Brief Report

DOI: 10.5582/irdr.2020.03065

An extremely rare combination of acute intermittent porphyria and Turner syndrome

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SUMMARY A very rare case of acute intermittent porphyria (AIP) co-existing Turner syndrome (TS) is reported for the first time. A 32-year-old woman was diagnosed with AIP due to recurrent acute abdominal pain, red urine and pathogenic mutation of Hydroxymethyl synthetase (HMBS) gene. At the same time, TS was confirmed by Karyotype analysis results of 46,X,i(X)(q10), which accompanied by primary amenorrhea, elevated serum concentrations of follicle-stimulating hormone (FSH). Since the first attack of AIP, the patient has been increasingly depressed, and Psychiatry identified major depression. Duloxetine was chosen after careful deliberation, and the patient's mood stabilized. AIP had not recurred after half a year. Since sex hormones are the exacerbating factor of acute attack of AIP, sex hormone replacement therapy for TS was not administered. In conclusion, the conditions of AIP co-existing TS are complicate, and the treatment still needs to be improved by multiple disciplines in the follow-up.

Keywords acute intermittent porphyrin (AIP), Turner syndrome, HMBS gene, isochromosome, depression

1. Introduction

Acute intermittent porphyria (AIP) is a rare autosomal dominant genetic disease characterized by a deficiency in porphobilinogen deaminase (PBGD), the third enzyme in the heme biosynthesis pathway. The enzyme is coded for by the hydroxymethylbilane synthetase (HMBS) gene; mutations in that gene cause decreased PBGD activity and accumulation of precursors, leading to nerve dysfunction and clinical manifestations of acute abdominal pain and various neurological and mental disorders (*1*).

Turner syndrome (TS), also known as congenital ovarian dysplasia (*2*), is caused by complete or partial deletion of the X chromosome and is one of the most common chromosomal disorders in women. Clinical manifestations include primary amenorrhea, a short stature, abnormal bones, congenital heart disease, endocrine abnormalities, and autoimmune diseases (*3,4*). Reported here for the first time is a case of AIP and TS occurring together, and this study discusses this complex condition and difficulty in terms of treatment selection.

2. Patient and Methods

The design of this study was reviewed and approved by the Ethics Committee of the Second Hospital of Hebei Medical University, and the patient provided written informed consent. All clinical data on the patient were collected. The patient underwent whole exome sequencing and chromosome karyotype analysis. The safety of drugs used to treat the patient was determined based on standards of the American Porphyria Foundation (*www.porphyriafoundation.com*) and the European Porphyria Network (*www.porphyria-europe.com*). The PubMed database was searched in July 2020 using the keywords "acute intermittent porphyria AND Turner syndrome", and no articles were found.

This case involved a 32-year-old woman. The woman had paroxysmal abdominal pain and depression for two years.

Two years ago, she developed severe abdominal pain after exertion, nausea and vomiting, and oliguria and constipation. A physical examination was unremarkable. An abdominal X-ray suggested partial ileus that was alleviated with symptomatic treatment. Since then, the patient had gradually worsening depression, increased apathy, increased self-blame, fatigue, a poor appetite, difficulty falling asleep, and early waking. The patient had severe shortness of breath and was unable to talk

or walk. The results of electrocardiography and cardiac ultrasound were normal. The Hamilton Depression Scale indicated major depression. Consultation with a psychiatrist led to the diagnosis of major depression. Within 2 years, the patient had 6 acute episodes of AIP, 4 of which were induced by severe depression.

The patient had primary amenorrhea. Her father's height was 173 cm and her mother's height was 170 cm. Her parents are not cousins. Moreover, there are no similar diseases in the family. Her younger brother and sister are in good health. Physical findings from the patient were a height of 153 cm (lifetime height of 165.5 cm), a BMI of 17.5 kg/m^2, and no shield chest;short and webbed neck, cubitus valgus, and Madelung deformity of the forearm and wrist. The patient had Breast development Tanner stage 3, Pubic hair Tanner stage 2. Measurement of sex hormone levels revealed hypergonadotropic hypogonadism (FSH: 97.92 mIU/mL, LH: 21.05 mIU/mL, and E2: 28 pg/mL). A Pelvic ultrasound revealed an underdeveloped uterus, and neither ovary was evident. Karyotype analysis revealed an Isochromosome Xq(46,X,i(X)q), indicating Turner syndrome. Dual-energy absorptiometry (DXA) revealed severe osteoporosis with low bone mineral density (BMD) in the lumbar spine (Z-score of -4.7) and low BMD in the femoral neck (Z-score of -3.9)

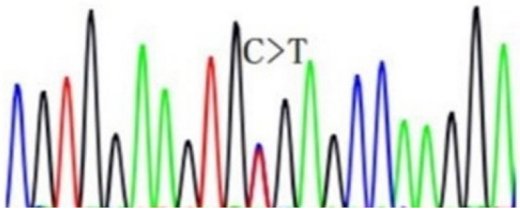

Figure 1. HMBS gene c. 673C>T (p. R225X).

