Clinical Case Report

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Liver transplantation for decompensated liver cirrhosis caused by progressive familial intrahepatic cholestasis type 3

A case report

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Abstract

Rationale: Progressive familial intrahepatic cholestasis (PFIC) type 3, characterized by high gamma glutamyl transferase (GGT), is an autosomal recessive genetic disease. It often occurs in patients' first years of age. However, high GGT type PFIC is still rare.

Patient concerns: The present study reports a case of liver transplantation for decompensated liver cirrhosis caused by PFIC type 3. An 18-year-old male presented with a history of abdominal distension and jaundice for 2 months. He had abdominal tenderness but no rebounding pain. Moreover, his dullness was felt over the liver and the spleen was palpable 8 cm below the ribs.

Diagnoses: Computed tomography and magnetic resonance cholangiopancreato graphy of the upper abdomen revealed cirrhosis, portal hypertension, collateral circulation formation, large spleen, and ascites. Blood biochemistry showed high alanine transaminase, aspartate transaminase, and GGT. The diagnosis of decompensated liver cirrhosis caused by PFIC-3 was finally confirmed by plasma gene detecting.

Interventions: The patient received an open surgery named allogeneic liver transplantation after successful matching of immune types between the recipient and donor. Peritoneal puncture and catheter drainage under B-ultrasound was performed when an encapsulated effusion between the liver and stomach arose.

Outcomes: The patient was discharged without specific discomfort and was almost free of fluid accumulation 51 days after the surgery. At the 6-month follow-up, he had no discomfort and the blood routine, liver functions showed no abnormalities.

Lessons: We found a new mutant fragment of *ABCB4* gene in the process of diagnosis. Liver transplantation remains the most definitive treatment for PFIC. Current medical therapies and surgical interventions such as biliary diversion have potentially created a synergistic outcome.

Abbreviations: ALT = alanine transaminase, AST = aspartate transaminase, CA = carbohydrate antigen, CT = computed tomography, DB = direct bilirubin, GGT = gamma glutamyl transferase, INR = international normalized ratio, MRCP = magnetic resonance cholangiopancreato graphy, PFIC = progressive familial intrahepatic cholestasis, PT = prothrombin time, RBC = red blood cell, UDCA = urodeoxycholic acid, WBC = white blood cell.

Keywords: cholestasis, cirrhosis, liver transplantation, PFIC-3, treatment

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DX, JH, and HW contributed equally to this work and should be considered co-first authors.

The Ethics Committee of the First Affiliated Hospital of Nanchang University was approval for this case.

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This study was approved by the ethical review committee of the First Affiliated Hospital of Nanchang University, and written informed consent was obtained from the patient.

The authors report no conflicts of interest.

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1. Introduction

Progressive familial intrahepatic cholestasis (PFIC) is an autosomal recessive genetic disease, caused by specific gene mutations, leading to an abnormal expression of a specific protein by liver parenchymal and stromal cells, and finally leading to hepatocellular cholestasis.[1,2] The disease is often confused with physiological jaundice and other causes of pathological jaundice in the newborn, and is difficult to distinguish as it usually occurs in the neonatal period to the first years of age.[3] A small percentage of PFIC patients die during childhood or adolescence, from sudden liver failure.[4] Clinically, intrahepatic cholestasis is the main manifestation of this disease, which is classified into low gamma glutamyl transferase type (low gamma glutamyl transferase [GGT] type) and high GGT type, based on different glutamyl transpeptidase activity.[5] With advances in PFIC research and gene diagnosis, low GGT type PFIC is divided into 2 subtypes, type PFIC-1 and type PFIC-2. Both are caused by abnormal bile formation and abnormal terminal bile duct drainage. High GGT type (PFIC-3 type) liver biopsy usually reveals interlobular bile duct hyperplasia, terminal bile duct biliary sludge formation, and periportal edema, suggesting that the cause might be obstructive lesions in the bile duct, rather than abnormal synthesis of bile. Reports of low GGT type PFIC have gradually increased; however, high GGT-type PFIC reports are still rare, and information on mutations associated with the corresponding genes is even rarer. In the process of diagnosis and treatment for decompensated cirrhosis caused by PFIC type 3 in our case, we also found a new mutant gene fragment of PFIC-3, which has never been reported previously. We present the case below.

