CASE REPORT

A novel mutation, IVS2-2A→G, associated with acute intermittent porphyria in a Chinese family

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Abstract

Porphyria is a group of disorders caused by the accumulation of porphyrin and porphyrin precursors due to the abnormalities in certain enzymes that normally participate in the production of haem. We report a case of a woman with severe menstruation-related abdominal pain, hyponatraemia, and psychiatric symptoms. Excessive porphobilinogen was found in her urine. A new mutation in intron 2 (IVS2-2A→G), which had never previously been reported in patients with porphyria or in healthy Chinese population, was identified in the heterozygous state in the patient and her mother.

Keywords: Acute intermittent porphyria, Porphobilinogen deaminase, Gene mutation, Menstruation.

Introduction

Porphyria is a group of disorders caused by the accumulation of porphyrin and porphyrin precursors due to the abnormalities in certain enzymes that normally participate in the production of haem.[1] Acute intermittent porphyria (AIP), an autosomal dominant disorder, is a common type of neurologic porphyria in which mutation of the porphobilinogen deaminase (PBGD) gene plays an important role.[2,3] The clinical manifestations of AIP include severe abdominal pain, nausea, vomiting and psychiatric symptoms, but not skin lesions.[4] Here, we report a case of AIP with mutant allele of the PBGD gene.

Case Report

A 23-year-old woman had given birth to a healthy female baby in September 2011 and resumed menstruating with a normal cycle in February 2012. Severe abdominal pain was experienced during the first postpartum menstrual period and lasted for several days. The patient came to hospital after the severe abdominal pain returned during the second and third postpartum menstrual periods. On admission, the patient's pulse(P) was regular at 82/min and her blood pressure (BP) was 100/80 mmHg. No rash was observed on her skin. Abdominal muscle stiffness was noted, but was not associated with tenderness or rebound tenderness. The patient was not anaemic, and her haemoglobin level was 120g/L. Her other blood chemistry parameters were: alanine aminotransferase (ALT), 81 U/L; aspartate aminotransferase (AST), 85 U/L; and sodium, 134 mmol/L. The patient exhibited delirium on the third day of admission. The blood sodium level decreased to 119 mmol/L after the onset of the psychiatric symptoms, while the levels of adrenocortical hormones and thyroid hormones remained normal. Plain abdominal radiographs, ultrasonic examination of the epigastrium and mesenteric vessels, computed tomography angiography (CTA) examination of the abdominal aorta, and examination of the blood lead and amylase levels were performed after admission. Other possible causes of abdominal pain were excluded. A qualitative urinalysis of porphobilinogen was performed, which was positive, confirming the diagnosis of acute intermittent porphyria. The patient's mother had experienced similar abdominal pain associated with postpartum menstruation 23 years previously; the pain resolved 2 years later spontaneously. So the woman's mother on the basis of her symptoms several years back was also suspected to have AIP. The patient's mother is now leading a healthy life.

After obtaining approval from the hospital's ethical committee and the consent of the patient and her family members, we sequenced the exons and exon/intron junctions of the PBGD gene in both the patient and her mother. Genomic deoxyribonucleic acid (DNA) was extracted from peripheral blood lymphocytes.[5] A new mutation in the second base before the start of exon 3 (intron 2), namely IVS2-2A→G, was identified in the heterozygous state in the patient and her mother (Figure-1). In contrast, no such variations are seen in healthy Chinese population (Figure-2), suggesting that this variation could play a role in AIP. Literature search and data from Gene Bank remained unrevealing, which makes this case the first to be reported. As the mutation is located at the intron/exon junction, we speculate that it could cause abnormal messenger ribonucleic acid (mRNA) splicing and thus affect the function of the PBGD gene.

