Anti Phospholipid Antibodies and Behçet's Disease

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Abstract

Behcet's disease (BD) is a multisystem variable vessel vasculitis that can cause oral and genital ulcers, papulopustular and nodular skin lesions, arthritis, uveitis, venous and arterial thrombosis, arterial aneurysms, central nervous system lesions and gastrointestinal ulcers. Anti phospholipid antibodies (aPL) were originally thought to bind anionic phospholipids such as cardiolipin and phosphatidylserine. However, it was subsequently recognized that the term "antiphospholipid" is a misnomer, since the best-characterized aPL are actually directed against specific phospholipid-binding proteins. Antiphospholipid (aPL) antibodies are known to induce arterial and venous thromboses, as occurs in antiphospholipid syndrome.There is growing evidence that cellular crosstalk between endothelial and immune-inflammatory cells could also promote thrombogenesis in BD. contribute to endothelial injury. It is important in determining the role of the presence of aPL for therapy of BD patients. Due to primary inflammatory vascular origin, the thrombotic events in BD are better responsive to glucocorticoids or immunosuppressive drugs than to anticoagulants. While standard therapy of APS includes long-term use of anticoagulants. It should be noted that the inappropriate use of anticoagulants in BD could be very dangerous especially in patients with pulmonary artery aneurisms because of the risk of vascular rupture

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Introduction

Behçet's Disease (BD) is a variable vessel vasculitis that involves several organs and systems, causing ulcers on the oral, genital, and intestinal mucosa, skin lesions that are most commonly in the form of papules, pustules or nodules, arthritis, uveitis, central nervous system lesions, venous and arterial thrombosis and arterial aneurysms **(1).**

Hulusi Behcet, a Professor of Dermatology from the University of Istanbul, first described and named the disease in 1937. However, the disease is also called "Adamantiades-Behçet's disease" in German because Benediktos Adamantiades had reported a patient who presented with various clinical manifestations like BD in 1930 **(2).**

Epidemiology:

The prevalence of Behçet's disease varies geographically, with the condition being most common along the ancient "Silk Road" route extending from Mediterranean countries such as Turkey and Iran to the Far East including Korea and Japan where the prevalence of HLA-B*51 is relatively high, compared to the rest of the globe. Reported prevalence of BD has found to be as high as > 1 case per 1000 population in Turkey **(3).**

The prevalence of BD in Egypt is 3.6/100,000, with no remarkable north-to south gradient but rather there is a higher concentration of cases in the big cities. The male-to female ratio is 2.6:1. Sex driven influence on the disease phenotype was notable unlike the effect of the age at disease onset. While, the CNS, DVT, and GIT involvement are higher in males, the joint affection and disease activity were increased in females **(4).**

BD mainly affects young men, the male predominance of the disease, pathergy positivity, and venous thrombosis are remarkable in Mediterranean and Middle East countries **(4).** Sub Saharan African patients had a higher frequency of neurological involvement and mortality and a lower frequency of HLA B-51 allele compared with those from North Africa and Europe, respectively **(5).**

Pathogenesis:

The exact pathogenic picture of BD is far from being clear. Whether it should be classified as an autoimmune or an autoinflammatory condition had been extensively debated. Early theories pointed to an autoimmune process triggered by an infectious or environmental agent in genetically predisposed individuals, innate and adaptive immune mechanisms playing a role in disease pathogenesis and tissue damage **(6).**

