**Behçet’s Disease and Factor V Leiden: A Thrombogenic Synergy Causing Budd-Chiari Syndrome in Adolescence**

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**Author Contributions**

Ameer Awashra led the conceptualization, supervision, visualization, and contributed to both the original draft and the review & editing of the manuscript. Zaid Sawaftah was responsible for data curation and contributed to the original draft. Salsabeel Bishawi and Aya Milhem contributed to visualization and the original draft. Aseel Eid focused on the original draft. Dawoud Hamdan contributed to both the original draft and the review & editing process. Ali Bani Odah was involved in the review & editing of the manuscript. Ahmed Sawafta contributed to the conceptualization and was actively involved in both the original draft and the review & editing. Jehad Khamaysa contributed to the conceptualization, data curation, formal analysis, and was involved in both the original draft and the review & editing. Yazan Ghannam contributed to the conceptualization, data curation, formal analysis, and was involved in the review & editing. Hadi Rabee contributed to data curation, supervision, and the review & editing of the manuscript.

## **Abstract:**

## Behçet’s Disease (BD) is a multisystem inflammatory disorder that can lead to severe vascular complications, including Budd-Chiari Syndrome (BCS), a rare but life-threatening condition characterized by hepatic vein obstruction. The co-occurrence of BD and inherited thrombophilia, such as Factor V Leiden mutation, significantly increases the risk of thrombosis, complicating the clinical management of affected individuals. In this case, a 16-year-old female initially presented with nonspecific symptoms of generalized fatigue and bone pain, which later progressed to abdominal distension and significant hepatosplenomegaly. Imaging and further diagnostic evaluation confirmed BCS as the initial manifestation of BD, a rare but severe complication. Genetic testing revealed a heterozygous mutation for Factor V Leiden and the presence of the HLA-B51 allele, highlighting a thrombogenic synergy between BD and inherited thrombophilia. Aggressive anticoagulation therapy was initiated, resulting in partial recanalization of the hepatic veins and stabilization of the patient’s condition. This case emphasizes the need for early consideration of BCS in BD patients, especially in those with concurrent prothrombotic disorders, as timely intervention is crucial for improving clinical outcomes. The interplay of autoimmune and genetic factors in this case provides valuable insights into the complex pathophysiology and management of BCS associated with BD.

**Key clinical message:**

Behçet’s Disease can lead to severe vascular complications like Budd-Chiari Syndrome, especially when combined with inherited thrombophilia such as Factor V Leiden mutation. This case of a 16-year-old female underscores the importance of early diagnosis and aggressive anticoagulation to manage the complex interplay of autoimmune and genetic factors, improving clinical outcomes.

**Introduction:**

Behçet’s Disease (BD) is a chronic, relapsing condition of unknown cause that leads to inflammation of blood vessels (1). It manifests through various symptoms, including eye inflammation (uveitis), mouth ulcers, skin lesions, and genital sores. While it can also affect the nervous, gastrointestinal, and vascular systems, these are less commonly involved (2). BD impacts multiple organ systems because it affects arteries and veins of all sizes, leading to complications like an increased risk of thrombosis due to vascular inflammation (3). A rare but serious complication of BD is Budd Chiari syndrome (BCS), which occurs in less than 5% of patients with vascular involvement and is more common in men (89.5%) (4).

BCS is characterized by the blockage of blood flow from the hepatic veins to the inferior vena cava (5). It can be classified as primary BCS, caused by internal factors like vein stenosis due to thrombosis or phlebitis, or secondary BCS, caused by external compression from a lesion such as a malignancy (6). BCS typically presents with symptoms like abdominal pain, ascites, and hepatomegaly (7). The primary cause of hepatic vein obstruction in BCS is thrombosis, and most patients have an underlying condition that increases their tendency to form thrombosis. In 75% of cases, at least one hereditary or acquired hypercoagulable state, such as factor V Leiden, can be identified. Multiple factors may contribute to the condition in 25% of patients (8).

In our case, we describe a 16-year-old female presented with generalized fatigue and bone pain, which progressed to significant abdominal distension and hepatosplenomegaly, leading to a diagnosis of BCS. Genetic testing confirmed BCS as the initial manifestation of BD, with additional findings of a heterozygous Factor V Leiden mutation contributing to her thrombosis risk. She was treated with aggressive anticoagulation therapy, resulting in partial recanalization of hepatic veins and stable management of her condition, allowing her to maintain a good quality of life with ongoing monitoring.

