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Case Report Open Access

Inherited Thrombophilia Could Be a Possible Rare Etiology to Result in Cirrhosis: A Case Report and Literature Review

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Abstract

We reported on a cirrhosis patient who was demonstrated on gene sequencing to have inherited thrombophilia. A 33-year-old male patient with 8-year recurrent abdominal distention, symptom aggravated with 4-month pitting edema of lower extremities bilaterally, was identified decompensated cirrhosis in local hospital. With exclusion of viral hepatitis, leukemia, lymphoma, autoimmune diseases, parasitic diseases and tuberculosis, we applied gene sequencing in this patient and identified an rs2227589 polymorphism from G to A in SERPINC1 which indicated an increased risk of thrombophilia. Thus, inherited diseases are important and should not be neglected among various causes of cirrhosis. It would induce disseminated hepatic veno-occlusion to cause fibrogenesis. So when a cirrhosis patient consulted, thrombosis should be taken into consideration and gene sequencing could help clarify the etiology and pathogenesis.

Keywords: Cirrhosis; Inherited Thrombophilia; Etiology; Gene Sequencing; SERPINC1 Mutation

List of abbreviations: HCC: Hepatocellular Carcinoma; DBIL: Direct Bilirubin; IBIL: Indirect Bilirubin; CT: Computed Tomography; MDT: Multi-Disciplinary Team; IHC: Immunohistochemistry; SERPINC1: Serpin family C member 1; NAFLD: Nonalcoholic Fatty Liver Diseases; DILI: Drug Induced Liver Injury; DVT: Deep Vein Protease Activated Receptor 1Thrombosis; SNP: Single Nucleotide Polymorphism; HSC: Hepatic Stellate Cells; PAR-1; VTE: Venous Thromboembolism; DOAC: Direct Oral Anticoagulant

Introduction

Cirrhosis is an end-stage liver disease. Patients with cirrhosis characterized by manifestations of portal hypertension and impairment of liver function. When the natural course of the disease progressed from compensated status to decompensated one, life expectancy of the patients would be shorted obviously. Complications including refractory ascites, spontaneous bacterial peritonitis,variceal bleeding, hepatorenal syndrome and encephalopathy increases mortality of cirrhosis [1]. Cirrhosis also make patients more vulnerable to develop hepatocellular carcinoma (HCC) [2]. The etiology includes viral hepatitis, auto-immune liver disease, nonalcoholic steatohepatitis, medicamentous liver lesion, congenital diseases and so on. Coagulation disorders could also be one of the etiology [3]. In patients with chronic viral hepatitis, concurrent thrombophilia related to protein C deficiency significantly accelerated the progress of fibrosis [4]. And heterozygotic carriage of Factor V Leiden mutation was associated with increased risk of fibrosis in western Caucasian hepatitis C patients [5]. But more evidences are still needed to confirmed the relationship between hypercoagulation and cirrhosis.And genetic basis of inherited thrombophilia still worth further investigations. So in this case, we reported a rare inherited thrombophilia induced cirrhosis and the diagnostic procedure to identified its genetic basis.

Case Report

A 33-year-old male patient with 8-year recurrent abdominal distention, symptom aggravated with 4-month pitting edema of lower extremities bilaterally, visited our hospital on June 25th, 2016. Eight years ago, the patient, presented abdominal distention

