in cerebral edema. More research is needed in the future to prove this hypothesis. Because hyponatremia is a common feature in AIP, the rapid correction of hyponatremia should be avoided to prevent ODS.

**Conclusion**

In summary, the pathophysiology of the neurological manifestations in AIP patients is not well understood, cortical laminar necrosis, PRES, ODS and RESLES can all exhibit CNS involvement in AIP. Additionally, hyponatremia may be important mediators in the mechanism of porphyric encephalopathy.

**Abbreviations**

AIP  
Acute Intermittent Porphyria  
MRI  
magnetic resonance imaging  
PRES  
Posterior reversible encephalopathy syndrome  
ODS  
Osmotic demyelination syndrome  
RESLES  
Reversible splenial lesion syndrome  
SCC  
splenium of the corpus callosum  
PBGD  
porphobilinogen deaminase gene  
HMBS
hydroxymethylbilane synthase
FLAIR
fluid-attenuated inversion recovery images
T2WI
T2-weighted images
T1WI
T1-weighted images
ADC
apparent diffusion coefficient
CSF
cerebral spinal fluid
PCR
polymerase chain reaction

**Declarations**

**Acknowledgements**

Not applicable.

**Competing interests**

The authors declare that they have no competing interests.

**Ethics approval and consent to participate**

All procedures followed were in accordance with the ethical standards of the responsible institutional committee on human experimentation and with the Helsinki Declaration of 1975 (revised in 2000). The study protocol was approved by the Ethics Committee of the Institutional Review Board at Peking Union Medical College Hospital (PUMCH). A written consent form, stating acceptance of genetic testing, was signed by the patients and their family members.

**Conflict of Interest**

The authors declare that they have no conflict of interest.

**Contribution list:**

Substantial contributions to conception, design and writing: JC and JY. MRI image analysis: FH, HY and JC. Gene mutation detection: QC. Drafting the article or revising it: TZ, YZ, XY, HZ.

**Funding**

This study was supported by Tsinghua University-Peking Union Medical College Hospital Initiative Scientific Research Program: 2019ZC. Manuscript writing were funded in this study. The funding bodies played no role in the design of the study, nor in the collection, analysis, or interpretation of the data.

**Availability of data and materials**

The data used and/or analysed to support the results of the current study are available from the corresponding author on reasonable request.
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Tables

Table 1 Clinical findings of these AIP patients with neurological symptoms
| Patient | Age | Time to Dx (number of attacks) | Clinical features | Neurological symptom | Non-neurological symptom | Serum Na (mEq/L) |
|---------|-----|--------------------------------|-------------------|---------------------|-------------------------|-----------------|
| 1       | F21 | 2 w                            | confusion, convulsion |                        |                          | 106             |
| 2       | F22 | 6 m                            | confusion, convulsion |                        |                          | 110             |
| 3       | F22 | 2m                             | Limb weakness       |                      |                          | 126             |
| 4       | F24 | 2w                             | confusion, convulsion, limb weakness |                  |                          | 113             |
| 5       | F22 | 6 mons (2)                     | Weakness of lower limbs, Involuntary activity, Urinary incontinence |                |                          | 112             |
| 6       | F24 | 1 year (5)                     | confusion, convulsion |                        |                          | 114             |
| 7       | F24 |                                | confusion           |                      |                          | 117             |
| 8       | F23 | 11mon, 2                  | Pains in the whole body, convulsion, urine retention |              |                          | 115             |
| 9       | F28 | 1mon, 1                  | Numbness of extremities, confusion, convulsion, dysphagia, dysarthria, respiratory failure needed invasive mechanical ventilation |             |                          | 120             |
| 10      | F34 |                                | confusion, convulsion |                        |                          | 112             |
| 11      | F34 |                                | confusion, convulsion |                        |                          | 128             |
| 12      | F21 | 5mon                          | confusion, convulsion and limb weakness |                |                          | 127             |
| 13      | F23 | 2mon                          | confusion, convulsion |                        |                          | 123             |
| 14      | F21 | 4d                            | confusion           |                      |                          | 112             |
| 15      | F27 |                                | Confusion, convulsion, dysphagia, respiratory failure needed invasive mechanical ventilation |       |                          | 116             |
| 16      | F17 | 6mons (2)                     | Confusion, convulsion, dysphagia, respiratory failure needed invasive mechanical ventilation |               |                          | 104             |
| 17      | F22 | 6d                            | Confusion, convulsion |                        |                          | 106             |
|   | F28  | 5 years | Confusion, convulsion | Cyclical attacks, abdominal pain, constipation | 108 |
|---|------|---------|----------------------|-----------------------------------------------|-----|
| 19 | F24  | 2mon    | Confusion, convulsion, limb weakness | Cyclical attacks, abdominal pain, constipation | 119 |
| 20 | F29  | 6mon    | long lasting pain in the limbs and fatigue, dysphoria and confusion | Cyclical attacks, abdominal pain | 108 |
| 21 | F24  | 5years  | Confusion, convulsion | Cyclical attacks, abdominal pain, constipation | 100 |
| 22 | F35  | 7mon    | Confusion, convulsion | abdominal pain, constipation | 113 |
| 23 | F27  | 7days   | Confusion, convulsion | Cyclical attacks, abdominal pain, constipation | 120 |
| 24 | F24  | 11mon   | limb weakness | Cyclical attacks, abdominal pain, constipation | 122 |
| 25 | F30  | 6years  | Confusion and limb weakness | Cyclical attacks, abdominal pain | 124 |
| 26 | F29  | 2years  | Confusion, convulsion | Cyclical attacks, abdominal pain, constipation, hypertension | 116 |
| 27 | F19  | 1mon    | Confusion, convulsion | Cyclical attacks, abdominal pain, constipation | 97  |
| 28 | F20  | 7days†  | sleepiness, confusion and then convulsion | abdominal pain, nausea, vomiting and dark tea-colored urine | 119 |