2. Presenting concerns

An 18-year-old male presented with a history of abdominal distension and jaundice for 2 months. His skin and sclera were yellow. The abdominal muscles were slightly tight; there was abdominal tenderness but no rebounding pain. He was diagnosed with cirrhosis, large spleen, and ascites in a local hospital.

3. Clinical findings

The patient had no related past illness, history of hepatotoxic drugs, and family history. He was physically fit and had normal mental health. There was no palmar erythema and no spider nevi on his chest. Chest auscultation was normal and there were no rales or cardiac murmurs. He had abdominal distension but no subcutaneous varicose veins on the abdominal wall. The right hypochondrium showed no tenderness, but shifting dullness was observed. Lower limbs had no edema. Moreover, dullness was felt over the liver and the spleen was palpable 8 cm below the ribs.

4. Diagnostic focus and assessment

On August 20, 2016, examination of ascetic fluid revealed yellow color, mild turbidity, no clots, negative Rivalta test result, and 10 cells/μL nuclear cells. On August 22, 2016, routine stool examination revealed occult blood 1+. Coagulation tests showed prothrombin time (PT) 15.3 seconds, international normalized ratio (INR) 1.45, and activated partial thromboplastin time (APTT) 43.8 seconds. Routine blood test showed white blood cell (WBC) 1.76×10^9 cells/L, red blood cell (RBC) count 3.93×10^{12} cells/L, hemoglobin 120 g/L, platelets (PLT) 37×10^9 cells/L, and neutrophil percentage 60.3%. Blood biochemistry revealed serum total protein, 64.5 g/L; albumin, 34.2 g/L; serum total bilirubin, 154.5 μmol/L; direct bilirubin (DB), 115.8 μmol/L; alanine transaminase (ALT), 79 U/L; aspartate transaminase (AST), 146 U/L; GGT, 294 U/L; tumor markers: carbohydrate antigen (CA)199, 33.15 U/mL; CA125, 513.70 U/mL; HBsAb, +; hepatitis B virus DNA, –; and ceruloplasmin, 262.00 mg/L. Computed tomography (CT) of the upper abdomen (Fig. 1) and chest revealed no obvious abnormality in the chest. Thus, a diagnosis of cirrhosis, portal hypertension, collateral circulation formation, large spleen, and ascites was made. On August 24, 2016, magnetic resonance cholangiopancreato graphy (MRCP; including the upper abdomen scan) revealed cirrhosis, ascites, and portal hypertension with collateral circulation, splenomegaly, megalosplenia, some calcified plaques in the spleen; and small gallstones.

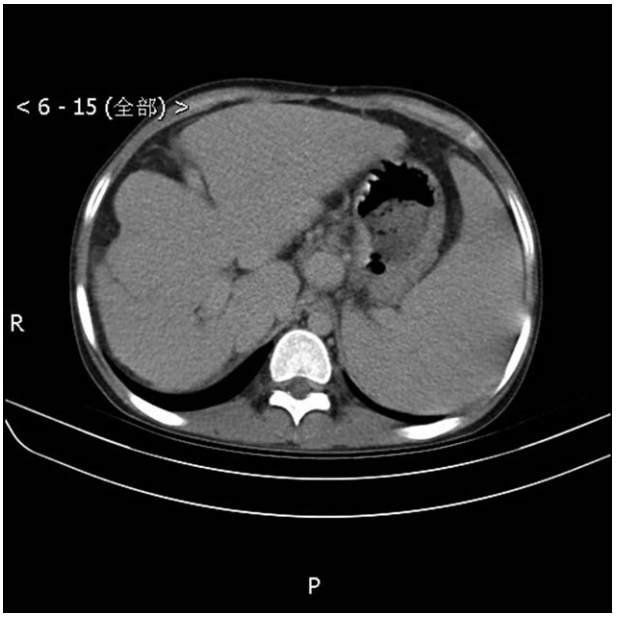

Figure 1. Computed tomography of the upper abdomen and chest revealed cirrhosis, portal hypertension, collateral circulation formation, large spleen, and ascites on August 22, 2016.

