# Case Report: A Menstruation-Associated Pancreatitis in Perimenopausal Woman

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**Case report**

**Keywords:** Hereditary pancreatitis, Menstruation-associated pancreatitis, PRSS1

**Posted Date:** June 7th, 2021

**DOI:** https://doi.org/10.21203/rs.3.rs-520112/v1

# Abstract

**Background:** Hereditary pancreatitis (HP) is a rare type of pancreatitis and patients are characterized with recurrent episodes of acute pancreatitis (AP) without common risk factors, such as gallstone, alcoholic consumption or drugs intake. The specific genes mutations, including PRSS1 and SPINK1, have been shown as the key risk factors for HP. The menstruation-associated pancreatitis is a rare type of HP, and patient always suffers the recurrent acute pancreatitis (RAP) which strictly follows her menstrual cycle. The genes sequencing which aims to recognize the etiology and determine the therapeutics should be taken into consideration for patients suspected of HP.

**Case presentation:** We presented a case of rare HP, whose episodes of recurrence were strictly dependent on her menstrual cycle. PRSS1 and SPINK1 genes sequencing were taken into consideration for menstruation-associated pancreatitis patient. Three conventional mutations (A16V, N29T and N54S) and two novel mutations (L14V and G62A) in the second exon of PRSS1 gene are found to be associated with the cause in our case. Long-term hormone replacement therapy, including deestrogesterone and ethinylestradiol, significantly decreases the recurrence of perimenopausal pancreatitis.

**Conclusion:** We found 2 novel mutations in the second exon of PRSS1 gene and long-term hormone replacement therapy significantly decreased the recurrence of AP. However, the increased risk of breast cancer and endometrial carcinoma need more attention.


# Background

Hereditary pancreatitis (HP) is a rare genetic condition, which is characterized by recurrent episodes of pancreatic attacks. It may progress to RAP or chronic pancreatitis (CP). The mutations of PRSS1 and SPINK1 genes have been suggested as the most common ones for the occurrence of HP. The menstruation-associated pancreatitis is a rare type of HP, and only 2 cases have been reported in young women until now. The PRSS1 gene mutations have been recognized one of the possible etiologies, and mutations in the second, third and tenth exons provide more evidence for the diagnosis. The patients are presented as recurrent acute pancreatitis (RAP), which appears in the coming one or two days of menstrual cycle and induces a poor quality of life. However, there is no report discussing menstruation-associated pancreatitis in perimenopausal woman and no therapy has been shown to be effective and safe for perimenopausal patient. Here, we presented a case of RAP in a perimenopausal woman, whose episodes of recurrence were strictly dependent on her menstrual cycle. The genes sequencing data indicated that three conventional mutations (A16V, N29T and N54S) and two novel mutations (L14V and G62A) in the second exon of PRSS1 gene are associated with its cause. Our study found that long-term hormone replacement therapy significantly decreased the recurrence of acute pancreatitis (AP). We recommend that the gynecologic examination should be taken once a year in case of the higher risk of breast cancer and endometrial tumor.

# Case Presentation

A 46-year-old female was referred to emergency department for a sudden severe abdominal pain and mild vomiting in December, 2016. She had no fever and jaundice during the course, also the alcoholic consumption or drugs intake were denied. The patient has experienced a total of 15 times RAP since 2005 to 2016. It was always occurred in the first two days of her menstrual cycle. Currently, the symptom appeared on the first day of this menstrual cycle.

The blood analyses showed that the neutrophilic granulocyte percentage was 15.81*10^9/L (3.7–9.2*10^9/L) and the serum amylase level was 64.8U/L (0-95U/L). The ALT, AST, bilirubin and triglycerides were all in the normal. The abdominal CT scan showed pancreatic edema and peripancreatic fluid collection (Fig. 1A). The patient showed no systemic inflammatory response syndrome (SIRS) and multiple organ failure (MOF) in the onset of 24h. She was diagnosed with mild acute pancreatitis (MAP). The somatostatin analogues, fluid resuscitation and pain relief therapies were included. On day 2, The MRCP was performed and there was no stone, tumor, malformation or anatomy variance found in the biliary system (Fig. 1B).

