Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Acute Intermittent Porphyria Presenting with Central and Peripheral Nervous System Involvement: First Report of the HMBS c.770T>C (p.Leu257Pro) Variant in a Chinese Patient

Rui Ma
Lanzhou University Second Hospital
Jie Pang
Lanzhou University Second Hospital
Xiaodong Ma
Lanzhou University Second Hospital
jihe Kang
Lanzhou University Second Hospital
Yingcun Bao
Lanzhou University Second Hospital
Xiaoling Li
ery_lixlery@lzu.edu.cn

Lanzhou University Second Hospital

Case Report

Keywords: acute intermittent porphyria, HMBS gene, osmotic demyelination syndrome, central and peripheral neuropathy, genetic diagnosis

Posted Date: November 1st, 2026

DOI: https://doi.org/10.21203/rs.3.rs-10351114/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Additional Declarations: No competing interests reported.

Abstract

Background

Acute intermittent porphyria (AIP) is a rare autosomal dominant disorder. Clinically, it typically presents with acute neurovisceral attacks in which severe abdominal pain is prominent. Notably, neurologic involvement may dominate the clinical picture. Definitive diagnosis rests on genetic confirmation of pathogenic HMBS variants. Because of its protean clinical profile, diagnosis and management are challenging, and cases dominated by neurologic symptoms are often misclassified..

Case presentation:

We present a case of a 20-year-old female with recurrent severe abdominal pain, progressive quadriplegia, hyponatremia, and neuropsychiatric disturbances. Genetic testing confirmed the diagnosis of AIP and identified a heterozygous mutation in the HMBS gene (c.770T > C, p.Leu257Pro). Clinical improvement was observed following heme infusion, high-carbohydrate therapy, and structured rehabilitation.

Conclusions

In patients presenting with unexplained abdominal pain accompanied by neuropsychiatric symptoms and hyponatremia, a high index of suspicion for AIP is warranted. Prompt metabolic and genetic testing facilitates early confirmation of the diagnosis, thereby helping to prevent irreversible neurological damage. The heterozygous HMBS gene mutation c.770T > C (p.Leu257Pro) identified in this AIP patient represents the first reported case in the Chinese population. The concurrent involvement of both the central and peripheral nervous systems suggests potential population specificity and phenotypic severity.

1. Background

The gold standard for diagnosing acute intermittent porphyria (AIP) is molecular analysis of the HMBS gene. Its clinical manifestations mainly include motor axonal neuropathy, epileptic seizures, and hyponatremia. Herein, we report a case of a 20-year-old Chinese female with AIP.

2. Case presentation

A 20-year-old woman presented with a 5-day history of progressive limb weakness, predominantly affecting the proximal muscles. This was accompanied by intermittent episodes of delirium and hallucinations, along with a recent weight loss of 15 kg. Three months prior to this presentation, she had experienced recurrent abdominal pain, during which she was treated for intestinal obstruction and

underwent both endoscopic retrograde appendicitis therapy and appendectomy. On examination, notable findings included flattening of the bilateral frontal creases and nasolabial folds, diminished pharyngeal reflexes, and an inability to protrude the tongue. Neurological assessment revealed quadriparesis, with a muscle strength of 0/5 in all limbs according to the modified Medical Research Council scale. Muscle tone was decreased, and tendon reflexes in the lower limbs were absent. Evaluation of sensory and cerebellar functions could not be completed due to poor patient cooperation. The patient denied any history of medication use, smoking, heavy drinking, surgeries, injuries, chronic diseases, excessive stress, chronic nutritional deficiencies, or infections.

The patient had hyponatremia, with a serum sodium level of 126.0 mmol/L. Cerebrospinal fluid analysis showed a white blood cell count of 1.00×10^6/L (1 cell/μL) and a total protein concentration of 0.27 g/L. Nerve conduction velocity and electromyography revealed markedly reduced compound muscle action potential amplitudes in the proximal motor nerves of both upper limbs, multifocal motor nerve involvement in all four limbs (characterized by axonal degeneration with partial demyelination), and significantly shortened bilateral H-reflex latencies (Supplementary Table 1–3). Autoimmune encephalitis antibody testing was negative. Clinicians considered Guillain-Barré syndrome and treated the patient with intravenous immunoglobulin, glucocorticoids, and B-complex vitamins. Brain MRI showed symmetrical signal abnormalities in the bilateral caudate heads, putamina, pons, and external capsules, consistent with osmotic demyelination syndrome (Fig. 1a-c). Contrast-enhanced imaging showed patchy enhancement within the pontine lesions. The patient developed reddish urine. Whole-exome sequencing of the patient and her parents, followed by parental segregation analysis, identified a heterozygous variant in the HMBS gene: NM_000190.4: exon11: c.770T > C (p. Leu257Pro), a missense mutation (Fig. 1d). The diagnosis of acute intermittent porphyria was confirmed. The patient received blood transfusions, high-carbohydrate therapy, and mechanical ventilation, along with comprehensive rehabilitation. At discharge, the patient had normal mental status and no abdominal pain. Neurological examination showed proximal upper limb muscle strength of 1+/5, distal upper limb strength of 2+/5, proximal lower limb strength of 2+/5, and distal lower limb strength of 3/5 on the MRC scale. Both deep and superficial sensations were intact in all four limbs.