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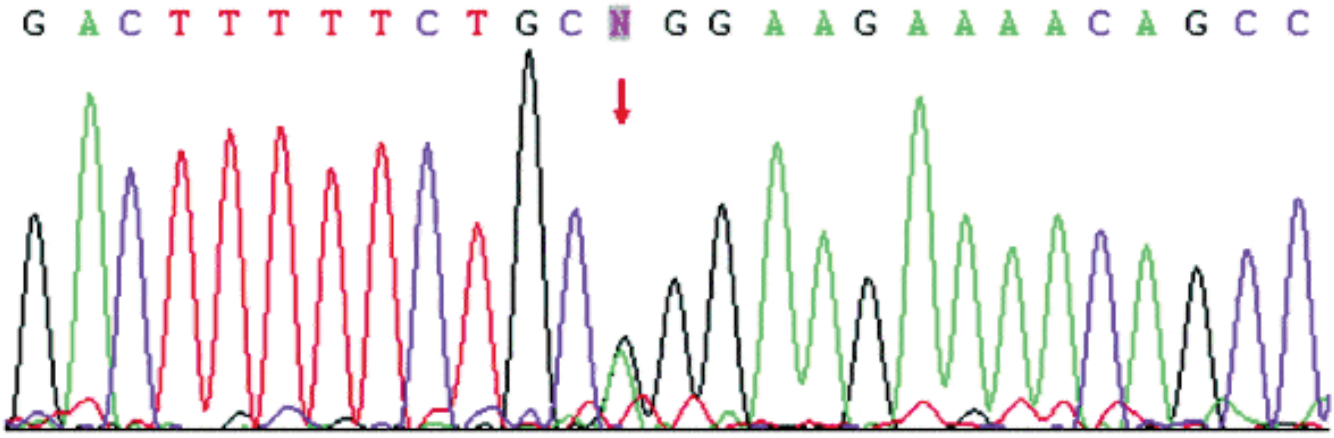

Figure-1: Heterozygous A/G genotype demonstrated by amplification and sequencing of the patient's porphobilinogen deaminase gene.

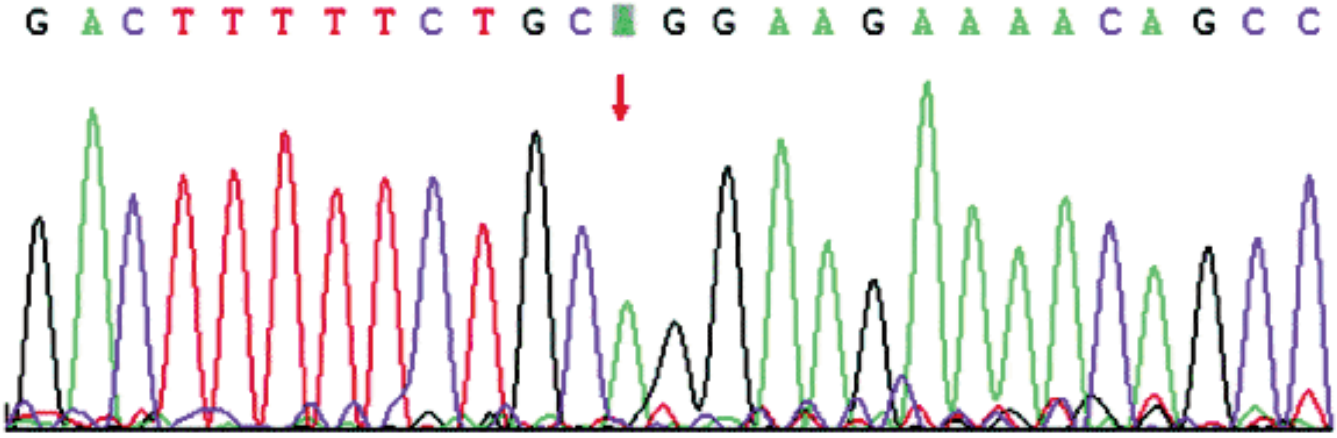

Figure-2: Homozygous A/A genotype in healthy people, which is consistent with the porphobilinogen deaminasegene sequence recorded in Gene Bank.

Previous studies have demonstrated that gonadotropin-releasing hormone agonism (GnRH-a) is an effective treatment for AIP,[6] so the patient has been treated with subcutaneous injection of leuprolide acetate (3.75 mg) monthly since January 2013. In addition, since June 2013 she has received oestrogen and progestogen to maintain a normal menstrual cycle, with no apparent adverse effects. The patient has not exhibited with abdominal pain or psychiatric symptoms since January 2013.