On October 11, 2016, the patient plasma was detected at the gene diagnosis center of Tongji Hospital affiliated to Tongji Medical College of Huazhong University of Science and Technology, and all 138 exons of the disease (related) genes and their adjacent regions were detected. The results of the genetic testing revealed a pathogenic mutation, c.2362C>T heterozygous mutation was present in the ABCB4 gene (Fig. 2A),

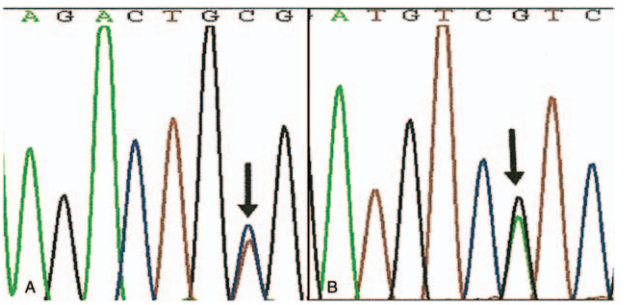

Figure 2. Gene diagnosis of the patient's plasma on October 11, 2016. (A) c.2362C>T heterozygous mutation in the *ABCB4* gene; (B) c.1798A>G heterozygous mutation in the *ABCB4* gene.

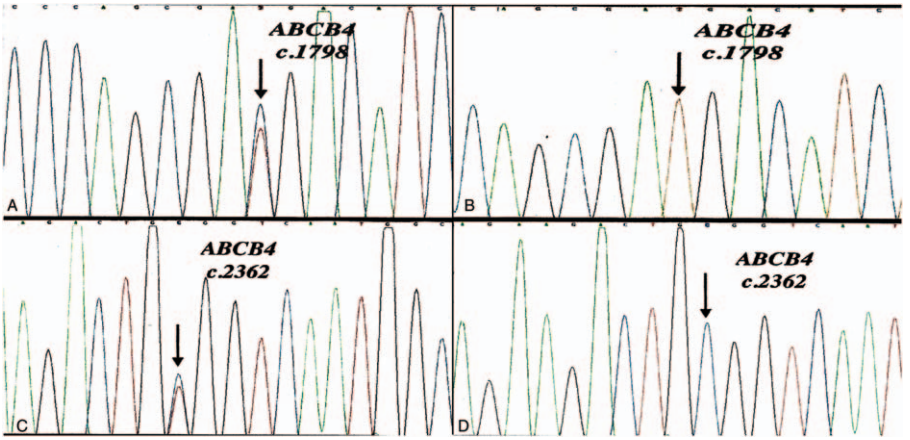

Figure 3. Gene diagnosis of the patient's parents and younger brother on October 11, 2016. (A) The heterozygous mutation of c.1798A>G in his mother and younger brother's *ABCB4* gene; (B) The protein p.Ile600Val of patient's father was wild-type; (C) The heterozygous mutation of c.2362C>T in his father and younger brother's *ABCB4* gene; (D) The protein p.Arg788Trp in patient's father and younger brother was wild-type.

and encoded a missense mutation of protein p.Arg788Trp, which had been reported.[6] Moreover, a suspicious pathogenic mutation had been detected, c.1798A>G heterozygous mutation was present in the *ABCB4* gene (Fig. 2B), which encoded a missense mutation of protein p.Ile600Val. Gene *ABCB4* is linked to the following diseases in online Mendelian inheritance in man (OMIM): cholestasis, intrahepatic cholestasis, cholestasis in pregnancy, 3, 614972, autosomal dominant inheritance, autosomal recessive inheritance; cholestasis, progressive familial intrahepatic, 3, 602347, autosomal recessive inheritance; and gallbladder disease, 1, 600803, autosomal dominant inheritance, autosomal recessive inheritance. A known heterozygous genetic mutation and a previously unreported heterozygous suspected pathogenic mutation were found in the *ABCB4* gene. ABCB4 mutations can lead to autosomal recessive familial progressive intrahepatic cholestasis (PFIC-3 as described in OMIM). Genetic analysis of the patient's parents was recommended for a definitive diagnosis.

The patient's genetic mutation was validated in his parents and younger brother. Results: detecting *ABCB4* gene exon by gene sequencing, the fifteenth exon c.1798 bases and the nineteenth exon c.2362 bases were heterozygous mutant and wild type. The heterozygous mutation of c.1798A>G in his mother and younger brother's fifteenth ABCB4 exon (Fig. 3A) led to a missense mutation in the gene encoding protein p.Ile600Val, the detection result of which in patient's father was wild-type (Fig. 3B). The heterozygous mutation of c.2362C>T in his father and younger brother's 19th *ABCB4* exon (Fig. 3C) led to a missense mutation in the gene encoding protein p.Arg788Trp, the detection result of which in his mother was wild-type (Fig. 3D).