Table II Summary of brain imaging findings, electrophysiological findings and molecular defects
| Patient | EEG findings | CT findings | MRI findings | MRI follow-up | Csf | mutation in PBGD gene |
|---------|--------------|-------------|--------------|---------------|-----|-----------------------|
| 1       | Negtive      | Brain edema |              |               |     | Ala330Pro              |
| 2       | Moderate abnormal |        | central pontine and extra pontine myelinolysis on FLAIR images | Normal | Trp283Term         |
| 3       | Normal       |             |              |               |     |                       |
| 4       | normal       |             |              |               |     |                       |
| 5       | central pontine and extra pontine myelinolysis on FLAIR images | No change (2 weeks) |           | NO           |     |                       |
| 6       | T2-weighted shows predominantly cortical increased signal |          |              | c.613-1 G>A |     |                       |
| 7       | normal       |             |              |               |     |                       |
| 8       | T2-weighted shows predominantly cortical increased signal | Aggravated 10 days, lesions reduced to 1st MRI (10mons) | Trp283Term |     |                       |
| 9       | hyper intense gyriform lesions on FLAIR images | regressed 6mons |           | Gln292fs |     |                       |
| 10      | Normal       |             |              |               |     | Arg173Trp              |
| 11      | Normal       |             |              |               |     | GLU209term             |
| 12      | Normal       |             |              |               |     | c.211-2G>A             |
| 13      | Normal       |             |              |               |     | c.88-1G>C              |
| 14      | Normal       |             |              |               |     | Glu250Gln               |
| 15      | Normal       |             |              |               |     | Arg173Trp              |
| 16      | central pontine and extra pontine myelinolysis on FLAIR | regressed 5mons |           | Lys70ASN |     |                       |
| 17      | Low density of |          |              |               |     | c.210G>A               |
|   |     |     |                                |                      |
|---|-----|-----|--------------------------------|----------------------|
| 18| Normal | Ala219Pro |
| 19| Normal | c.87+5G>T |
| 20| hyperintense gyriform lesions on FLAIR images | Gly218Glu |
| 21| normal | I336Hfs*23 |
| 22| Brain edema | normal | c.912+1G>C(splicing) |
| 23| Normal | Normal | c.826-1G>C |
| 24| Normal | Arg173Trp |
| 25| Normal | c.88-1G>C |
| 26| Normal | Arg173Trp |
| 27| central pontine and extra pontine myelinolysis on FLAIR | Aggravated 18 days |
| 28| isolated lesion of the SCC, with T2 and FLAIR hyperintensity, T1 hypointensity | regressed 15 days |

**Figures**
Figure 1

AB MRI on 14th day after onset (2015-12-10), T2-weighted images showing high signal and isointense T1-weighted in cerebral cortex. C,D, E 25 days after onset (2015-12-21), contrast-enhanced axial T1-weighted MRI, showing gyriform enhancement of the cerebral cortex. F,G Repeated brain MRI at 10 months (2016-10-31) showing that the gyriform cortical lesions larger than before.
Axial fluid-attenuated inversion recovery (FLAIR) images (2017-10-14) showed (A) an hyperintense region in the central portion of pons (central pontine myelinolysis) and (B) symmetrical hyperintense signal in the putamen and caudate (extra-pontine myelinolysis). Repeated brain MRI at 5 month (2018-3-28) showed resolution of the hyperintensity in pons (C) and basal ganglia(D). Images show complete resolution of hyperintense lesions.
Figure 3

Axial fluid-attenuated inversion recovery (FLAIR) images (2017-12-18) show bilateral cortical and subcortical hyperintense lesions (A and B). Follow-up FLAIR (2018-1-18) images show complete resolution of hyperintense lesions (C and D)
Figure 4

A novel PBGD gene frameshift mutation was identified in the family 6 and 20. A, 4 families pedigree with PBGD gene mutation (The arrow indicated the proband); B, Case 6, A novel PBGD gene mutation 10th intron splicing mutation c.613-1 G>A was identified in the proband and her mother; Case 8, a mutation c.848G>A (Trp283Term) was identified in the proband, sister and mother; Case 20, A novel PBGD gene mutation c.653 G>A (Gly218Glu) was identified in the proband; Case 16, a mutation c.210 G>T (Lys70ASN) and her mother