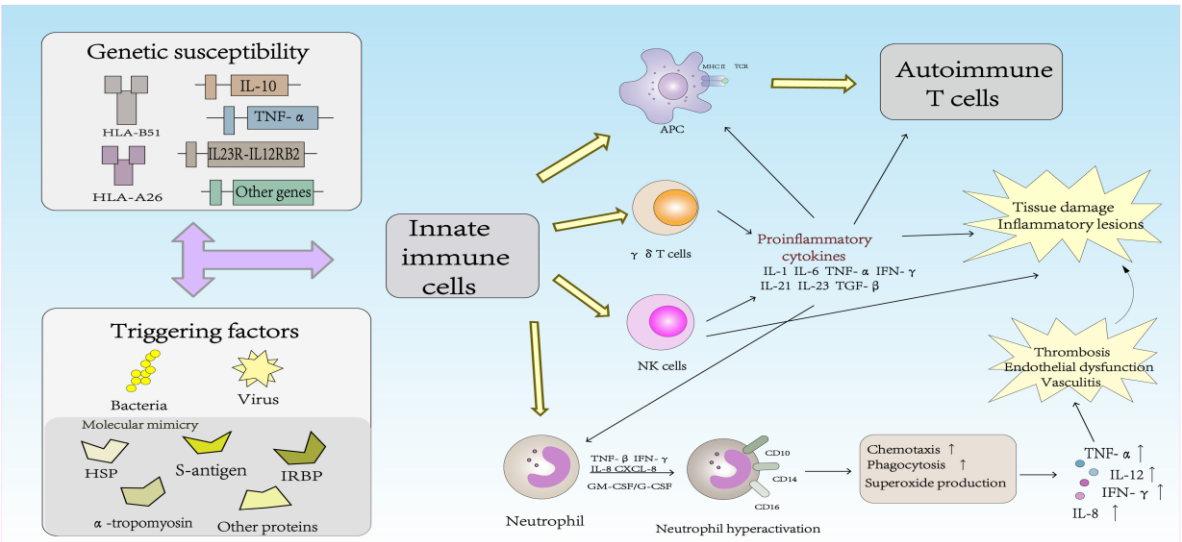

Figure 1: The pathogenesis of Behcet's disease (7).

IL: interleukin, TNF: tumor necrosis factor, IFN: interferon, TGF, transforming growth factor, HSP: heat shock protein, IRBP: interphotoreceptor retinoid binding protein.

Clinical Manifestations:

Behçet disease, a chronic recurrent systemic inflammatory vascular disease, that can affect blood vessels of any type and size. The disease can present with variable clinical manifestations and the most commonly involved systems are oral, ocular, cutaneous and urogenital **(8)**.

Vascular Manifestations:

Vascular involvement is one of the major causes of morbidity and mortality in BD. Male gender and young age are associated with venous thrombosis in BD. Prevalence of vascular involvement among BD patients varies from 15% to 40% in different series **(9).**

Unlike other systemic vasculitis, BD is characterized by coincident involvement of both arteries and veins of all sizes and presents a unique tendency for aneurysm formation **(10)**. It includes venous thrombosis, particularly in lower extremity, arterial occlusion, and aneurysm of pulmonary artery and aortic artery **(Figure 7) (11).**

Different epidemiological studies confirmed that the most frequent type of vascular involvement in BD is superficial thrombosis, followed by deep vein occlusions, and more rarely, by aneurysm formation on the arterial side **(10).**

1-Venous Involvement:

The deep and superficial veins of the lower limbs are the most commonly affected vascular districts in BD comprising about 70–80% of all involved vessels **(12)**. Although venous thrombosis in the lower extremities is not specific to BD, young age, male sex and a relapsing disease course eventually resulting in thrombotic occlusion are pathognomonic of BD (**13).**

Femoral and popliteal veins are the most frequently involved veins and are followed by crural, external iliac, and common iliac veins. When compared to DVT associated with non-BD reasons, bilateral involvement, less complete recanalization, and more collateral development are more frequent in BD **(14).**

Severe post thrombotic syndrome (PTS) may develop in half of cases and claudication in one-third of cases. PTS is associated with varying combinations of leg pain, swelling, hyper-pigmentation, varicose collateral veins and, in severe cases, venous ulcers **(9).**

