CASE REPORT

Case Report: A case of PAI-1 4G/5G heterozygosity causing Budd-Chiari Syndrome [version 1; peer review: awaiting peer review]

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Abstract
Budd-Chiari syndrome (BCS) is a hepatic venous outflow obstruction. A 36-year-old Caucasian female was admitted with symptomatic hypoglycaemia. Lab tests revealed mild leucocytosis, thrombocytopenia and hepatic cytolysis. The abdominal ultrasound showed mild hepatomegaly due to hypertrophy of the left and caudate lobes, no blood flow on the right and medium hepatic veins and multiple intra-hepatic collateral vessels. Upper endoscopy showed grade I varicose veins. Further studies ruled out common prothrombotic disorders but identified an inherited thrombophilia: a plasminogen activator inhibitor 1 (PAI-1) 4G/5G heterozygous polymorphism. On presentation, this patient had signs of cirrhosis and secondary portal hypertension from imaging results at the time of diagnosis but no symptoms. Four years after the diagnosis the patient continues asymptomatic, which is very unusual. This patient's outcome will be favourable as long as their cirrhosis is compensated by the collateral vessels' permeability. Our case highlights a new association between primary BCS secondary to a prothrombotic inherit mutation: the PAI-1 4G/5G polymorphism.

Keywords
Budd-chiari Syndrome, Thrombosis, Hepatology, Liver disfunction
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Introduction

Budd-Chiari syndrome (BCS) is defined as a hepatic venous outflow tract obstruction -regardless of the level or mechanism of obstruction. It is considered primary when the hepatic venous outflow obstruction originates from an endoluminal venous lesion, and secondary in cases of compression or invasion originating from outside the hepatic veins. It can be acute, subacute or chronic in its presentation1–5.

About 80–85% of the patients have symptoms at the onset of the disease6. Classic manifestations include abdominal pain, fever, ascites and peripheral edema1–5.

Furthermore, an underlying risk factor for thrombosis is found in up to 87% of BCS patients7,8. Myeloproliferative disorders are responsible for 40-50% of primary BCS cases in the presence of JAK2 V617F mutation. There is also an established association with prothrombotic disorders, acquired or inherited, such as factor V Leiden mutation, G20210A prothrombin gene, deficiency in protein C and S, factor II and antiphospholipid syndrome9,10. A genetic variant of the methylenetetrahydrofolate reductase gene (MTHFR) has also been found to increase the risk of BCS9. Plasminogen Activator Inhibitor-1 (PAI-1) mutation leads to impaired fibrinolysis or hypofibrinolysis increasing the risk of prothrombotic disorders. PAI-1 is a crucial physiological inhibitor of fibrinolysis and regulates fibrinolysis by inhibiting tissue type plasminogen activator (tPA) and urokinase type plasminogen activator (uPA) which results in reduced fibrinolytic capacity. The genetic polymorphism in the promoter region of the PAI-1 gene can manifest as the 4G/4G or 4G/5G polymorphism and has been associated with altered PAI-1 plasma concentrations and activity levels. Prothrombotic disorders predispose to hepatic venous outflow tract obstruction and development of BCS.

The prognosis of BCS patients varies according to the presence and development of liver failure. Stratification and prognosis of BCS is currently obtained using the Model for End-Stage Liver Disease (MELD) and Child-Pugh scores11.

Management options include anticoagulation as first line therapy and, when appropriate, transjugular intrahepatic porto-systemic shunt (TIPS). A combined strategy can lead to a 5-year survival rate between 80–90%. Patients not responding to the above-mentioned measures should be referred for liver transplantation.

We report a rare case of polymorphism 4G/5G as a cause of a prothrombotic disorder resulting in BCS.

Case report

A 36 year old female Caucasian, farmer, farmer, presented to our Accident and Emergency Department with symptomatic hypoglycemia in March 2014 leading to hospital admission for further study. The patient did not indicate any abdominal pain, constitutional symptoms, gastro-intestinal complaints, alcohol or drug consumption and had no relevant changes on physical examination.

The patient had a past medical history of high blood pressure, obesity, depression and idiopathic thrombocytopenia and was not taking any oral contraceptive pill.

Laboratory results showed (normal ranges in parentheses): white blood count (WBC) 11.600/u/l (4000–10.000), haemoglobin (Hb) 11.5g/dl (12.5–14.5), platelets 69.000u/l,(150.000–400.000) International normalized ratio (INR) 1.2 (0.7–1.1), aspartate aminotransferase (AST) 1305IU (10–34), alanine aminotransferase (ALT) 1123IU (10–55), γ glutamyltransferase (GGT) 167UI (<65) creatinine 1.6mg/dl (0.4–1.0), albumin 3.2 (>4.5), total bilirubin 2.2mg/dL (0.6–1.1), direct bilirubin 1.3mg/dL (0.1–0.3), C-reactive protein 55mg/d (<5). Serological testing for viral hepatitis was negative (hepatitis B surface antigen (HBsAg), hepatitis B e antigen (HBeAg), anti-hepatitis C virus and hepatitis A virus, Epstein-Barr virus, cytomegalovirus).