3. Discussion and conclusions

In this case, the patient was found to harbor a heterozygous variant in the HMBS gene: c.770T > C (p. Leu257Pro). The HMBS gene (NM_000190.4) consists of 14 exons and encodes a 361-amino-acid protein. The c.770T > C variant is classified as a variant of uncertain clinical significance and is either extremely rare or absent in the gnomAD database. Previous reports have identified this variant only in a Russian cohort, where it was associated with polyneuropathy[3]. To our knowledge, this is the first report of this genetic variant in the Chinese population, suggesting that it may be associated with more severe clinical manifestations in this ethnic group.

In this first reported Chinese case of AIP associated with the HMBS c.770T > C (p.Leu257Pro) mutation, we observed concurrent central and peripheral nervous system damage. We propose a shared etiology

for this presentation: the neurotoxicity of delta-aminolevulinic acid (ALA). The mechanisms of ALA neurotoxicity—GABA mimicry, oxidative stress, and mitochondrial dysfunction—provide a unified pathophysiological basis for simultaneous injury to both nervous systems. Therefore, the apparent combined onset is unlikely to be coincidental. This is further supported by the patient's presentation with central pontine myelinolysis on MRI despite normonatremic conditions and strictly controlled sodium correction, indicating that the central lesions were more likely a direct consequence of the metabolic disturbance in AIP than a complication of electrolyte management.

Management with heme arginate and high-carbohydrate therapy led to resolution of abdominal and neuropsychiatric symptoms. While heme therapy cannot reverse established neuropathy, it halts progression[(2)]. Subsequent motor improvement in our patient was achieved through structured rehabilitation, highlighting its essential role in recovery and prevention of complications from immobility.

Follow-up at 6 months post-discharge revealed initial improvement by 3 months, followed by a relapse of acute porphyria with psychiatric symptoms and limb weakness. Symptoms resolved with repeated symptomatic treatment. The patient is now considering liver transplantation, highlighting the recurrent nature and poor long-term prognosis of AIP.

This case underscores diagnostic challenges in AIP: our patient initially underwent unnecessary exploratory laparotomy and appendectomy for abdominal pain, a common scenario given the condition’s mimicry of surgical emergencies[(1)]. Thus, in cases of recurrent abdominal pain with neuropsychiatric features or electrolyte disturbances, AIP should be considered to avoid invasive procedures. In the present case, we have excluded nodo-paranodopathies (based on inconsistent clinical, electrophysiological, and genetic features), toxic neuropathies (due to a clear negative exposure history), and Vasculitic neuropathy (incompatible with the symmetric demyelinating pattern on electromyography).

In conclusion, a high index of suspicion for AIP is warranted in patients with acute neurological symptoms, abdominal pain, and hyponatremia. Early diagnosis, heme therapy, and tailored rehabilitation are crucial. Genetic testing remains key to confirming diagnosis and preventing irreversible neurological injury.

Abbreviations

AIP Acute intermittent porphyria

ALA aminolevulinic acid

Declarations

Acknowledgments

We thank all authors for their contributions to this study.

Author contributions

Rui Ma: Conceptualization; writing – original draft; writing – review and editing; data curation. Jie Pang: Investigation; data curation; writing – original draft. Xiaodong Ma:Investigation; data curation. Jihe Kang: Investigation; writing – original draft; data curation. Yingcun Bao: Data curation; writing – review and editing; investigation. Xiaoling Li: Investigation; writing – original draft; visualization;writing – review and editing; supervision; conceptualization.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This study was supported by grants from National Natural Science Foundation of China (8236025), Youth Doctoral Support Project of Gansu Provincial Department of Education (2023QB-090), Youth Science and Technology Plan Project of Lanzhou Science and Technology Bureau (2023-4-50), Cuiying Scientific and Technological Innovation Program of Lanzhou University Second Hospital (CY2024-YB-A05).

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethics approval and consent to participate

Written informed consent for publication of this case and the accompanying images was obtained from the patient. Furthermore, we confirm that a copy of the consent form will be made available for review by the Editor-in-Chief of this journal on request. No Institutional Review Board (IRB) approval was necessary because this articleis a case report.

Conflict of interest

The authors have no conflict of interest to declare.