along with left epigastric pain, was admitted to the local hospital, where he was diagnosed as splenomegaly, portal and splenic vein thrombosis and cavernous transformation of the portal vein, given thrombolytic therapy and then was discharged. Four months ago, the patient noticed pitting pretibial edema occasionally shown in his lower extremities. The edema vanished in the morning and aggravated in the day. Yet the patient waited until three months ago to visit the local hospital again. This time the patient had a 39.5 °C fever, edema, and gross hematuria, but presented no nausea or vomiting. He was diagnosed with urinary tract infection and was given a primary treatment of cephalothin and heteropathy. Since the primary treatment made no obvious progress, the patient was then transferred to a city hospital for better treatment. After admission, the patient went through a full assessment. Blood routine test showed decreased platelets of 84×10^9/L and decreased leukocytes of 2.13×10^9/L but normal hemoglobin. Urine routines showed positive urine protein (1+), erythrocytes (1761/$_u$L), leukocytes (14.7/$_u$L) and bacteria (4120/$_u$L). Meanwhile, the patient had positive fecal occult blood. His blood biochemical test suggested impaired liver function: elevated total bilirubin of 40.3 $_u$mol/L (DBIL 15.3 $_u$mol/L vs IBIL 25.0 $_u$mol/L), decreased albumin (36.2g/L) and decreased cholinesterase (4191 U/L). Though the creatinine and urea nitrogen seemed normal, there was moderate reduction of calcium and phosphorus. Urinary tests showed that his proteinuria was 690.2 mg/24h and urinary microalbumin was 275 mg/L, indicating renal impairment. His coagulation test showed prolonged prothrombin time of 20.9s, activated partial thromboplastin time of 44.5s and decreased plasma fibrinogen of 1.51 g/L, indicating coagulation dysfunction. The patient had positive autoantibody to nuclear antigen (1:100+) and negative results in other autoantibodies including anti-phospholipid antibody. All hepatitis virus screenings were negative as well. The thyroid function and electrocardiograph showed no significance. Abdominal ultrasound detected splenomegaly and uneven echo in liver along with moderate abdominal effusion. The arteriovenous ultrasound of lower extremities showed no abnormality; neither did the Color Doppler Flow Imaging. CT scan detected similar manifestation including cirrhosis, splenomegaly, and ascites along with opening of lateral circulation in esophageal and gastric, splenic and left renal regions. Unfortunately, the pathogenesis was still not clear and the patient was diagnosed with nephritis and decompensated cirrhosis. Thus only symptomatic treatments such as liver-protection, diuresis and traditional Chinese medicines were given to the patient. For further identification of the etiology, the patient consulted doctors in multi-disciplinary team (MDT) clinic of our hospital and was admitted in department of infectious diseases. His medical history revealed no infectious diseases and allergy. He had only one surgical operation, i.e., a catheter directed thrombolysis in splenoportal vein in 2008. The patient also denied drug-abuse and abuse of alcohol. The vital sign is stable and the patient was with clear consciousness in physical examination. In abdominal palpation, we touched an extremely enlarged spleen with line I of 30cm, line II of 10cm, and line III of 12cm. Moderate edema was visible in lower extremities. There was no other significant sign in the rest organs or systems. Based on the tentative diagnosis of decompensated cirrhosis, we gave the patient systematic auxiliary examinations and focused on etiological screening including immunological markers, parasites antibodies, inflammatory factors, bone marrows biopsy, and precise imageological examination. By doing so, we hoped to differentiate the etiology from viral hepatitis related cirrhosis, leukemia, lymphoma, autoimmune diseases, parasitic diseases and splenic tuberculosis. However, results of the laboratory examinations revealed no new clue: blood routine and biochemical tests were almost the same as before and all the regular viral markers, immune markers, and parasitic antibodies were negative. Bone marrow biopsy showed activated hematopoietic cell proliferation. Sequential immunohistochemistry (IHC) detected disseminated partial CD20 (+) or partial CD3ε (+) lymphocytes, RBC (+) erythrocytes and reactive CD138 (+) plasmacytes which took 3-5% of karyocytes. But none of the IHC result was clinically significant. Ultrasound in our hospital identified thrombus in the right branch of portal vein, blood flow retardation in the left and mural thrombus in splenic veins. CT scan in our hospital also identified a filling defect with low density in intrahepatic portal vein branches. Obscurity of the main portal vein and cavernous transformation suggested constriction or thrombosis. Enhanced magnetic resonance imaging was consistent with all the previous imageological findings: cirrhosis, splenomegaly, portal hypertension and signs of vascular stenosis (Figure 1).

The white arrow indicated the liver cirrhosis. The red arrow indicated the splenomegaly. The yellow arrow indicated vascular stenosis. As the patient presented multiple organ dysfunction and thrombotic tendency, we speculated that he had coagulation system disease that led to visceral thrombosis. According to consultation opinion from department of hematology, we arranged activity detections of protein S, protein C and antithrombin III, gene mutation detections of factor II and factor V, gene mutation analysis of antithrombin and full gene analysis of protein C. And the result showed the activities of protein S, protein C and antithrombin III were all impaired (Table 1). Further gene analysis showed that neither factor V mutation (G1691A) nor factor II (G20210A) mutation was found. Protein C full gene analysis reported a heterozygous mutation and a homozygous mutation in 5' promoter region and a heterozygous synonymous mutation and a heterozygous mutation in the exon 5 and 6 respectively. Serpin family C member 1 (SERPINC1) mutation analysis reported a heterozygous mutation in the intron next to Exon 1 ((c.41+141G>A)) and two heterozygous synonymous mutations in Exon 5 details in (Table 2, Figure 2). The SERPINC1 indicated the gene encoding antithrombin. And the rs2227589 polymorphism from G to A confirmed a moderate thrombotic risk according to in silico study and previous reports [6,7]. Therefore, this patient was officially diagnosed as thrombophilia (Diagnostic timeline in Figure 3).