Abdominal ultrasound with Doppler revealed mild hepatomegaly due to hypertrophy of the left and caudate lobe; heterogeneity of the liver parenchyma; no blood flow in the right and middle hepatic vein; re-permeabilization of the para-umbilical vein; multiple intra-hepatic collateral vessels; splenomegaly and a small amount of free fluid in the pelvic recesses. Upper endoscopy showed grade I variceous veins.

On MRI scan, the patient had imaging signs of cirrhosis on a magnetic resonance imaging (MRI) scan [Figure 1 and Figure 2], secondary portal hypertension and caudate lobe hypertrophy which allowed the diagnosis of asymptomatic BCS.

The liver enzymes normalized 2 weeks after admission without any kind of treatment of the underlying causes.

A complete study of thrombotic risk factors did not identify any of the following anomalies: JAK2 V617F mutation, deficiency in protein C and S, Factor II, factor V Leiden mutation, G20210A prothrombin gene, or MTHFR (677

![Figure 1. Coronal plane magnetic resonance imaging (MRI) scan indicating hepatomegaly and distortion of the liver architecture.](image-url)
The patient was found to be heterozygous for the 4G/5G variant of the PAI-1 gene. The patient was negative for lupus anticoagulant, anti-b2-glycoprotein and anticardiolipin-b antibodies. The patient was discharged with oral warfarin (5mg/day) and followed up at the anti-coagulation clinic.

The patient has been attending gynecology appointments, referring due to menometrorrhagia without significant hemoglobin variation while on warfarin. The patient attends the Hepatology Unit every 3 months, and recent lab results display a mild cholestatic pattern with mild anemia. Abdominal CT scans have not revealed any new findings for the last 4 years.

**Discussion**

Primary Budd-Chiari syndrome is a venous outflow obstruction that is associated with at least one inherited or acquired prothrombotic risk factor as the underlying cause of thrombosis. The clinical manifestations can be variable but up to 20% of the patients are asymptomatic. Our patient has a rare form of asymptomatic Budd-Chiari. The absence of symptoms strongly correlates to the development of a large collateral hepatic vein to balance the pathogenesis of portal hypertension of the BCS. A detailed study for prothrombotic disorders must be performed on every patient diagnosed with BCS as patients usually present with at least one prothrombotic risk factor.

For this reason, a schematic approach was used to rule out known risk factors for thrombosis as described in the current literature. We extended the investigation of inherited thrombophilias and performed a genetic test of PAI-1 that came back positive for 4G/5G heterozygosity.

To our knowledge this is the first report in the literature to describe an association between heterozygosity for the 4G/5G variant of the PAI-1 and BCS. Hemostasis is a result of the equilibrium between prothrombotic and antithrombotic mechanisms in response to tissue injury. The elevation of PAI-1 is a cause of impaired fibrinolysis leading to increased risk of venous thrombosis. The polymorphism 4G/5G results from a single deletion/insertion of a guanosine residue in promoter region of PAI-1. Inheritance of both 4G alleles (homozygous 4G/4G) has been associated with elevated PAI-1 levels leading to hypofibrinolysis and increased thrombotic risk. However, this association is still a matter of debate in the medical literature. The present case report highlights heterozygous 4G/5G as a cause of increased prothrombotic risk, due to elevated PAI-1 levels which caused an hypofibrinolytic state with formation of blood clots within the hepatic vessels, destruction of liver parenchyma ending in BCS. Our case supports the possible effect of an inherited prothrombotic mutation causing the PAI-1 4G/5G polymorphism that has rarely been described previously.

The treatment options for BCS include medical management of the underlying risk factors for thrombosis. Prothrombotic drugs such as oral contraceptives are contraindicated. The presence of myeloproliferative disease should prompt immediate treatment of the underlying haematological disorder.

As such, due to the high prevalence of underlying thrombophilia, anticoagulants are recommended in all patients regardless of the presence of clinical manifestations. Other therapeutic approaches include decompressing therapies such as recanalization strategies (thrombolytic therapy, stenting and angioplasty) surgical shunting and TIPS and, as a last resort, orthotopic liver transplantation (OLT). Due to the rarity of this condition and the lack of clinical trials with BCS most treatment options are based on retrospective studies, case reports and expert opinion. Recent developments in imaging techniques and biomolecular tests have made the discovery of underlying causes possible, optimizing treatment strategies and improving overall survival, which is now up to 5 years after the diagnosis in 90% of the cases.

Our patient was discharged with a vitamin K antagonist (warfarin) as per the international recommendations by an expert panel consensus on management of BCS anticoagulation therapy until the treatment of the underlying condition is achieved, when it is found.

**Conclusions**

We describe in detail a very rare case of an inherited thrombophilia secondary to a heterozygous 4G/5G polymorphism of the PAI-1 gene, that has not previously been described as associated with BCS. Hence, we suggest that future investigations on BCS must include genetic tests of PAI-1.

Frequently, BCS patient’s prognosis is determined by the development of liver vessels collaterals that compensate the portal hypertension thereby reducing liver dysfunction leading to absent physical symptoms. The combined medical and invasive approach can lead to a 5-year survival rate close to 90%.

**Consent**

Written informed consent for the publication of this case report and any associated images was obtained from the patient.
Data availability

Underlying data

All data underlying the results are available as part of the article and no additional source data are required.

Grant information

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References

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