3. Results and Discussion

AIP is a rare inherited disease, with an annual incidence of 0.13 per million and an estimated prevalence of 5.9 per million (*5*). TS is an uncommon sex chromosome aneuploidy (45,X) that affects approximately 1 in 2,000 to 1 in 2,500 live female births (*6-8*). Therefore, a combination of AIP and TS is a very rare clinical entity.

The patient was diagnosed with AIP based on genetic testing. A heterozygous missense variation, c. 673C>T, in the HMBS gene of the patient was identified (p.R225X) (Figure 1). According to the ACMG guidelines, it is a known pathogenic variation (PMID:8533808) (*9*), and it is also the most common HMBS gene variation observed in Chinese patients with AIP (research results to be published).This mutation occurs in exon 11, which is a termination mutation, resulting in the premature termination of the HMBS protein at position 225 during translation into amino acids, and the loss of all 136 amino acids in the C-terminal, including the C261 residue that is a binding site for a cofactor that facilitates 1-hydroxymethylbilane (HMB) formation, and the loss of function of PBGD.

The patient was diagnosed with Turner syndrome based on a karyotype analysis. The specific karyotype is 46,X,i(X)(q10) (Figure 2), that is, an isochromosome for the long arm of the X chromosome. The short arm of the X chromosome is missing and replaced by an accurate copy of the long arm, which is one of the most common structural abnormalities of sex chromosomes (*10*). The SHOX gene, located at the distal end of the short arm of the X chromosome, is associated with chondro-development and is a phenotype of human dwarfism. Deletion of the SHOX gene will lead to height defects. Thus, almost all patients with Turner syndrome have a short stature, *i.e*. a final height,

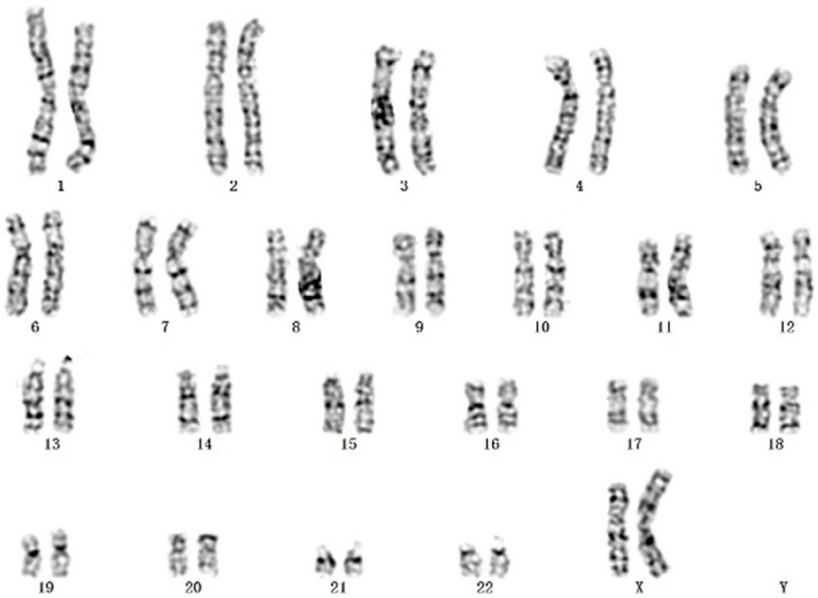

Figure 2. Karyotype analysis of the patient: An isochromosome for the long arm of the X chromosome 46,X,i(X)(q10).

usually no more than 150 cm, about 20 cm shorter than the expected lifetime height (*11*). However, the patient diagnosed with TS in the current case did not have a short stature but a natural height of 153 cm, which is just 10 cm shorter than the expected lifetime height (163 cm). The mechanism for this is unknown and worth exploring. The patient had natural breast development, suggesting partial prepubertal ovarian function.

Worsening depression is evident in patients with AIP and TS. A systematic review indicated that patients with TS had an increased risk of depression, and once depression developed, symptoms were more severe and more likely to recur. This is associated with decreased sex hormone levels and a short stature in patients with TS. The current patient was diagnosed with TS at the age of 32, and the delay in diagnosis resulted in a chronic deficiency of sex hormones and substantially increased the patient's risk of depression (*12*). According to the literature, patients with AIP can develop various mental and emotional issues at any time during the course of the disease, such as anxiety, depression, insomnia, behavioral abnormalities, personality changes, and even hallucinations and delirium. Depression is a very common one (*13*). In the current case, depression occurred after the first attack of AIP and gradually worsened, indicating that AIP caused the patient's depression. Various mood disorders, including depression, are aggravating factors for AIP (*14*). The untreated depression in the current patient markedly increased the incidence and severity of AIP attacks. In summary, the current patient had a high risk of depression due to TS. AIP induced depression , conversely , depression aggravated the severity of AIP, thus forming a vicious cycle. Accordingly, relief of depression is key to solving the problem.