Items	Result	Reference value	Unit
Protein S: Competence	54.70	63.5-145	%
Protein C: Competence	34.00	60-140	%
Antithrombin -III: Competence	55.00	83-128	%

Table 1: Activity of protein S, protein C and anti-thrombin III

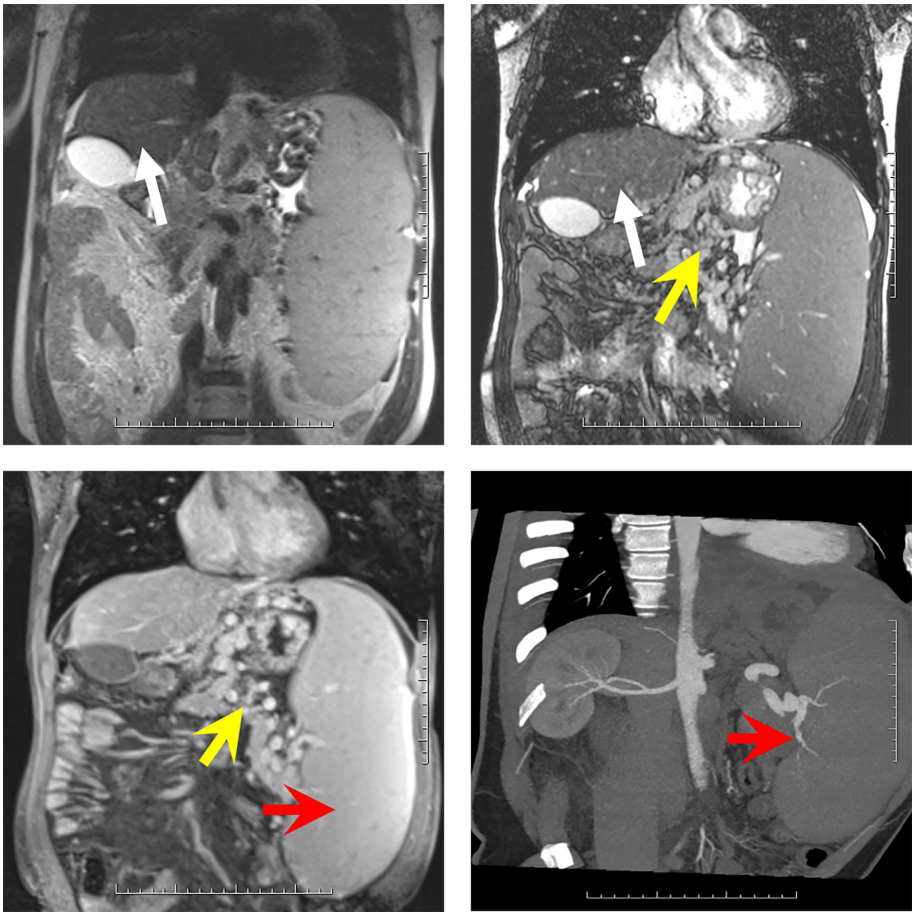

Figure 1: Abdominal enhanced magnetic resonance imaging

Genes	Locus	Result	Comments
Factor V	G1691A	Negative	
Factor II	G20210A	Negative	
Protein C	5' promoter	-1654C>T (heterozygous)	SNP rs1799808, un-pathogenic
		-1641G>A (homozygous)	SNP rs1799809, un-pathogenic
	Exon 1	Negative	
	Exon 2	Negative	
	Exon 3	Negative	
	Exon 4	Negative	
	Exon 5	3357G>T (heterozygous)	SNP rs5936, synonymous mutation, un-pathogenic
	Exon 6	6403G>T (heterozygous)	SNP rs2069928, un-pathogenic
	Exon 7	Negative	
	Exon 8	Negative	
	3' UTR	Negative	
SERPINC1	Intron next to Exon 1	c.41+141 G>A (heterozygous)	SNP rs2227589, risk factor of thrombosis
	Exon 5	c.981 A>G	SNP rs5877, synonymous mutation
		c.1011 A>G	SNP rs5878, synonymous mutation

Table 2: Mutation analysis in thrombophilia related genes

R was a degenerate base which represented A or G. c.41+141 was the mark of location. It indicated that the heterozygous mutation located on the No.141 base in the intron next to Exon1 which ended at No.41 base in the coding DNA sequence.