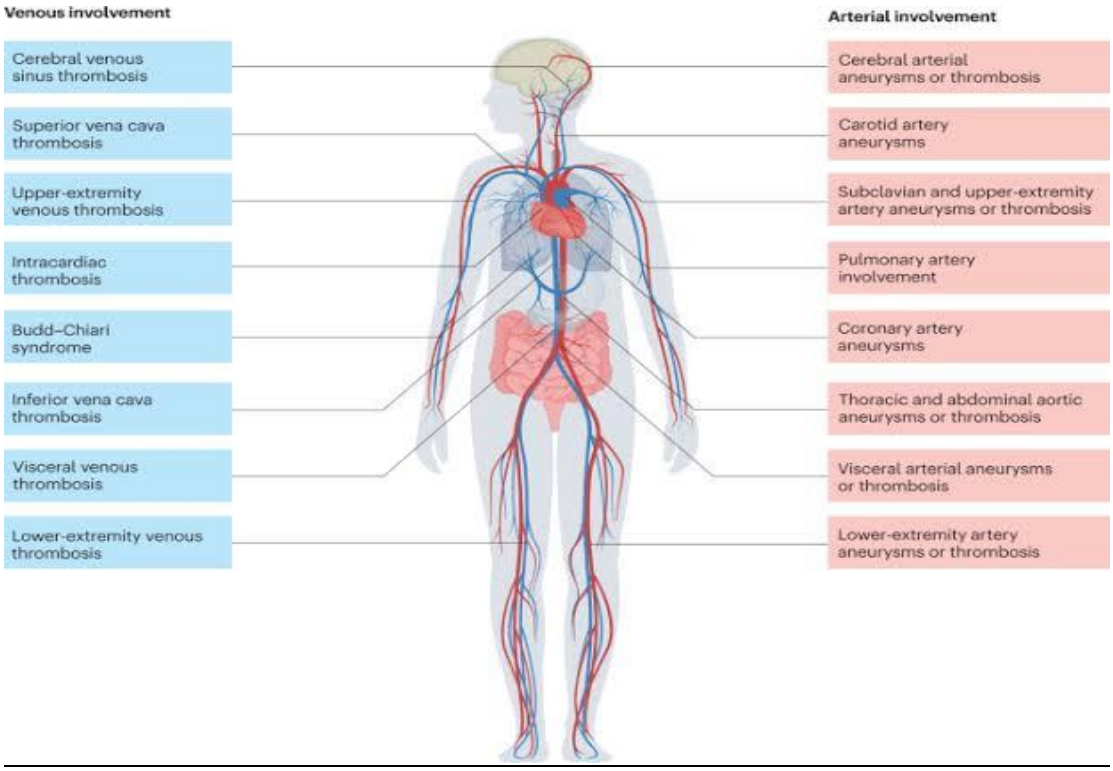

Figure 2:Vascular involvement in Behcet disease (13).

Uncommon sites such as superior or inferior vena cava, hepatic vein with Budd Chiari syndrome, portal vein, cerebral venous sinus, intracardiac thrombi in the right ventricle may be involved. The occurrence of thrombosis at these unusual sites is relatively specific to BD **(10).** Budd–Chiari syndrome is an uncommon, potentially life-threatening disorder involving hepatic outflow tract obstruction due to hepatic or supra-hepatic IVC involvement**(15).**

Cerebral venous sinus thrombosis CVST mostly involves the superior sagittal and transverse sinus and is more common in pediatric patients with BD. The most frequent signs of CVST in patients with BD are usually headache, papilledema, fever, nausea/vomiting, focal neurologic deficits, seizures and confusion. Relapses are occasionally observed; however, the outcome is generally favorable **(16).**

2-Arterial Involvement:

Peripheral arterial manifestations are much less common than the venous ones. Their frequency is estimated at <5%. They occur late in the course of the disease, 5–10 years after the first symptoms of BD. The majority presents as aneurysms rather than with thrombi. Claudication of the affected limb or digital ulcerations and necrosis are the main symptoms. The thoracic and abdominal aorta may also be affected, the abdominal aorta being the artery which is most commonly aneurysmatic (60%) **(17).**

