CASE REPORT

REVISED Case Report: A case of PAI-1 4G/5G heterozygosity causing Budd-Chiari Syndrome [version 2; peer review: 1 approved with reservations, 1 not approved]

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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 the cirrhosis is compensated by the collateral vessels' permeability. Our case highlights a new association between primary BCS secondary to a prothrombotic inherited mutation: the PAI-1 4G/5G polymorphism.

Keywords

Budd-chiari Syndrome, Thrombosis, Hepatology, Liver dysfunction

Open Peer Review

Approval Status

	1	2
version 2 (revision) 16 Jan 2020	 view	 view
version 1 02 Sep 2019	 view	 view

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Any reports and responses or comments on the article can be found at the end of the article.

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Author roles: **Sousa D:** Conceptualization, Writing – Original Draft Preparation, Writing – Review & Editing; **Antunes Silva S:** Writing – Review & Editing; **Jorge C:** Writing – Review & Editing; **Martins Fernandes R:** Writing – Review & Editing; **Rodrigues AI:** Writing – Review & Editing; **Viana Coelho M:** Writing – Review & Editing; **Guimarães JF:** Writing – Review & Editing; **Osorio RM:** Writing – Review & Editing; **Morais J:** Writing – Review & Editing; **Rios E:** Writing – Review & Editing; **Figueiredo A:** Writing – Review & Editing

Competing interests: No competing interests were disclosed.

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REVISED Amendments from Version 1

The manuscript has been rewritten taking reviewers considerations into account.

Any further responses from the reviewers can be found at the end of the article

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 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 disease onset⁶. 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 patients^{7,8}. *JAK2* V617F positive myeloproliferative disorders are responsible for 40–50% of primary BCS cases. On the one hand, there is an established association with prothrombotic disorders, acquired or inherited, such as factor V Leiden mutation, deficiency in protein C and S, factor II and antiphospholipid syndrome^{7,8}. On the other hand, the prothrombin gene G20210A mutation has only been associated with portal vein thrombosis and not BCS⁹. A genetic variant of the methylenetetrahydrofolate reductase gene (homozygous *MTHFR*) has also been found to increase the risk of BCS^{9,10}. Plasminogen Activator Inhibitor-1 (*PAI-1*) mutation leads to impaired fibrinolysis or hypofibrinolysis increasing the risk of prothrombotic disorders in the splanchnic venous circulation^{9,11}. *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 scores⁵.

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

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

Case report

A 36-year-old, female, caucasian 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 mention 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. Currently medicated with 0.15mg Desogestrel + 0.02mg Ethinyl Estradiol 1id, pantoprazole 20mg 1id, ebastine 20mg.

Laboratory results showed (normal ranges in parentheses): white blood count (WBC) 11.600u/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 lobes; heterogeneity of the liver parenchyma; no blood flow on the right and middle hepatic veins; 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 varicose veins.

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

Figure 1. Coronal plane magnetic resonance imaging (MRI) scan indicating hepatomegaly and distortion of the liver architecture.

Figure 2. Axial plane magnetic resonance imaging (MRI) scan indicating hepatomegaly and distortion of the liver architecture.

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 and 1298). 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 (IgM 0.61 UA/mL and IgG <0.10 UA/mL) and anticardiolipin-b antibodies (IgM 2.72 MPL/mL and IgG 3.72 GPL/mL). The patient was discharged with oral warfarin (5mg/day) and follow-up appointments at the anti-coagulation clinic.

The patient has been attending gynecology appointments 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 and upper endoscopy have not revealed any new findings over 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 asymptomatic⁶. Our patient has a rare form of asymptomatic Budd-Chiari. The absence of symptoms strongly correlates with development of a large collateral hepatic vein to balance the pathogenesis of portal hypertension of the BCS^{1,2}. 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^{1,2}.

For this reason, a schematic approach was used to rule out known risk factors for thrombosis as described in the current

literature^{2,4,5,7}. We extended the investigation of inherited thrombophilias and performed a genetic test of *PAI-1* that came back positive for 4G/5G heterozygosity.

To the best of our knowledge, (virgula) 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. PAI-1 is a central regulative factor for the fibrinolytic system because it can modulate the plasminogen activation system by forming irreversible inhibitory complexes combining with uPA and tPA which produces an hypofibrinolytic state. Consequently, the elevation of PAI-1 is a cause of impaired fibrinolysis leading to increased risk of venous thrombosis^{11,12}. The polymorphism 4G/5G results from a single deletion/insertion of a guanoside residue in promoter region of *PAI-1*¹³. Inheritance of both 4G alleles (homozygous 4G/4G) has been associated with elevated PAI-1 levels leading to hypofibrinolysis and increased thrombotic risk¹⁴. However, this association is still a matter of debate in the medical literature¹². 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 and destruction of liver parenchyma ending in BCS¹¹. 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^{1,5}. 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)^{1,5}.

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 cases².

Our patient suspended the oral contraception and 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 found¹⁵.

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, to the best of our knowledge, been previously described as associated with BCS. Hence, we suggest that future investigations on BCS include genetic testing of *PAI-1*.

Frequently, BCS patients 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 is available as part of the article and no additional source data is required

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Current Peer Review Status: ? ✖

Version 2

Reviewer Report 27 January 2020

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Xingshun Qi

Department of Gastroenterology, General Hospital of Northern Theater Command (formally General Hospital of Shenyang Military Area), Shenyang, China

After re-reviewing and checking my previous corresponding comments, I am sorry that the authors did not improve their paper well, because they did not carefully read the references.

