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**A Case Report of Gilbert Syndrome Presenting with Acute Cholecystitis**

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**Key Clinical Message：**

A 38-year-old male with Gilbert syndrome presented with acute cholecystitis, jaundice, and elevated liver enzymes. This case highlights the importance of genetic testing for unexplained jaundice, avoiding misdiagnosis, and guiding personalized treatment for Gilbert syndrome.

**Keywords:**

Gilbert syndrome; unconjugated hyperbilirubinemia; UGT1A1 gene mutation

**1.Introdution**

Gilbert syndrome is a hereditary condition caused by a defect in bilirubin conjugation, often due to UGT1A1 gene mutations. Clinically, GS is typically benign, with episodic jaundice triggered by stress, fasting, or infections, and normal liver function. Although it is generally mild, GS can present diagnostic challenges, particularly in differentiating it from other causes of jaundice in acute illness. Here, we report a case of GS with acute cholecystitis, emphasizing the diagnostic complexity and the importance of genetic insights in management.

**2. Case History**

A 38-year-old male patient was admitted on August 5, 2024, with a chief complaint of "sudden upper abdominal pain for 3 days." The patient had experienced intermittent pain in the upper abdomen for 3 days prior to admission, mainly located in the right upper abdomen. The pain was mild, did not radiate to other areas, had no regular pattern of attack, and was not relieved by any particular method. It was unrelated to food intake or body position, accompanied by chills and fever, and jaundice of the whole body skin, eyes, and urine. After hospitalization and examination in our hospital, the patient was considered to have "acute cholecystitis." He was treated with anti-infection, antispasmodic analgesics, hepatoprotective and bilirubin-lowering, and acid suppression to protect the gastric mucosa. The upper abdominal pain was relieved, but the cause of jaundice was unclear, so an ERCP was performed, which showed no bile duct obstruction, dilatation, or stones, suggesting IgG4-related autoimmune cholangitis, and the patient was transferred to our department.

**3.Methods**

The patient had been found to have scleral icterus 20 years ago, mainly with increased indirect bilirubin, which was considered physiological and not treated, and improved on its own. The patient's parents are not consanguineous, and neither parent's family has similar patients. Physical examination on admission: heart rate 101 beats/min, jaundice of the whole body skin and sclera, and no other significant abnormalities were found. Laboratory tests: white blood cells 10.20x10^9/L, hemoglobin 124g/L, red blood cells 2.27x10^12/L, platelets 244x10^9/L, CRP 3.15mg/L, PCT 0.154ng/ml, reticulocytes accounted for 0.043. Direct antiglobulin test: negative. Liver function: AST 1173U/L, ALT 804U/L, ALP 145U/L, GGT 241U/L, LDH 824U/L, TBiL 220.0μmol/L, DBiL 71.5μmol/L, IBiL 148.5μmol/L; coagulation time was normal; IgG 2.54g/L; HAV, HBV, HCV, HEV virological markers were all negative, and autoimmune liver disease antibodies were all negative. Glucose-6-phosphate dehydrogenase test showed no abnormalities. Abdominal CT: The liver surface was smooth, no widening of the liver fissure, no abnormal density shadow, the gallbladder was full, no abnormal density shadow, the gallbladder wall was slightly thickened and rough, and the intrahepatic bile ducts were slightly dilated. The common bile duct and intrahepatic bile ducts were not dilated.

**4.Conclusion and Results**

Based on the patient's symptoms, signs, and auxiliary examinations, a hereditary metabolic disease-related jaundice was considered. Such diseases are related to heredity, and the patient was informed of the precautions for genetic testing. The exons related to bilirubin abnormalities were sent out for gene sequencing, and the examinee was found to have three mutations in UGT1A1 (gene reference sequence NM\_000463.3): a sub-effective variant c.-3275T>G in the non-coding area, a sub-effective variant c.-53\_-52dupTA in the non-coding area, and a pathogenic variant c.686C>A(p.Pro228Glu) in the first exon(Figure 1). Through the return of genetic testing results, the diagnosis was confirmed as congenital non-hemolytic indirect hyperbilirubinemia: Gilbert syndrome (GS). The patient was continuously treated with anti-infection and liver protection to reduce bilirubin after admission, and the bilirubin continued to decrease, ALT, AST gradually returned to normal, and the patient was discharged.