Consent for publication

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

References

1. Bonkovsky HL, Maddukuri VC, Yazici C, Anderson KE, Bissell DM, Bloomer JR, et al. Acute Porphyrias in the USA: Features of 108 Subjects from Porphyrias Consortium. The American Journal of Medicine. 2014;127(12):1233–41. doi:10.1016/j.amjmed.2014.06.036

2. Lin CSY, Lee MJ, Park SB, Kiernan MC. Purple pigments: The pathophysiology of acute porphyric neuropathy. Clinical Neurophysiology. 2011;122(12):2336–44. doi:10.1016/j.clinph.2011.07.036
3. Pischik E, Mehtälä S, Kauppinen R. Nine mutations including three novel mutations among Russian patients with acute intermittent porphyria. Hum Mutat. 2005;26(5):496–496. doi:10.1002/humu.9381

Figures

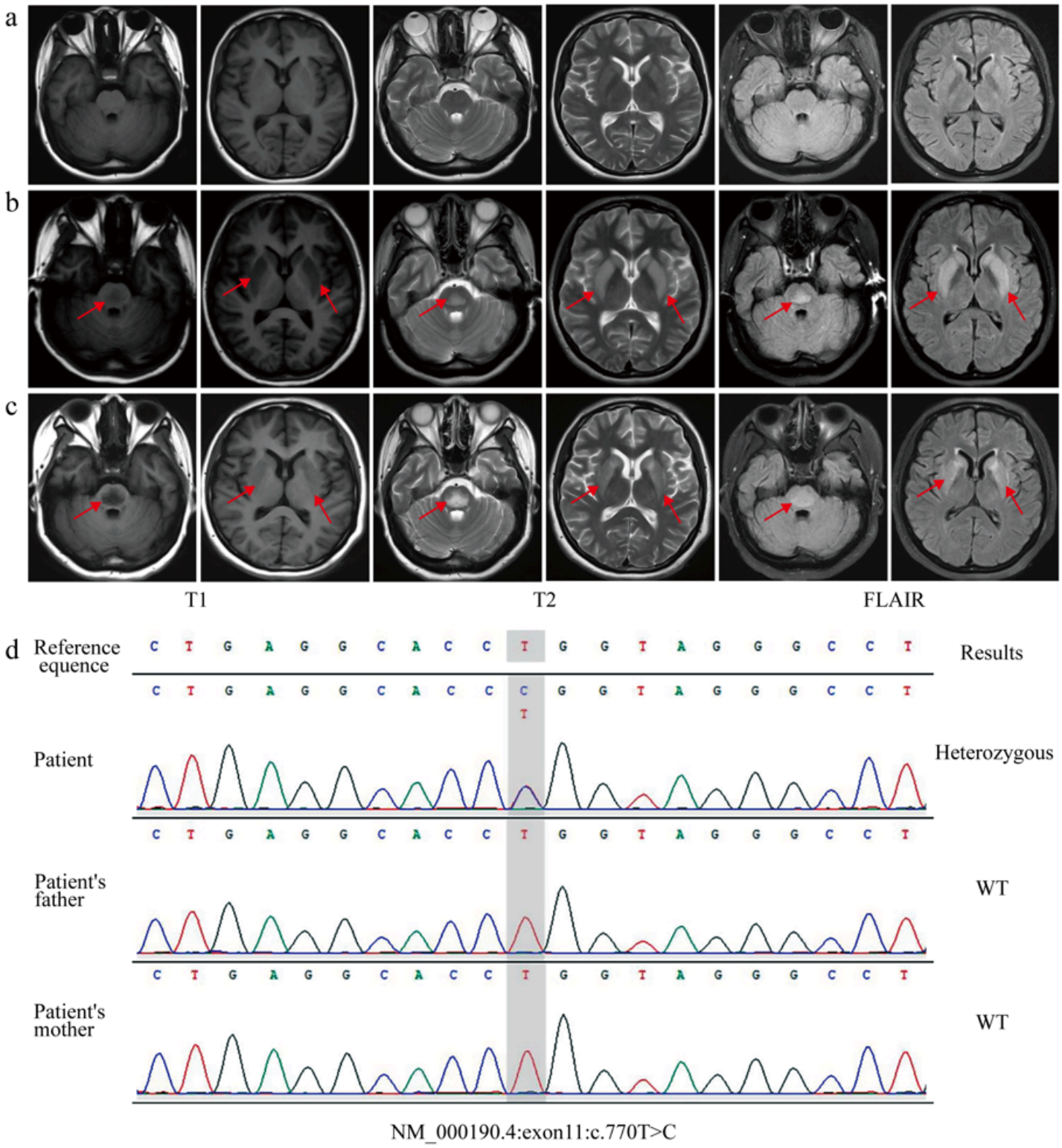


Figure 1

a Initial axial T1WI, T2WI, and FLAIR images show no significant abnormalities in the pons or basal ganglia. b Four days later, follow-up MRI reveals symmetrical signal changes in the bilateral caudate heads, putamina, pons, and external capsules, consistent with osmotic demyelination syndrome (ODS). c Eighteen days later, lesions in the basal ganglia have partially resolved, while pontine involvement has

progressed; contrast-enhanced imaging shows patchy pontine enhancement. d The patient in this case has a variation in the HMBS gene.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryMaterial.docx
- CAREchecklist.docx