Despite being the most frequent form of arterial involvement, pulmonary arterial involvement (PAI) rate is only 5–10% among all vascular manifestations. It affects mainly males. PAI can manifest as aneurysm formation, thrombosis, or both, but aneurysm formation is more frequent **(18).**

PAI is characterized by aneurysms (in 72% of cases) and in situ thrombosis (in 28% of cases). PAI is typically bilateral, multiple and mostly located on the lower lobe arteries **(13).**

Large aneurysms (>3 cm) have a poor prognosis with risk of rupture and pose a great challenge for medical and surgical management. Mortality rate is ~25% in patients with PAI **(19).**

Rarely, coronary arteries with the formation of giant or multiple aneurysms or pseudoaneurysms, thrombi and occlusions/stenosis are involved, causing the symptomatology of myocardial ischemia or infarction in a young patient. Mostly, the coronary artery involvement is accompanied by other vascular manifestations such as aortic or other arterial aneurysms or DVT **(20).**

A special subtype of vascular involvement in BD is the Hughes-Stovin syndrome (HSS). This is the combination of deep vein thrombosis and pulmonary arterial aneurysms. Not uncommonly an intracardiac thrombus is also present, To date, it is hypothesized that all patients with HSS have BD and that isolated HSS without any other BD symptoms is incomplete BD **(21).**

Diagnosis and Investigations

The diagnosis of BD is mainly based on clinical manifestations after ruling out other potential causes. There is no specific laboratory, histopathological, or genetic findings for the diagnosis of BD. Furthermore, there is a large geographical variation both in the disease prevalence and the disease manifestations **(14).**

Therefore, the diagnosis of BD may be difficult in patients presenting with only major organ involvement such as posterior uveitis, neurologic, vascular, and gastrointestinal manifestations. The emergence of other disease manifestations aiding the definite diagnosis of BD can take months and even years in this group of patients. The disease can also remain limited in some patients, which causes diagnostic difficulty **(22).**

In fact, recent data highlight an increase in the frequency of incomplete BD in Far Eastern, in this group of patients, diagnosis is made according to the presence of specific clinical manifestations of BD by 'expert opinion'. The specific clinical findings such as genital ulcers, ocular, vascular, and parenchymal neurological involvement were proposed to be defined as strong elements for the differential diagnosis of Behçet's disease **(6).**

There is no characteristic or pathognomonic laboratory finding in BD. Erythrocyte sedimentation rate and C-reactive protein levels are usually mildly elevated, mainly in cases with arthritis, erythema nodosum-like lesions, or vascular disease. Autoantibodies such as rheumatoid factor, antinuclear, anticardiolipin, and antineutrophil cytoplasmic antibodies are generally absent. However, it was reported that BD patients with gastrointestinal involvement had higher levels of anti-Saccharomyces cerevisiae antibodies compared to BD patients without gastrointestinal involvement **(14).**

There is a significant presence of antiphospholipid antibodies in BD patients compared to controls **(23)**. Elevated levels of anticardiolipin antibodies (aCL) were observed in 50% of the patients with thrombosis in a group of Iranian patients with BD **(24).** Significantly high levels of

aCL antibodies were detected in different neurological complications including headache, migraine, dementia, epilepsy and cognitive impairment **(23).**

- **Vascular imaging:**

Doppler ultrasonography is helpful in diagnosing venous thrombosis and arterial aneurysms in the extremities and in determining whether the thrombosis is acute, subacute or chronic. CT and CT angiography of the chest and abdomen are needed to diagnose larger, proximal vessel involvement. Echocardiography is used for imaging intracardiac thrombosis and transoesophageal echocardiography may be needed to rule out endocarditis **(25).**