5. Therapeutic focus and assessment

After admission, the patient was treated with ademetionine1,4-butanedisulfonate to alleviate the liver disease and eliminate jaundice; moxifloxacin, mezlocillin sulbactam sodium, and cefoperazone sulbactam sodium to control infections; omeprazole to inhibit gastric acid secretion; artificial liver to improve the liver and eliminate jaundice; recombinant human granulocyte colony-stimulating factor (rhG-CSF) to increase WBC count; and urodeoxycholic acid (UDCA), albumin, and diuresis to support treatment. On October 22, 2016, the endotoxin level was 0.0344 EU/mL. Blood biochemistry revealed serum total protein, 52.1 g/L; albumin, 33.1 g/L; serum total bilirubin, 111.9 μmol/L; DB, 90.2 μmol/L; ALT, 58 U/L; and AST, 107 U/L. The coagulation functions were PT 14.2 seconds and fibrinogen <0.25 g/L. WBC count was 1.09×10^9 cells/L, hemoglobin 106 g/L, and PLT 38×10^9 cells/L. On October 26, 2016, CT of the upper abdomen (compared with the former performed on August 22, 2016) revealed that the spleen was much larger with no apparent changes in cirrhosis, ascites, and portal hypertension with collateral circulation. Some new-onset symptoms were intermittent low-grade fever (highest temperature, 38.0°C), increased frequency of defecation (maximum, 7 per day), and blood stained stool.

With a definitive diagnosis of the disease and genotype, active medical for 2 months did not result in overall improvement. As he had developed decompensated cirrhosis with spontaneous bacterial peritonitis and coagulation dysfunction, the patient received allogeneic liver transplantation under general anesthesia after successful matching of immune types between the recipient and donor, on November 2, 2016. The blood loss during surgery was 3000 mL. Transfusions of 300-mL plasma, cold precipitation 10 U, PLT 10 U, and autologous blood transfusion 2900 mL were provided. The patient received immunosuppressants, antiinfectives, anti-inflammatory, antacids, anticoagulant, and other symptomatic and supportive treatments after his postoperative vital signs were stable. Five days later, the patient passed dark yellow feces and had no fever. Laboratory results after 10 days showed WBC, 6.74×10^9 cells/L; RBC, 3.30×10^{12} cells/L; hemoglobin, 112 g/L; PLT, 62×10^9 cells/L; lymphocyte percentage, 20.3%; neutrophil, 4.90×10^9 cells/L; and neutrophil percentage, 72.7%. Coagulation functions were PT, 12.5 seconds; PT ratio, 1.22; PT activity, 69.6%; INR, 1.20; activated partial thromboplastin time, 35.1 seconds; fibrinogen, 2.12 g/L; and thrombin time, 17.2 seconds. Blood biochemistry revealed albumin, 31.6 g/L; serum total bilirubin, 81.6 μmol/L; DB, 66.9 μmol/L; ALT, 100 U/L; AST, 33 U/L; GGT, 894 U/L; alkaline phosphatase (ALP), 185 U/L; creatinine, 51.7 μmol/L; blood urea nitrogen, 7.7 mmol/L; uric acid, 254 μmol/L; glucose, 4.02 mmol/L; K^+, 3.37 mmol/L; Na^+, 133.2 mmol/L; Cl^-, 96.1 mmol/L; Ca^{2+}, 2.08 mmol/L; and prealbumin, 186 mg/L. The serum total bilirubin and DB levels decreased, PT was nearly normal, WBC count improved to normal, and PLT count increased.