To formulate an accurate diagnosis and provide adequate management of the RAP, the patient and her immediate relatives were suggested to sequence PRSS1 and SPINK1 genes, which are directly associated with the HP. Unfortunately, both of her parents were unavailable to access our hospital, and only the patient and her two sisters received the sequencing. Compared with the original sequencing, no difference was found in SPINK1 gene for all of them. Notably, five mutations in exon 2 of PRSS1 gene (L14V, A16V, N29T, N54S and G62A) were revealed in our patient, two of which (L14V and G62A) have never been discovered before (Fig. 1C)[1,2]. In addition, no mutation was found in PRSS1 gene in the patient's sisters. The contraceptive has been shown as an effective therapy for two young case with menstrual cycle associated RAP. Then, the gynecological examination was performed, and the pelvic ultrasound examination was normal. The sex hormone analyses indicated lower levels of progesterone (0.2ng/ml, 0.77-2.30ng/ml) and luteinizing hormone (3mlu/ml, 17-77mlu/ml). Thus, the contraceptive, which contains 2mg deestrogesterone and 30mg ethinylestradiol in each dose, was recommended for daily oral administration.

## Discussion And Conclusions

# Rare cause of RAP and diagnosis

AP is an inflammatory disorder of pancreas, which is induced by gallstone, alcoholic consumption and hyperlipemia. It has also been recognized as a rare drug-related adverse event associated with the use of antibiotics, antineoplastic, anticonvulsant or immune checkpoint blockades (such as anti-PD-1 or anti-CTLA-4). Besides, the mutations of specific genes related to trypsin activation and secretion play a role in the etiology of minority of cases with HP, which may process to the RAP. The diagnosis of AP requires at least the presence of two of the three following criteria: (i) abdominal pain consistent with the disease, (ii) serum amylase and/or lipase greater than three times the upper limit of normal), and (iii) characteristic findings in contrast enhanced CT[3].

# Genes mutations and HP

Patients with genetic risk factors for HP spend the majority of their lives without suffering from RAP. The PRSS1 gene mutation was firstly described as a main cause for HP. More studies have explored the high incidence between trypsin activation and genes mutations by the genome-wide association study (GWAS). A gene clusters, including PRSS2, SPINK1, CASR, CFTR and CTRC, have been reported to affect the risk of AP[4]. However, the details of these genetic factors in reference to AP or chronic pancreatitis need to be further illustrated. ThRe finding of genetic variants in patients with AP has significant clinical implications, but the etiologies should be firstly excluded before the diagnosis of HP.

# New discoveries in menstruation-associated HP and therapy

HP is a genetic condition characterized by recurrent episodes of pancreatitis and the majority of cases are caused by variants in the PRSS1 and SPINK1 genes. Previous studies have identified a series of mutations in the second, third and tenth exon of PRSS1, including R122H, N29I, Arg122, which play crucial role in HP. Here, we presented a case of perimenopausal pancreatitis whose episodes of recurrence was strictly dependent on menstrual cycle. The PRSS1 and SPINK1 genes were sequenced and three common mutations and two novel ones (L14V and G62A) in the second exon of PRSS1 gene were identified, which may be the primary cause of HP. The oral contraceptive which contains levonorgestrel and ethinylestradiol have been suggested to reduce its recurrence in menstruation-associated recurrence of HP[5,6]. However, the main difference between our case and the previous ones is that the menstruation-associated RAP happens to a perimenopausal woman. Currently, no report has explored the therapeutic strategy for perimenopausal woman suffered from menstruation-associated HP.