Growing evidence indicates that venous wall thickness (VWT) of the lower extremity veins is increased in BD compared to that found in several inflammatory diseases and healthy controls, VWT was especially increased among those BD patients with no apparent vascular involvement suggesting that VWT could be an early indication of vascular inflammation **(26).**

Anti phospholipid antibodies (aPL)

Anti phospholipid antibodies (aPL) were originally thought to bind anionic phospholipids such as cardiolipin and phosphatidylserine. However, it was subsequently recognized that the term "antiphospholipid" is a misnomer, since the best-characterized aPL are actually directed against specific phospholipid-binding proteins **(27).**

The so-called "lupus anticoagulant" (LA) effect is a functional property of a heterogenous group of antibodies, with its name derived from its original description in patients with systemic lupus erythematosus (SLE). Antibodies with LA activity interfere with clotting in vitro assays and prolong phospholipid-dependent clotting times such as the activated partial thromboplastin time (aPTT). The first two patients with this finding also had a hemorrhagic diathesis**,** this finding led to the initial mistaken impression that the antibodies had an anticoagulant effect, when in fact they are most commonly prothrombotic. LA activity is strongly associated with thrombosis and pregnancy loss. Antibodies against beta2 GPI or PT (prothrombin time) are the most common cause of an LA effect **(28).**

The risk of thrombosis increases with the number of positive tests for aPL. In particular, patients with positive tests for LA, anticardiolipin (aCL) antibodies, and anti-beta2GPI antibodies have a higher risk of a first or recurrent thrombotic event than patients having only one or two positive tests **(29).**

APL-induced activation of several types of cells, resulting in multiple procoagulant and proinflammatory effects, and activation of complement are the major drivers of the vascular and obstetric complications of antiphospholipid syndrome (APS). Activation of vascular and immune cells by aPL potentiates thrombosis through upregulation of surface adhesion molecules and release of proinflammatory cytokines and procoagulant substances including extracellular vesicles and other cellular remnants. Cells that are activated in response to aPL include endothelial cells, monocytes, neutrophils, and platelets **(30).**

II-Antiphospolipid antibodies and Behcet disease:

There is growing evidence that cellular crosstalk between endothelial and immune-inflammatory cells could also promote thrombogenesis in BD. Acquired and inherited abnormal levels of different thrombophilic factors have been reported in patients with BD, inherited changes in thrombophilic factors include changes in fibrinolysis, anticoagulant and procoagulant factors, acquired changes in thrombophilic factors including antiphospolipid antibody, increased homocysteine levels and high Von Willebrand factor concentrations may contribute to endothelial injury. Antiphospholipid (aPL) antibodies are known to induce arterial and venous thromboses, as occurs in antiphospholipid syndrome **(13).**

However, in BD, the mechanisms by which endothelial cell injuries activate the coagulation pathways are largely unknown. It is important in determining the role of the presence of aPL for therapy of BD patients. Due to primary inflammatory vascular origin, the thrombotic events in BD are better responsive to glucocorticoids or immunosuppressive drugs than to anticoagulants. While standard therapy of APS includes long-term use of anticoagulants. It should be noted that the inappropriate use of anticoagulants in BD could be very dangerous especially in patients with pulmonary artery aneurisms because of the risk of vascular rupture **(23).**