**Case History/Examination:**

A 16-year-old female with no significant past medical history began experiencing generalized fatigue and bone pain localized to her upper limbs, shoulders, and back. These symptoms persisted for approximately two months before she sought medical attention. Initially, her presentation was non-specific, prompting consideration of a broad differential diagnosis that included viral infections, autoimmune conditions, and hematologic disorders. Despite visiting a private clinic where she was prescribed iron supplements and multivitamins, her symptoms did not improve, raising suspicion of an underlying chronic condition.

Ten days after her initial consultation, the patient noticed increased abdominal girth and a sensation of fluid accumulation. However, she delayed seeking further medical advice. At the same time, her menstrual cycle was slightly delayed with reduced flow, which was initially overlooked but later understood to be part of the systemic manifestations of her condition. As her abdominal distension worsened, her family sought additional medical attention, leading to her referral for further evaluation.

**Methods:**

A comprehensive assessment, including a PAN CT scan, revealed significant hepatosplenomegaly, a large volume of peritoneal ascites, and a nutmeg liver appearance. These findings suggested a serious underlying pathology, with the differential diagnosis including portal hypertension, congestive hepatopathy, and hepatic vascular obstruction. The scan also indicated diminished right hepatic vein IV contrast opacification, raising significant concerns of hepatic vascular pathology and leading to a strong suspicion of BCS (see Figure 1).

To further investigate the extent of her condition, 1700 cc of straw-colored ascitic fluid was drained. Analysis of the fluid revealed a low white blood cell count and negative culture results, consistent with non-infectious ascites. The absence of infection, coupled with imaging studies, confirmed the diagnosis of BCS. A subsequent MRI of the liver with IV contrast revealed no visible hepatic veins, confirming the chronic nature of BCS. The MRI also noted a significantly enlarged liver (21.5 cm) with heterogeneous parenchymal enhancement and an enlarged spleen (15.5 cm).

Further diagnostic evaluation, including genetic testing, confirmed that BCS was the initial manifestation of BD. The diagnosis was substantiated by the identification of the HLA-B51 allele, along with corresponding clinical findings, which collectively accounted for the hepatic complications observed in the patient. Additionally, a thrombophilia workup identified a heterozygous mutation for Factor V Leiden, further explaining the patient’s predisposition to thrombosis. This genetic mutation, combined with the vascular manifestations of BD (see Table1), necessitated aggressive anticoagulation therapy.

**Conclusion and Results:**

The patient was initiated on enoxaparin 60 mg subcutaneously twice daily to address the thrombosis. In addition, propranolol was prescribed to manage portal hypertension, thereby reducing the risk of variceal bleeding. To further control fluid retention, spironolactone and furosemide were added to her regimen. Omeprazole was included as a prophylactic measure against gastrointestinal bleeding, a known risk associated with both portal hypertension and anticoagulation therapy.

Following this treatment plan, the patient required ongoing monitoring to ensure therapeutic efficacy and to manage any potential complications. This included regular INR monitoring, imaging studies, and gastrointestinal management, such as endoscopic evaluation to assess for varices. Notably, after prolonged anticoagulation therapy, follow-up imaging revealed partial recanalization of the hepatic veins and the intrahepatic segment of the IVC, indicating a positive response to treatment (see Figure 2).

Throughout her follow-up, the patient’s condition remained stable. She continued on anticoagulation therapy with regular INR monitoring to ensure therapeutic levels were maintained, preventing both clotting and bleeding complications. Despite the chronic nature of her condition, the patient maintained a good quality of life. The long-term management plan included continued anticoagulation therapy, regular imaging to monitor liver size and function, and close follow-up with hepatology and hematology specialists. Additionally, the patient was educated on the signs and symptoms of potential complications, such as gastrointestinal bleeding, which could necessitate urgent medical attention.

**Discussion:**

BD, an auto-inflammatory systemic vasculitis of unknown cause, was first described by Hulusi Behçet who reported three cases with the triad of symptoms: aphthae, genital ulcers, and uveitis. Over time, other features were identified and added to the disease spectrum. BD is also referred to as "Silk Route disease" due to its geographic distribution in Mediterranean countries along the ancient trade routes that passed through these regions (9), as it is most prevalent in Turkey, with rates ranging from 80 to 370 cases per 100,000 people, while in countries such as Japan, Korea, China, Iran, Iraq, and Saudi Arabia, the prevalence ranges between 13.5 and 35 per 100,000. Outside the Silk Road region, immigrants and refugees from the Mediterranean countries are at an increased risk of developing the disease. In the U.S. and Europe, prevalence estimates range from 0.12 to 7.5 per 100,000. BD tends to affect males more in the eastern Mediterranean and females more in northern Europe (10–12). The patient in our case is from Tamoun, Palestine, which lies in the Mediterranean area, making her more susceptible to the disease.