Discussion

AIP is a common type of porphyria caused by low PBGD activity due to variations in the PBGD gene. Decreased PBGD activity can reduce the conversion of porphobilinogen (PBG) into hydroxymethylbilane, which in turn attenuates the feedback inhibition and increases the activity of δ-aminolevulinic acid synthase (δ-ALAS), thus increasing the levels of ALA and PBG and consequently urinary excretion thereof.

Symptoms of involvement of the central nervous system (CNS) in AIP include personality changes, mental disorders, melancholy, hallucination, delirium and mania. However, the mechanisms by which AIP causes neurological lesions of AIP are unclear. Several studies have demonstrated the toxic effects of PBG and ALA on CNS.[7] The progression of the disease from latency to the active stage is associated with menstruation and gestation in some patients, including the patient in this case report, suggesting that endogenous steroids play essential roles in the development of AIP. Specifically, endogenous steroids could induce the synthesis of cytochrome P450 and thus affect the synthesis of haem, which in turn could decrease the haem level and thus induce the disease.[8] Hyponatraemia is common in patients with AIP. Many aspects of the disease could be

involved in the development of hyponatraemia, of which the most important is that AIP could damage the hypothalamus, which could lead to syndrome of inappropriate secretion of antidiuretic hormone (SIADH).[9]

The patient's mother had exhibited similar symptoms, including severe abdominal pain and psychological symptoms that had lasted for about 2 years about 20 years earlier. Although exploratory laparotomy had been performed in the local hospital to investigate the reason for her abdominal pain, but no definite diagnosis had been made. The knowledge of the clinicians and the medical technology available in primary hospitals are generally limited, making it difficult for them to diagnose such rare genetic diseases. The natural disease course of the mother of this patient suggests that this disease can possibly resolve spontaneously. However, the specific mechanism by which this occurs remains unclear. No detailed data and only a few case reports regarding AIP in Chinese patients, and even less information about the genetics of AIP in Chinese patients, are available.[10]

Conclusion

Genetic testing could aid the diagnosis of AIP as well as differential diagnosis; in addition, genotyping could also play a critical role in estimating the probability that a patient's child will inherit this disease. Fortunately, genetic testing did not detect the mutation in the infant daughter of the patient in the present case.

Acknowledgements

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References

1. Moore MR, McColl KM, Rimington C, Goldberg A. Disorders of porphyrin metabolism. New York: Plenum Publishing Corporation; 1987.
2. Balwani M, Desnick RJ. The porphyrias: advances in diagnosis and treatment. Blood 2012; 120: 4496-504.
3. Cantatore-Francis JL, Cohen-Pfeffer J, Balwani M, Kahn P, Lazarus HM, Desnick RJ, et al. Hepatoerythropoietic porphyria misdiagnosed as child abuse: cutaneous, arthritic, and hematologic manifestations in siblings with a novel UROD mutation. Arch Dermatol 2010; 146: 529-33.
4. Puy H, Gouya L, Deybach JC. Porphyrias. Lancet 2010; 375: 924-37.
5. Sakabe J, Susa S, Daimon M, Lan MY, Kato T. A novel 12-base pair deletion mutation in exon 15 of the porphobilinogen deaminase gene in a Taiwanese patient with acute intermittent porphyria. Blood Cells Mol Dis 2008; 41: 202.
6. Bode H. GnRH agonists in acute intermittent porphyria. Dtsch Med Wochenschr 1992; 117: 1940-1.
7. Yeung Laiwah AC, Moore MR, Goldberg A. Pathogenesis of acute porphyria. Q J Med 1987; 63: 377-92.
8. Innala E, Backstrom T, Bixo M, Andersson C. Evaluation of gonadotropin-releasing hormone agonist treatment for prevention of menstrual-related attacks in acute porphyria. Acta Obstet Gynecol Scand 2010; 89: 95-100.
9. De Block CE, Leeuw IH, Gaal LF. Premenstrual attacks of acute intermittent porphyria: hormonal and metabolic aspects - a case report. Eur J Endocrinol 1999; 141: 50-4.
10. Kong XF, Han Y, Li XH, Gao DY, Zhang XX, Gong QM, et al. Recurrent porphyria attacks in a Chinese patient with a heterozygous PBGD mutation. Gene 2013; 524: 401-2.