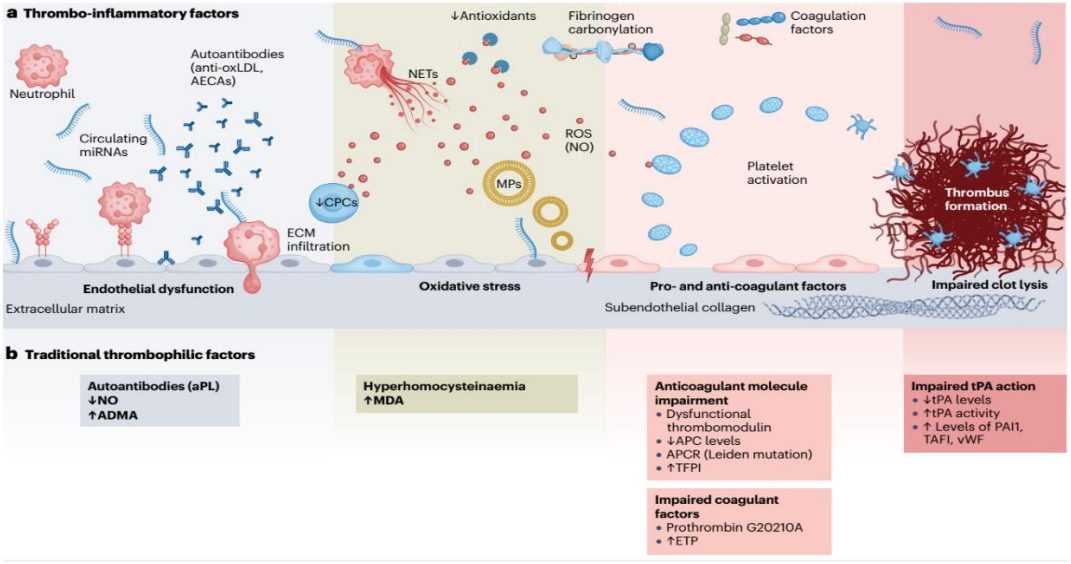

Figure 3: The main pathogenetic mechanisms in vascular Behçet disease (13).

(miRNAs) microRNAs, (ROS) reactive oxygen species, (NETs) neutrophil extracellular traps, (CPCs) circulating progenitor cells, (MPs) microparticles, (NO) nitric oxide, (ADMA) asymmetric dimethylarginine, (aPL) antiphospholipid antibodies (MDA) malondialdehyde , (APC) activated protein C, (APCR) APC resistance , (TFPI) tissue factor pathway inhibitor, (ETP) endogenous thrombin potential, (AECAs) anti-endothelial cell antibodies, (ECM) extracellular matrix, (oxLDL) oxidized low-density lipoprotein, (PAI1) plasminogen activator inhibitor 1, (TAFI) thrombin-activatable fibrinolysis inhibitor, (tPA) tissue-type plasminogen activator, (vWF)von Willebrand factor.

Vascular events affect up to 45% of BD patients involving both arterial and venous vessels of all sizes, but deep vein thrombosis (DVT) and superficial vein thrombosis (SVT) of the lower extremities are the most common vascular manifestations of the disease **(14).**

There is a significant presence of antiphospholipid antibodies in BD patients compared to controls. Elevated levels of anticardiolipin antibodies were observed in 50% of the patients with thrombosis in a group of Iranian patients with BD **(24).** postulated aCL antibodies as one of the risk factors in developing atherothrombosis. ACL antibodies were associated with significant retinal vascular pathology, cerebral infarction and thrombophlebitis **(31).**

Interestingly, arterial aneurysms have been observed in patients with aPLs. So, patients with arterial aneurysm may have aPLs as an additional risk factor for thrombosis. Neuro-BD represents an important differential diagnosis for primary APS with predominant cerebral vessels involvement. Cerebral venous sinus thrombosis and parenchymal lesions present in both diseases. Significantly high levels of aCL antibodies were detected in different neurological complications including headache, migraine, dementia, epilepsy and cognitive impairment **(32).**

Neuro-BD represents an important differential diagnosis for primary APS with predominant cerebral vessels involvement. Cerebral venous sinus thrombosis and parenchymal lesions present in both diseases. Significantly high levels of aCL antibodies were detected in different neurological complications including headache, migraine, dementia, epilepsy and cognitive impairment **(33).**

The persistent positivity of autoantibodies after a decrease in activity will be an indication for anticoagulant therapy in future. However, some studies observed increased levels of aPL due to long-term treatment with infliximab [anti-tumour necrosis factor (TNF) monoclonal antibody] and corticosteroids **(34).**

No Conflict of interest.

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