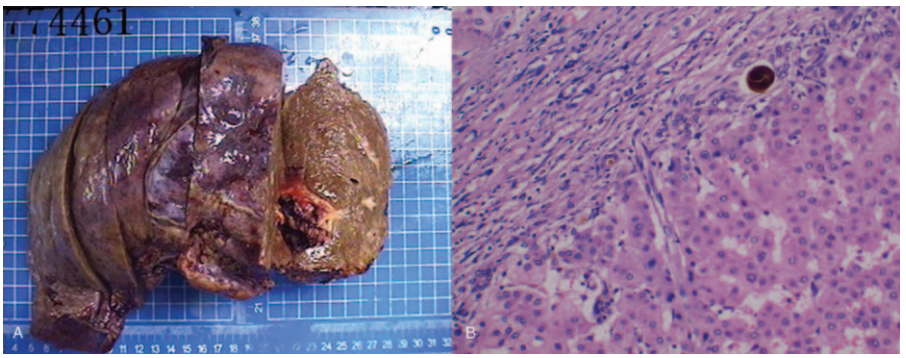

Figure 4. Postoperative histopathology of the recipient liver. (A) The slice of the liver. (B) Hepatic tissue under the microscope.

On November 28, 2016, the patient developed abdominal distension. Multislice CT showed: liver cirrhosis, splenomegaly, portal hypertension, and multiple collateral circulation caused by esophageal and gastric varices; a large cystic density between the liver and stomach, considered as a benign cystic lesion (encapsulated effusion); fluid in abdominal cavity. On November 29, 2016, the patient underwent peritoneal puncture and catheter drainage under B-ultrasound. About 1200 mL of brownish green bile fluid was extracted. Total bilirubin in the ascitic fluid was 272.2 μmol/L. Combined with imaging techniques, it was diagnosed as a stricture of the middle and upper bile duct, with biliary fistula. A plastic stent of 8.5 Fr*12ï¿1/2cm was inserted into the common bile duct under endoscopy. Multilayer CT on December 19, 2016 revealed cystic low-density shadow between the liver and stomach (possible to be encapsulated effusion, the change after drainage is less than before). Subsequently, the amount of peritoneal fluid was usually >60 mL. By December 20, 2016, the patient had no specific discomfort and was almost free of fluid accumulation. After removing the drainage tube, he was discharged on December 23, 2016.

6. Follow-up and outcomes

On postoperative histopathology, the recipient liver showed nodular in nearly size, dilatation of some bile ducts, and beige stones were visible (the sections of the liver, Fig. 4A), and fibrous hyperplasia, lobules formed by the dividing hepatocytes, mild edema in some hepatocytes, many chronic inflammatory cells infiltrating the portal area (under the microscope, Fig. 4B).

After discharge, the patient was administered long-term oral immunosuppressants and ursodeoxycholic Acid. He was followed up once a week and blood routine, liver functions and serum concentrations (Fk506) were measured at each visit. The follow-up continued for 6 months, and the patient had no discomfort. At last follow-up on May 27, 2017, his reports showed WBC, 4.12×10^9 cells/L; RBC, 5.45×10^{12} cells/L; hemoglobin, 168 g/L; PLT, 71×10^9 cells/L; lymphocyte percentage, 38.6%; neutrophil, 2.10×10^9 cells/L; neutrophil percentage, 51%; serum albumin, 53.4 g/L; serum total bilirubin, 28.9 μmol/L; DB, 6.7 μmol/L; ALT, 13 U/L; AST, 22 U/L; GGT, 18 U/L; ALP, 52 U/L. Renal function and blood electrolytes showed no abnormalities. Tacrolimus blood concentration was 7.4 ng/mL. Table 1 summarizes the timeline of this patient.