BCS is the obstruction of hepatic venous outflow anywhere along the venous system connecting the hepatic venules to the inferior cavoatrial junction. This condition is uncommon, with a prevalence of one in a million. BCS may be caused by thrombotic or non-thrombotic events, with the latter being more common. Most cases of BCS have underlying hypercoagulable conditions with at least one inherited or acquired blood clotting disorder identified (8). The following table shows the most common etiologies of BCS (See Table 2):

Over 8 years, a study was conducted on 493 patients with BD to investigate the incidence of BCS and its impact on the disease progression. The findings revealed that BCS is a common complication in people with BD, contributing to a poorer clinical prognosis (13). Furthermore, a multicenter European survey identified BD as the primary cause of BCS in less than 5% of cases. However, in regions where BD is more common, such as Turkey, studies report a higher frequency, with BD accounting for 9-13% of BCS cases (14). In general, BCS is a relatively frequent complication of BD with an incidence of 0.3% to 26%. (15) it increases the mortality rate up to 61% in BD patients. (16)

Several potential mechanisms have been proposed for the development of BCS in patients with BD, including endothelial dysfunction, Factor V Leiden (FVL) mutation, protein C and S deficiencies, and impaired fibrinolysis (17). FVL mutation, where factor V in the coagulation pathway becomes resistant to inhibition by natural anticoagulants, has been found responsible for nearly 38% of the genetic defects linked to venous thrombosis in BD, increasing its risk sixfold (18). Regarding the BD patient presented in our case, a heterozygous change in the FVL gene was detected. This combination of prothrombotic conditions is believed to be the cause of the patient's development of BSC.

BCS is often underdiagnosed due to its varied clinical presentations, which can range from asymptomatic to acute, chronic, or fulminant forms (19). Most patients with BCS, however, present with symptoms such as fever, hypertension, abdominal pain, ascites, abdominal distention, liver failure, gastrointestinal bleeding, lower extremity edema, and encephalopathy These symptoms are generally linked to the rate of the underlying obstructive process (20,21).

A crucial step in diagnosing BCS is to consider it in patients who present with fulminant liver failure accompanied by sudden onset of ascites and hepatomegaly, severe ascites with relatively preserved liver function or a known thrombogenic disorder presenting with liver disease (21). The diagnosis is confirmed by identifying obstruction in the hepatic venous outflow tract using imaging methods such as conventional and Doppler ultrasound, MRI, CT, and catheter venography (19,21). Furthermore, BCS is classified into three types based on the location of the obstruction: Type I involves the inferior vena cava (IVC), Type II affects the hepatic veins, and Type III is a mixed type (20).

In terms of management, the initial approach typically involves medical treatment, including anticoagulation therapy, to control clinical outcomes. However, its effectiveness can be limited; thus, many patients will require interventional procedures during follow-up (21,22). The choice of intervention depends on the length of the obstructed segment and the degree of occlusion. For short-segment stenosis (less than 4 cm) of the IVC or hepatic veins, angioplasty with or without stent placement is preferred to restore blood flow. Conversely, in cases of long-segment thrombotic occlusion of the hepatic veins, which is more severe, a transjugular intrahepatic portosystemic shunt (TIPS) may be necessary to alleviate congestion. If these treatments fail, liver transplantation might be required (22).

In a specific study, treatment options for BD-associated BCS included immunosuppressive agents and corticosteroids as central components of the therapeutic strategy. For BCS caused by other factors, the study emphasized that treatment generally involves a combination of anticoagulants and surgical interventions. (14) Another study proposed an algorithm for managing BD-associated BCS. For uncomplicated cases, corticosteroids and immunosuppressants are recommended as first-line treatments. In cases complicated by refractory thrombosis, anticoagulants may be added. If refractory portal hypertension persists despite medical therapy, a transjugular intrahepatic portosystemic shunt (TIPS) can be employed. If TIPS fails or in cases of hepatic failure, liver transplantation is considered the final option. (23)

The prognosis for BCS is influenced by factors such as the extent of liver damage and the effectiveness of treatment. Recent data reveal a five-year survival rate exceeding 80%(24). Early and accurate diagnosis, coupled with prompt intervention, can result in favorable outcomes, especially in acute cases (21). In contrast, chronic BCS often presents with more variable prognoses; however, patients who respond effectively to medical management or interventions such as TIPS tend to fare better. Liver transplantation remains a viable option for patients with end-stage liver disease, though its success is contingent upon the pre-transplant liver condition and the presence of comorbidities (20,21). Consequently, diligent monitoring and adherence to lifestyle modifications are essential for optimizing long-term management and improving overall outcomes (21).

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