In this version, the authors said "A genetic variant of the methylenetetrahydrofolate reductase gene (homozygous MTHFR) has also been found to increase the risk of BCS 9,10". However, reference 9 did not mention "methylenetetrahydrofolate reductase gene" at all. Indeed, I had provided a relevant reference for this point. The authors were not willing to read or use this reference.

In this version, the authors said "Plasminogen Activator Inhibitor-1 (PAI-1) mutation leads to impaired fibrinolysis or hypofibrinolysis increasing the risk of prothrombotic disorders in the splanchnic venous circulation 9,11". However, reference 9 did not mention "Plasminogen Activator Inhibitor-1 (PAI-1) mutation" at all. It seems that they did not find any appropriate reference for explaining such a phenomenon.

The authors said "Unfortunately we do not have more MRI imaging to illustrate our case report" as a reply. This reply cannot be approved, because the present images could not provide a definite diagnosis of BCS.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Budd Chiari syndrome and portal vein thrombosis

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Reviewer Report 23 January 2020

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Cengiz Korkmaz

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Authors must use international writing rules for laboratory results. Please use "anti-Beta2 GPI antibody" "anticardiolipin antibodies (ACA Ig G and M".

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Version 1

Reviewer Report 25 November 2019

<https://doi.org/10.5256/f1000research.22156.r56811>

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Xingshun Qi

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- In Introduction section, the authors said "Myeloproliferative disorders are responsible for 40-50% of primary BCS cases in the presence of JAK2 V617F mutation." These words are not accurate. Please see the reference regarding meta-analysis of prevalence of JAK2 V617F mutation in BCS cases (PMID: 21395632)¹. Maybe the authors wanted to express the words "JAK2 positive MPD is about 40-50% in BCS cases".
- In Introduction section, the results of a meta-analysis found "the prothrombin G20210A mutation is associated with PVT, but not Budd-Chiari syndrome." (PMID: 24793031)² When the authors said "There is also an established association with prothrombotic disorders,

acquired or inherited, such as factor V Leiden mutation, G20210A prothrombin gene, ...", please consider the accuracy of your words.

- In Introduction section, please consider the results of a meta-analysis "Homozygous MTHFR mutation and hyperhomocysteinemia may be associated with the occurrence of BCS" (PMID: 24773704)³, when you said "A genetic variant of the methylenetetrahydrofolate reductase gene (MTHFR) has also been found to increase the risk of BCS". Please emphasize "homozygous".
- When you said "Plasminogen Activator Inhibitor-1 (PAI-1) mutation leads to impaired fibrinolysis or hypofibrinolysis increasing the risk of prothrombotic disorders.", please cite a reference.
- Is there any evidence regarding the association of PAI-1 mutation with splanchnic vein thrombosis?
- Please review the accuracy of your words "... female Caucasian, farmer, farmer, presented to ...".
- Give more images of contrast-enhanced MRI scans to demonstrate the hepatic veins.
- Please give the information regarding oral contraceptives.
- As for chronic BCS, please observe the risk of varices. Please consider endoscopy.

References

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Is the background of the case's history and progression described in sufficient detail?

Partly

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?

Partly

Is sufficient discussion included of the importance of the findings and their relevance to

future understanding of disease processes, diagnosis or treatment?

Partly

Is the case presented with sufficient detail to be useful for other practitioners?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Budd Chiari syndrome and portal vein thrombosis

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 26 Dec 2019

Domingos Sousa, Centro Hospitalar Universitário do Algarve, Faro, Portugal

Dear reviewer,

Many thanks for all your inputs

Thanks for the precious suggested references.

Unfortunately we do not have more MRI imaging to illustrate our case report

The manuscript has been reviewed taking your considerations into account.

Kind regards,
Domingos Sousa

Competing Interests: No competing interests were disclosed.

Reviewer Report 07 October 2019

<https://doi.org/10.5256/f1000research.22156.r54039>

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Cengiz Korkmaz

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Authors reported a case who developed BCS due to heterozygous mutation for PAI-1 gene. The

case is interesting and instructive. But I have some concerns:

1. In the past medical history, authors reported that the pt had ITP. What was the last situation on ITH in terms of therapy. Was she under the any treatment such as glucocorticoids?
2. Authors must state laboratory parameters correctly according to international rules; anti-b2-glycoprotein? anticardiolipin-b?
3. In discussion section, authors should give us a little bit more literature data about the role of PAI-1 gene mutation on deep venous thrombosis.

Is the background of the case's history and progression described in sufficient detail?

Yes

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?

Yes

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?

No

Is the case presented with sufficient detail to be useful for other practitioners?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Rheumatology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 26 Dec 2019

Domingos Sousa, Centro Hospitalar Universitário do Algarve, Faro, Portugal

Dear reviewer,

Many thanks for all the inputs

The manuscript has been reviewed taking your considerations into account

1. Under no treatment for ITP. No steroid therapy.
2. anti-b2-glycoprotein (IgM 0.61 UA/mL and IgG <0.10 UA/mL) and anticardiolipin-b antibodies (IgM 2.72 MPL/mL and IgG 3.72 GPL/mL).
3. We found new evidence supporting the role of PAI-1 on DVT.

Kind regards,

Domingos

Competing Interests: No competing interests were disclosed.

Reviewer Response 16 Jan 2020

cengiz korkmaz, Eskisehir Osmangazi University, Eskişehir, Turkey

Authors must use international writing rule for laboratory results. Please use "anti-Beta2 GPI antibody" "anticardiolipin antibodies (ACA Ig G and M"

Competing Interests: No competing interests were disclosed.

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