7. Discussion

PFIC is an autosomal recessive disease. Its exact prevalence remains unknown, but the estimated incidence ranges from 1 per 50,000 to 1 per 100,000 births.[7] It usually occurs because of genetic mutation, and eventually leads to intrahepatic cholestasis, marked by severe itching of the skin. The disease is classified into 3 types.[8] PFIC-1 known as Byler disease, a fatal familial intrahepatic cholestasis syndrome, and infant cholestasis syndrome. The gene mutation originates from ATP8B1 in 18q21–22.[9] PFIC-2 is from the ATP-binding cassette family B member 11 (*ABCB11*) gene encoding the bile salt excretion protein (BSEP) in 2q24. PFIC-3 originates from ATP-binding cassette subfamily B member 4 (*ABCB4*) gene mutation in 7q21, which encodes the multidrug resistance 3 (MDR3) protein. Gene analysis is the most definitive diagnosis, but is difficult and cannot be widely adopted in clinical settings. The final diagnosis must be based on clinical manifestations, family history, and gene analysis results. Apart from intrahepatic cholestasis, the typical manifestations include severe skin itching in childhood, malabsorption of long fatty acids and lipid-soluble vitamins, progressive jaundice, and hepatosplenomegaly. Blood biochemistry shows increased ALP. In particular, GGT is not high in PFIC-1 and PFIC-2 but extremely high in PFIC-3. The GGT level is increased, but the total cholesterol, low-density lipoprotein (LDL), and oxidized LDL levels are normal. The normal GGT level distinguishes PFIC-1 from other types of intrahepatic cholestasis. PFIC-3 can occur in adults and develop into biliary cirrhosis in the initial stage of the disease.[10] Recently, *TJP2* gene mutation, which codes intimate connexin, has been reported to cause PFIC, defined as PFIC-4.[11] It also shows low serum GGT levels. Liver biopsy indicates portal fibrosis, chronic inflammation, intrahepatic cholestasis, central venous wall sclerosis, and hepatic cell edema. The intrahepatic cholestasis in PFIC-1 occurs in the hepatic capillaries, whereas in PFIC-2 it occurs in hepatic cells. Research is underway to identify the mutated genes to aid the clinical diagnosis. PFIC should be distinguished from other forms of infant intrahepatic cholestasis. In clinical settings, ultrasound examination of the liver and gallbladder, and MRCP can exclude common biliary atresia, choledochal cyst, spontaneous rupture of choledochal cyst, enlargement of lymph nodes in liver portal compression, and Caroli disease. Other rare diseases can be diagnosed by dynamic duodenal fluid examination, radionuclide hepatobiliary scintigraphy, ultrasound of the liver and gallbladder, MRCP, and examination of metabolites or hepatic pathology.

Pharmaceutical, medical, and surgical therapies play important roles in the management of patients with PFIC, both as definitive therapy for cases with previous transplant. In some complicated cases, all of them have been used to manage posttransplant cases.

UDCA has been shown to improve symptoms and liver function tests in some patients with PFIC and is typically

Table 1

Case report timeline.

Complaint/investigations	Details
Presenting symptoms	Abdominal distension and jaundice for 2 months; diagnosed with cirrhosis, large spleen, and ascites in a local hospital.
First investigations	Abdominal tenderness but no rebounding pain, dullness was felt over the liver, and the spleen was palpable 8 cm below the ribs; examination of ascetic fluid, coagulation tests, routine blood test, blood biochemistry, tumor markers were demonstrated
CT	Cirrhosis, portal hypertension, collateral circulation formation, large spleen, and ascites
MRCP	Cirrhosis, ascites, and portal hypertension with collateral circulation, splenomegaly, egalosplenia, some calcified plaques in the spleen; and small gallstones
Treatment	Ademetionine1,4-butanedisulfonate, moxifloxacin, mezlocillin sulbactam sodium and cefoperazone sulbactam sodium, omeprazole, artificial liver, recombinant human granulocyte colony-stimulating factor, urodeoxycholic acid, albumin, and diuresis were chosen
Plasma gene detecting	Patient: c.2362C>T and c.1798A>G heterozygous mutation in the *ABCB4* gene; patient's parents and younger brother: the 15th exon c.1798 bases and the 19th exon c.2362 bases were heterozygous mutant and wild type in the *ABCB4* gene
Second investigations	Intermittent low-grade fever (highest temperature, 38.0°C), increased frequency of defecation (maximum, 7 per day), and blood stained stool; endotoxin level, elood biochemistry, eoagulation functions, and white blood cell count was detected
CT	The spleen was much larger with no apparent changes in cirrhosis, ascites, and portal hypertension with collateral circulation
Surgical intervention	Allogeneic liver transplantation under general anesthesia; postoperative pathology: nodular in nearly size, dilatation of some bile ducts, and beige stones were visible (the sections of the liver); and fibrous hyperplasia, lobules formed by the dividing hepatocytes, mild edema in some hepatocytes, many chronic inflammatory cells infiltrating the portal area (under the microscope)
Postoperative symptom	Abdominal distension
Multislice CT	Liver cirrhosis, splenomegaly, portal hypertension, and multiple collateral circulation caused by esophageal and gastric varices; a large cystic density between the liver and stomach, considered as a benign cystic lesion (encapsulated effusion); fluid in abdominal cavity
Intervention	Peritoneal puncture and catheter drainage under B-ultrasound
Multilayer CT	Encapsulated effusion after drainage is less than before
Postoperative follow-up	Six-month follow-up: no discomfort; blood test results demonstrated satisfactory prognosis; consecutive follow-up needed