First-line antidepressants are currently chosen based mainly on symptoms. Escitalopram and sertraline are chosen for anxiety. Duloxetine and venlafaxine are suggested for apathy. Mirtazapine is used for insomnia, loss of appetite, agitation, and suicidal ideation. The main symptom in the current patient was apathy. Because drugs can contribute to AIP, clinicians treating patients with AIP must choose drugs by carefully reviewing the latest drug safety information, including that from the American Porphyria Foundation (*www.porphyriafoundation.com*) and the European Porphyria Network (*www.porphyria-europe.com*). Duloxetine was deemed the most appropriate drug for the current patient. In this case, duloxetine was efficacious and symptoms were significantly alleviated. The patient had not suffered any acute AIP attacks in the half year prior to this report.

Severe osteoporosis is another major clinical manifestation that was noted the current patient. Osteoporosis is related to ovarian failure and an estrogen deficiency in patients with TS. The basic approach to preventing osteoporosis in women with TS is to start hormone replacement therapy as early as age 11-13, to titrate to the adult dose two years later, and to continue until menopausal age (*7*). Given that the current patient also had AIP, a sex hormone, and especially progesterone, would aggravate AIP, so hormone replacement therapy was not administered for the time being. Once AIP is stable, hormone replacement therapy may be cautiously attempted.

As mentioned earlier, the diagnosis of AIP or TS is often missed or delayed due to nonspecific symptoms, leading to increased morbidity and mortality. With that in mind, diagnosis requires a high index of suspicion, and treatment should be started as soon as possible.

In conclusion, AIP and TS may occur together, and the treatment for a patient with these comorbidities needs to be improved upon during follow-up by specialists in multiple disciplines.

References

1. Spiritos Z, Salvador S, Mosquera D, Wilder J. Acute intermittent porphyria: current perspectives and case presentation. Ther Clin Risk Manag. 2019; 15:1443-1451.
2. Classic pages in obstetrics and gynecology by Henry H. Turner. A syndrome of infantilism, congenital webbed neck, and cubitus valgus. Endocrinology. Am J Obstet Gynecol. 1972; 113:279.
3. Gravholt CH, Andersen NH, Conway GS, *et al*. Clinical practice guidelines for the care of girls and women with Turner syndrome: Proceedings from the 2016 Cincinnati International Turner Syndrome Meeting. Eur J Endocrinol. 2017; 177:G1-G70.
4. Gravholt CH, Viuff MH, Brun S, Stochholm K, Andersen NH. Turner syndrome: Mechanisms and management. Nat Rev Endocrinol. 2019; 15:601-614.
5. Elder G, Harper P, Badminton M, Sandberg S, Deybach JC. The incidence of inherited porphyrias in Europe. J Inherit Metab Dis. 2013; 36: 849-857.
6. Bondy CA, Turner Syndrome Study Group. Care of girls and women with Turner syndrome: a guideline of the Turner Syndrome Study Group. J Clin Endocrinol Metab. 2007; 92:10-25.
7. Stochholm K, Juul S, Juel K, Naeraa RW, Gravholt CH. Prevalence, incidence, diagnostic delay, and mortality in Turner syndrome. J Clin Endocrinol Metab. 2006; 91:3897-3902.
8. Cockwell A, MacKenzie M, Youings Sv, Jacobs P. A cytogenetic and molecular study of a series of 45,X fetuses and their parents. J Med Genet. 1991; 28:151-155.
9. Lee GY, Astrin KH, Desnick RJ. Acute intermittent porphyria: a single-base deletion and a nonsense mutation in the human hydroxymethylbilane synthase gene, predicting truncations of the enzyme polypeptide. Am J Med Genet. 1995; 58:155-158.
10. Wolff DJ, Van Dyke DL, Powell CM; Working group of the ACMG laboratory quality assurance committee. Laboratory guideline for Turner syndrome. Genet Med. 2010; 12:52-55.
11. C G Brook, G Mürset, M Zachmann, A Prader. Growth in children with 45,XO Turner's syndrome. Arch Dis

Child. 1974; 49:789-795.
12. Morris LA, Tishelman AC, Kremen J, Ross RA. Depression in Turner syndrome: a systematic review. Arch Sex Behav. 2020; 49:769-786
13. Duque-Serrano L, Patarroyo-Rodriguez L, Gotlib D, Molano-Eslava JC. Psychiatric aspects of acute porphyria: a comprehensive review. Curr Psychiatry Rep. 2018; 20:5.
14. Augoulea A, Zachou G, Lambrinoudaki I. Turner syndrome and osteoporosis. Maturitas. 2019; 130:41-49.

Received June 14, 2020; Revised July 13, 2020; Accepted July 28, 2020.

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Released online in J-STAGE as advance publication August 6, 2020.