Unfortunately, the patients ignored doctors' advices and left hospital by himself. Thus further treatment of antithrombotic therapy or transplantation could not be applied. We are now following the patient over phone to observe his long-term prognosis.

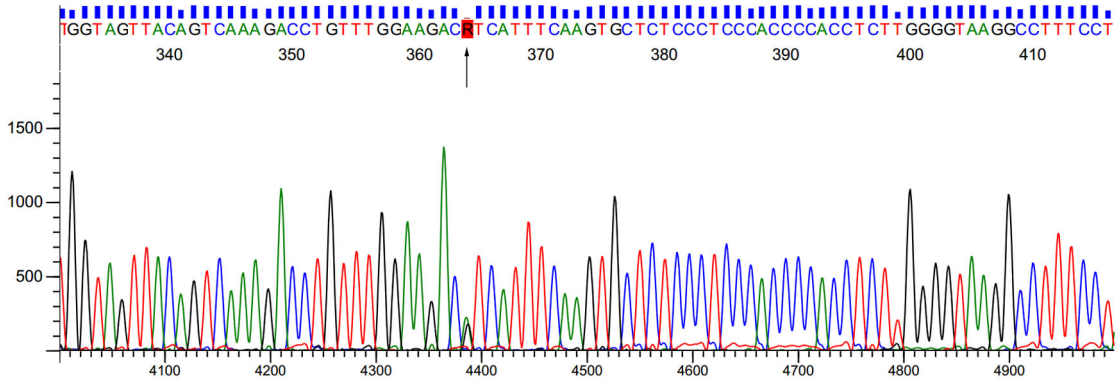

Figure 2: Sequencing data of heterozygous c.41+141 G>A mutation in SERPINC1

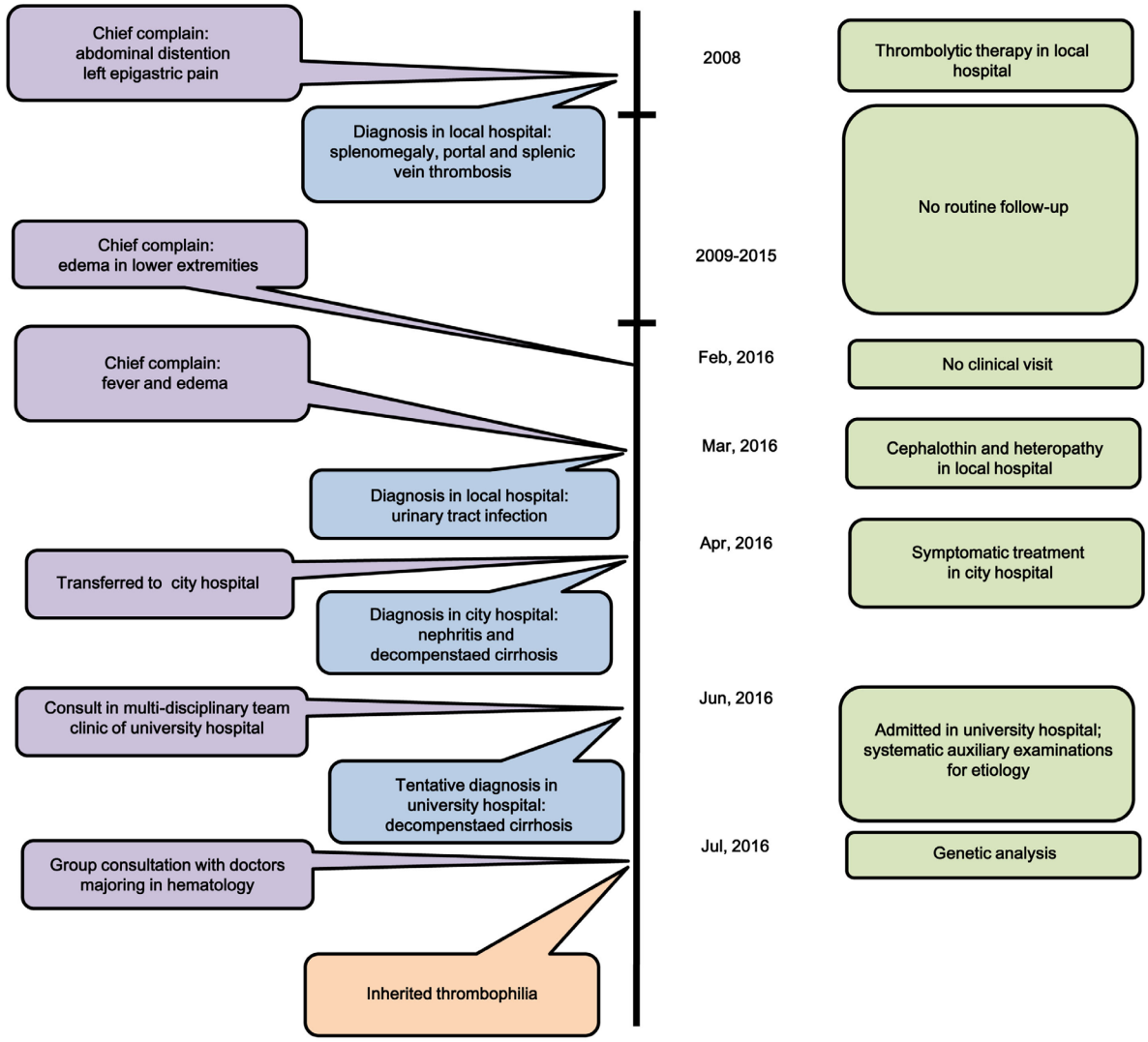

Figure 3: Diagnostic timeline of the patient

Discussions

Due to the patient's poor compliance, we could not give him further treatment after he was diagnosed. But the case provided us considerable clues for diagnosing a patient with thrombophilia induced cirrhosis. Cirrhosis refers to a category of progressive liver diseases characterized by similar pathologic changes of distortion and irregular regeneration of liver nodules. Numerous etiological factors could cause cirrhosis. The most common causes include chronic viral hepatitis, alcoholic liver disease, nonalcoholic fatty liver disease (NAFLD) and hemochromatosis. In developed countries, hepatitis C is the major viral hepatitis, while in developing countries such as China, hepatitis B is the major one. Other etiological factors range from autoimmune liver diseases; drug induced liver injury (DILI), infection, heart failure to hereditary metabolic diseases [8]. In this case, the patient had the onset of cirrhosis at a relatively young age. And the symptoms had been discontinuously lasting for eight years. This suggested that he had an inherited