CT = computed tomography, MRCP = magnetic resonance cholangiopancreato graphy.

considered the preferred therapy.[12] Recently, the degree of floppase activity in MDR3 was linked to UDCA treatment.[13] A prospective multicenter study assessed the efficacy and safety of the serotonin reuptake inhibitor sertraline, for the treatment of children with refractory cholestatic pruritus.[14] Oliveira et al[15] thought that the genetic defect in PFIC-3 appears to explains the pathogenesis of intrahepatic cholestasis in pregnancy; their understanding may might provide insights into for developing new therapeutics therapies. After analyzing >150 BSEP mutations, Dröge et al[16] demonstrated that the extent of exon skipping depends on the genomic and cellular contexts, and that regulation of splicing may have therapeutic potential for PFIC-2.

Biliary diversion procedures decrease the enterohepatic circulation of bile, reducing its toxic effects. Both partial external biliary diversions (PEBD) and partial internal biliary diversions (PIBD) have been described. PEBD, which was first described by Whitington, uses a 10- to 15-cm jejunal conduit between the gallbladder and the abdominal wall, creating a permanent biliary stoma.[17] PIBD has the advantage of avoiding an external stoma and the complications associated with it. The most common PIBD links the gallbladder drainage to the colon.[18–20] However, its safety and efficacy are as yet unproven.[21] Both PEBD and PIBD are intended to interrupt the enterohepatic circulation to improve pruritus and growth, but no clinical trial has demonstrated the superiority of either surgical approach over others. Notwithstanding this, we have the general impression that ileal excision may not be as effective as PEBD. A common approach has been to perform PEBD, and the possible conversion to ileal bypass later in life depended on its outcome and the preference of the patient. If a biliary diversion approach fails or if complications arise (e.g., hepatocellular carcinoma in patients with PFIC-2), the disease would progress to biliary cirrhosis in patients with PFIC-3, and liver transplantation would be the only effective treatment option so far.[8,22]

In future, nonsurgical opportunities might be available in the early phase, to replace surgery for treatment of aforementioned diseases. Inhibition of intestinal bile acid absorption, but not PEBD or PIBD, is currently under research as an alternative approach for treatment. Miethke et al[23] recently inhibited ileal bile acid reuptake and promoted bile acid excretion by using the competitive ASBT inhibitor SC-435 in Abcb4 mice, a model of PFIC type 3. The inhibitor reduced plasma total bilirubin and ALT levels, improved liver histology, and alleviated inflammatory expression compared to controls, which suggests that ASBT might be a promising pharmacological target for PFIC-3.

8. Conclusion

Customizing therapy for individual patients, identifying the relationships between PFIC genotypes, discovering new genetic causes of PFIC in patients with current genotypes, and continuing research on the pathogenesis of PFIC are top priorities for field moving ahead. Although an increasing number of studies have referred to targeted gene therapies and the medical management of PFIC has improved, liver transplantation remains the most definitive treatment for PFIC. Current medical therapies and surgical interventions such as biliary diversion have potentially created a synergistic outcome. Different types of PFIC have different and corresponding therapies. For example, in patients with PFIC-1, the best clinical outcome and quality of life can be achieved with an appropriate combination of all 3 therapies. However, although reports on liver transplantation for PFIC-3 are lacking, it appears to be the best treatment with excellent long-term outcomes. However, in contrast to the finding reported in this article, living-donor liver transplantation can reduce immunological rejection, but whether it will increase the probability of cholestasis and reduce the success rate of transplantation and survival rate is unknown. This report on cadaver liver transplantation, changes in gene detection level after surgery, and changes in protein expression level needs further follow-up.

This article reports the outcomes of cadaveric liver transplantation for PFIC. Hence, whether living-related liver transplantation is

contraindicated for PFIC patients is not clear. This is because reduction in success and survival rates towing to the mutant genes of close relatives in the donor liver have not been studied among liver transplantation patients. Suspected PFIC mutation detection of liver donor relatives before surgery may help to circumvent the risk.

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