# Long-term monitoring and precaution

Estrogen could alter the response of the exocrine pancreas to physiologic and pathologic stimuli, which may explain the association between menstruation and RAP[7]. Besides, sexual hormones are known to activate a series of genes during the menstrual cycle, which may induce the activation of protease inhibitors and secretion of matrix metalloproteinases and cytokines[8]. With reference to the subject mentioned above, the patient was recommended to receive the oral contraceptive. Our patient has received 5 years regular medication until now and the AP has not been recurred.

Previous studies have demonstrated that long-term use of oral contraceptive is associated with higher risk of breast cancer and endometrial carcinoma[9]. Our case was suggested to take the routinely gynecological examination once a year. After five years' follow-up, no adverse effect was found during the therapies. We conclude that long-term hormone replacement therapy is safe for RAP in perimenopausal woman. However, we should still take the precaution for the increased risk of breast cancer and endometrial carcinoma by long-term use of contraceptive. In addition, other issues that should be further considered, including the timings of reducing the dose or discontinuing the hormone replacement therapy.

# Abbreviations

AP: acute pancreatitis

CP: chronic pancreatitis

GWAS: genome-wide association study

HP: Hereditary pancreatitis

MAP: mild acute pancreatitis

MOF: multiple organ failure

RAP: recurrent acute pancreatitis

SIRS: systemic inflammatory response syndrome

# Declarations

### Ethics approval and consent to participate

This study was approved by the Institutional Review Board of The First Affiliated Hospital of Harbin Medical University (No. 201822).

### Consent for publication

Written inform consent for publication was obtained from all participants.

### Availability of data and materials

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

### Competing interests

The authors declare that they have no competing interests.


### Funding

This work was in part granted by National Natural Science Foundation of China (81770639).


### Authors' contributions

Le Li, Wang-Jun Zhang, Bei Sun and Gang Wang in planning this study, Wang-Jun Zhang, Yue Yuan, Jie Li and Long Cheng collecting the data. Le Li, Wang-Jun Zhang and Yue Yuan drafting the manuscript.

### Acknowledgments

Not applicable.

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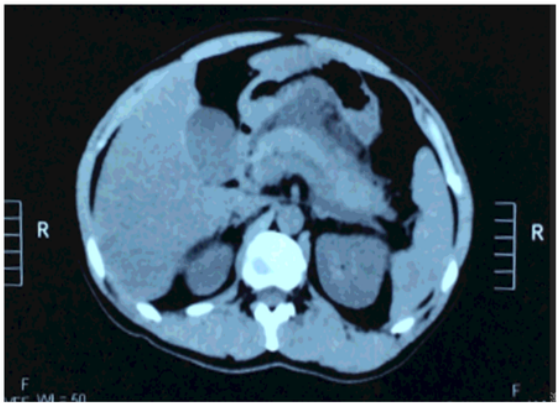
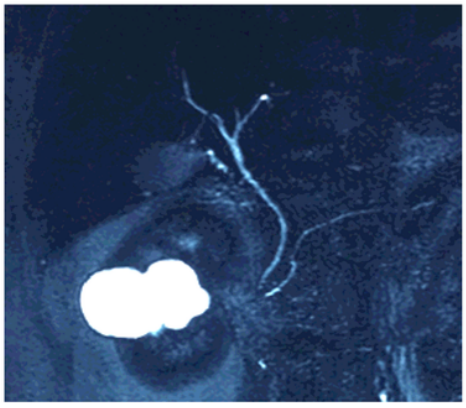
# Figures

A




B



C

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----------10----------20----------30----------40----------50----------60----------70----------80----------90-------
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----------VAVPFDDDDKIVGGYTCEENSLPYQVSLNSGYHFCGGSLISEQWVVSAAHCYK----------------------------------------
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## Figure 1

(A) The pancreatic edema and peripancreatic fluid collection were found in CT scan. (B) The MRCP found no stone and any obstruction in biliary tract system. (C) The comparison of exon 2 of PRSS1 between original sequence (upper) and the patient sequence (lower). The two newly discovered mutations (red) and those have been identified (green) were all shown in different colors.