**5. Discussion**

Gilbert syndrome (GS) is a hereditary liver disease caused by UGT1A1 gene mutations, which result in the enzyme activity being about 30% of that of normal people, leading to the accumulation of unconjugated bilirubin in the blood [1-2]. Although GS is an autosomal recessive inherited disease, some literature suggests that heterozygous patients may also show some degree of hyperbilirubinemia [3]. The global incidence of GS is about 5%, more common in males, often manifesting as mild jaundice, without liver dysfunction, but some patients have abdominal discomfort, fatigue, nausea, etc., which may be caused by anxiety and other psychological factors. The prognosis of the disease is generally good, and no special treatment is needed. Rest, abstinence from alcohol, and other methods can alleviate symptoms, and benzobarbital can be tried if necessary to promote bilirubin excretion [4]. In some situations, such as fasting, emotional tension, severe infection, pregnancy, etc., the jaundice in GS patients will worsen [5]. In this case, the patient had a mild increase in white blood cells, suggesting the possibility of infection, which led to an increase in bilirubin and obvious jaundice. In recent years, with the increase in health checks, more patients with hidden or mild jaundice have been discovered. Clinically, they are easily misdiagnosed as hepatocellular jaundice, hemolytic jaundice, and even undergo liver tissue biopsy several times, causing psychological and economic burdens on patients [6].

Although GS is generally considered a benign disease that does not progress to severe liver disease, in some cases, such as when combined with chronic hepatitis B, fatty liver, etc., jaundice may worsen, and even liver failure may occur [7]. In this case, the diagnosis was mainly based on clinical manifestations and laboratory tests. After excluding hemolysis and other liver diseases, it was confirmed through UGT1A1 gene testing. UGT1A1 gene mutations are an important step in determining the cause of unexplained hyperbilirubinemia [8]. Molecular diagnosis avoids invasive diagnostic methods such as liver puncture, allowing the establishment of the correct treatment program at an early stage of the disease. Therefore, for patients with unexplained jaundice, if routine examinations fail to find a clear cause, the possibility of hereditary metabolic disease-related jaundice should be considered, relying on gene sequencing technology to provide an important reference for clinical doctors' diagnosis.

The main gene mutations of GS are mutations in the promoter or the first exon region. Tang et al. believe that UGT1A1 gene mutations may also affect the development of other diseases, such as UGT1A1 gene mutations inducing breast cancer or colorectal cancer [9]. It is worth noting that UGT1A1 gene mutations in GS patients also participate in drug metabolism pathways, such as the key drug irinotecan in chemotherapy, which can lead to increased drug concentration in the blood and increase the risk of drug toxicity reactions [10]. Therefore, when GS patients use drugs whose main elimination pathway is glucuronidation mediated by UGT1A1, special attention should be paid to drug dosage and toxicity.

****AUTHOR CONTRIBUTIONS****

**ShuQi Yang**: Data Curation,Investigation,Methodology,Writing-Original Draft；**Yijie Lin**: Methodology,Supervision,Writing-Review,Formal Analysis；**HuaTang Zhang**: Data Curation,Investigation；**Xing Wang**: Supervision,Validation;**Yan-Yan Qiu**: Investigation,Software;**Yan-Yan Lin**:Methodology,Project administration;**XuePing Yu**: Conceptualization,Methodology, Resources, Supervision,Validation, Writing-Original Draft,Writing-Review & Editing.

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**CONFLICT OF INTEREST STATEMENT**

We have no conflict of interest.

**DATA AVAILABILITY STATEMENT**

Data available on request from the authors.

**ETHICS STATEMENT**

This study was approved by the ethics committee of Ethics Committee of Quanzhou First Hospital(approval no.K282).We certify that the study was performed in accordance with the 1964 declaration of HELSINKI and later amendments.

**CONSENT**

Written informed consent was obtained from the patient to publish this report in accordance with the journal’s patient consent policy.

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11. **Graph**

**Figure 1:** Patient's UGT1A1 gene sequencing results (arrows and boxes indicate mutation sites)

*Note: a. The patient's promoter region -3275T>G homozygous mutation NM\_000463.3:c.-3275T>G variation; b. The patient's promoter region TATAA box TA insertion heterozygous mutation NM\_000463.3: c.-53\_-52dupTA variation; c. The patient's first exon region 686C→A heterozygous mutation NM\_000463.3:c.686C>A(p.Pro228Glu) variation*