or chronic disease other that an acute or malignant disease. For patients like him, along with the exclusion of viral hepatitis, alcoholic liver diseases, NAFLD, autoimmune liver disease and so on, the hereditary metabolic diseases should be a prevailing concern. Secondly, portal and splenic vein thrombosis and cavernous transformation of the portal vein was found at first onset and the manifestations were still observed all along the course. Hepatic blood-flow obstruction induced cirrhosis had been confirmed in cardiac hepatopathy and Budd-Chiari syndrome [9]. Analogically, cirrhosis in this case could be related to thrombosis. Another important clue was that edema of lower extremities which could result from deep vein thrombosis (DVT) occasionally appeared all along the course of the disease. It was estimated that almost 50% patients with thrombophilia would suffer DVT [10]. Though the arteriovenous ultrasound of lower extremities from the previous hospital showed no abnormality, the possibility of incomplete DVT could not be neglected. Moreover, coagulation dysfunction identified from laboratory tests and multiple thrombosis from imaging test were consistent with manifestation of thrombophilia. Along with history of recurrent thrombosis, it suggested that the patient could be attacked by inherited thrombophilia. As a result, microthrombosis resulted secondary hepatic veno-occlusion could be the etiology. Thrombophilia is an abnormality of blood coagulation. It is featured with increasing risks of thrombosis. Usually, it is identified when a patient has thromboembolic events. Genetic mutations could lead to dysfunction of important factors in the coagulation cascade, and cause thrombophilia. Such diseases are named as inherited thrombophilia. Factor V leiden mutation, factor II mutation, inherited protein S deficiency, protein C deficiency and antithrombin (III) deficiency, all belong to inherited thrombophilia [11-14]. Antithrombin works to inactivate thrombin and factor Xa to inhibit the synthesis of fibrin [15]. Its deficiency results in significant fibrin formation. As an essential compound of white thrombus, fibrin deposition would make patients vulnerable to thrombosis [16]. Inherited antithrombin deficiency is an autosomal dominant disease. Over 100 kinds of gene mutation contribute to this disease. Most mutation is heterozygous because homozygous mutation is fatal [17-19]. We found a single nucleotide polymorphism (SNP), rs2227589 in SERPINC1 gene that resulted in antithrombin deficiency in our case. Such heterozygous mutation was first identified by Anton AI in 1997 and proved by Austin H in 2011 to increase the risk of thrombosis [6,7]. Both study put forward the result that subjects with rs2227589 SNP of A allele have moderate but significantly decreased anticoagulation activity than that of GG alleles (anti-FXa activity: 97.0±7.3% vs. 94.6±8.4%; p=0.032; antithrombin levels: 99.5±5.8% vs. 94.8±5.6%; p=0.001; respectively). Thus such mutation should be considered as our patient's genetic foundation of thrombophilia. There were two types of mutation induced antithrombin deficiency, type I was that the variant protein could not be secreted and type II was that its anticoagulation activity was impaired. According to our findings, the mutation in our case resulted in the impaired activity of antithrombin. Type II took precedence. In a recent study, Morena- Barrio M. investigated the inner mechanism lying in the mutation induced type II deficiency of antithrombin. He found mutations influencing Met283, His401, Pro439 and Pro461 would weaken the stability of antithrombin and induce its transition to the conformation with low heparin affinity and no inhibitory activity [20]. It provided us new strategy to analyze this case and the conformation induced by the mutation would be further studied afterwards. Cirrhosis is mediated by the activation of the hepatic stellate cells (HSC). Hypercoagulable state seems related to liver fibrogenesis [21]. In patients with Budd-Chiari syndrome, thrombosis in hepatic vein is already accepted as the cause of cirrhosis [22]. And in HCV infected subjects and NAFLD cases, disseminated microthrombi is one of the causes that leads to accelerated aggravation of cirrhosis [23,24]. One of the possible reasons could be that obliteration of venulae resulted in consequent hepatocytes apoptosis and replacement of fibrosis tissue. Another reason could be that coagulation cascade was triggered to activate the synthesis of thrombin and downstream pathways, eventually activating protease activated receptor 1 (PAR-1) mediated HSC [25]. In our case, it seemed that when antithrombin deficiency happened, over activation of thrombin led to over-activation of HSC. And under the synergies of disseminated congestion induced apoptosis and fibrogenesis, this disease easily developed to advanced fibrosis and rapidly progressed to cirrhosis. Patients with thrombophilia tends to receive long-term anticoagulant therapy due to the presence of thrombotic complications. They often receive warfarin or heparin products as anticoagulant therapy for primary or secondary prevention of venous thromboembolism (VTE) [26]. Now direct oral anticoagulant (DOAC) agents such as rivaroxaban and dabigatran come out as alternatives and show positive results [27]. However, there is no specific guideline for inherited thrombophilia. Only a few cases reported DOACs treatment for patients with such disease. Findings suggested rivaroxaban is promising in patients with protein C deficiency, Factor V Leiden mutation and antithrombin deficiency, yet treatment failure is possible and a switch to another DOAC or historical drug could be a resolution [28-30]. More evaluation is needed in anticoagulant therapy on inherited thrombophilia patients.

Conclusions

In conclusion, among various causes of cirrhosis, inherited diseases are important and should not be neglected. Metabolic disorder is not the only inherited diseases causing cirrhosis, genetic coagulation abnormity as well would do so. Inherited thrombophilia would induce disseminated hepatic veno-occlusion to cause fibrogenesis. And over activation of thrombin would induce over activation of HSC that accelerates fibrosis to cirrhosis. Researchers have identified over 100 significant gene mutations as risk factors of inherited thrombophilia. So when a cirrhosis patient consulted, thrombosis should be taken into consideration and gene sequencing could help clarify the etiology and pathogenesis.

Declaration

Informed Consent

Written informed consent was acquired from the patient and all rights were revered by the patients.

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Conflict of interests

Authors declares that there is no conflict of interests in the article and no additional permission need to be acquired for its publication.

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