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Review article

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Vascular Behçet syndrome: from pathogenesis to treatment

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Abstract

Behçet syndrome is a rare, chronic inflammatory disease of unknown aetiopathogenesis, most commonly presenting with mucocutaneous and ocular manifestations. Vascular involvement, most frequently superficial vein and deep vein thrombosis, can occur in up to 50% of patients with Behçet syndrome. Venous thrombosis at atypical sites (inferior and superior vena cava, suprahepatic veins with Budd–Chiari syndrome, portal vein, cerebral sinuses and right atrium and/or ventricle) and arterial involvement (mostly in situ thrombosis and aneurysms of the pulmonary arteries, as well as aneurysms of the abdominal aorta, and peripheral and visceral arteries) are also unique features of Behçet syndrome. Behçet syndrome is considered a natural model of inflammation-induced thrombosis in humans, with an impaired immune-inflammatory response rather than traditional cardiovascular risk factors contributing to thrombogenesis. Specifically, neutrophil hyperactivation and neutrophil-mediated mechanisms of damage directly promote endothelial dysfunction, platelet activation and thrombogenesis in Behçet syndrome. This unusual pathogenesis directly determines the treatment approach, which relies mostly on immunosuppressants rather than anticoagulants for treatment of thrombosis and for secondary prevention. This Review discusses the main histopathological, pathogenetic and clinical aspects of vascular Behçet syndrome, addressing their implications for therapeutic management. Future perspectives in terms of pathogenetic studies, disease monitoring and treatment strategies are also discussed.

Sections

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Key points

- Vascular involvement occurs in up to 50% of patients with Behçet syndrome, mostly in the form of superficial and deep vein thrombosis.
- Behçet syndrome is considered a natural model of inflammation-induced thrombosis in humans, as thrombogenesis is mostly due to an impaired immune-inflammatory response rather than traditional cardiovascular risk factors.
- Neutrophil hyperactivation and neutrophil-mediated mechanisms of damage directly sustain endothelial dysfunction, platelet activation and thrombogenesis in Behçet syndrome.
- Venous thrombosis at atypical sites (such as Budd–Chiari syndrome, inferior and superior vena cava, and cerebral venous sinus thrombosis), and pulmonary and non-pulmonary artery involvement are also unique features of Behçet syndrome.
- Thrombosis treatment and secondary prevention in Behçet syndrome currently relies mostly on immunosuppressants rather than on anticoagulants.
- Research is needed to address the contribution of epigenetic modulators in Behçet syndrome thrombogenesis, to assess the diagnostic performance of vascular imaging to support Behçet syndrome diagnosis, and to identify new pharmacological and non-pharmacological therapeutic approaches.

Introduction

Behçet syndrome is a chronic inflammatory disease classified as one of the systemic vasculitides and was initially described as a triad of manifestations: oral and genital aphthosis and non-granulomatous uveitis. However, Behçet syndrome can affect almost any organ, and articular, cutaneous, vascular, neurological and gastrointestinal manifestations are frequently reported[1], presenting alone, or in various combinations at the same time or at different phases of the disease[2,3].

Vascular events occur in ~15–50%[4–6] of patients with Behçet syndrome, usually in the early stages of the disease[2]. The highest prevalence has been reported in Romania (50%) and in Lebanon (37%)[7], with male patients having a significantly higher risk of venous vascular involvement than female patients (hazard ratio (HR) 6.0, 95% CI 1.7–21.0)[8], probably owing to an increased hypercoagulable state in men compared with women[9]. The most common manifestations of the so-called angio-Behçet (that is, with cardiovascular involvement) are superficial vein thrombosis (SVT) and deep vein thrombosis (DVT) affecting mainly the upper and lower extremities[10]. The most severe cases can eventually lead to post-thrombotic syndrome (PTS), a chronic disabling condition related to venous insufficiency after a DVT event[10]. Thromboses in atypical sites (including the inferior vena cava (IVC) and superior vena cava (SVC), the hepatic and portal veins, the cerebral venous sinus or the right heart) are also a specific feature of Behçet syndrome[11]. Arterial involvement is not infrequent in Behçet syndrome, affecting around 3–5% of patients and displaying specific features[12]. Indeed, Behçet syndrome is one of the few chronic inflammatory disorders that cause aneurysms in the peripheral, visceral and pulmonary districts[13,14], and venous involvement occurs in many patients with arterial manifestations of Behçet syndrome[15,16]. Arterial thrombosis may also occur in Behçet syndrome, albeit more rarely than aneurysms or venous thrombosis[13]. The pathogenesis of Behçet syndrome is not fully understood, but infection-related, genetic, epigenetic and immunological factors are known to contribute to disease development[17]. Vascular manifestations are largely induced by an impaired inflammatory response, and Behçet syndrome has been defined as a natural model of thrombo-inflammation[14]. This is especially relevant to defining the therapeutic strategy, which relies mostly on immunosuppression rather than on anticoagulant treatment[18].

This Review discusses the main characteristics of the vascular involvement in Behçet syndrome, focusing on histological and pathogenetic aspects, clinical features, disease monitoring and treatment strategies, to provide a comprehensive and critical perspective.

Histopathology and pathogenesis

Histopathology of vascular Behçet syndrome

There are no histopathological features specific to Behçet syndrome with vascular involvement[19], although features present in classical vasculitides, such as panarteritis, concentric intima-media thickening, granuloma formation, necrotizing vasculitis and immune deposits, are absent. The main histopathological features of venous disease in Behçet syndrome include thickened vein walls, a lumen occluded with an organized thrombus that usually sticks to the vessel wall, and the presence of inflammatory cells. The histopathological features of arterial disease in Behçet syndrome include arterial aneurysms indicative of obliterative endarteritis, potentially disrupted medial elastic fibres in most cases, and inflammatory cell infiltration, particularly around the vasa vasorum. Furthermore, in active aortitis, the cellular infiltrate is composed mainly of neutrophils, lymphocytes and plasma cells, together with histiocytes and eosinophils, particularly in the walls of the vasa vasorum. Aneurysms are filled with a thick thrombus. In the chronic phases, dense periadventitial and intimal fibrosis and organized thrombi can be observed.

Inflammatory factors

Inflammatory factors have a central role in the thrombogenic process in Behçet syndrome, leading this disease to be considered a prototypical inflammation-induced thrombosis[13,20,21]. Neutrophils promote thrombo-inflammation via different mechanisms of damage, which ultimately lead to platelet activation, endothelial dysfunction and impaired fibrinolysis[22,23]. There is growing evidence that cellular cross-talk between endothelial and immune-inflammatory cells could also promote thrombogenesis in Behçet syndrome (Fig. 1a).

Neutrophil-mediated mechanisms of damage. Thrombo-inflammation in Behçet syndrome is primarily induced by activated leukocytes recruited to sites of endothelial injury. Neutrophils are the most common leukocyte to infiltrate around the vasa vasorum of the vessel wall[24,25]. Neutrophil activation, partly induced by a contribution from the HLA-B51 allele[26] and by infectious, hormonal[27] and environmental stimuli[17,28], results in enhanced production of reactive oxygen species (ROS), mainly by the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase complex[29]. In turn, ROS can oxidize fibrinogen, altering its structure and the overall architecture of the clot, including a reduced porosity and formation of a tight fibrin network with filaments of decreased average size[29]. These structural alterations impair fibrinogen function, increasing fibrin polymerization and reducing susceptibility to plasmin-induced lysis, thereby explaining the

increased thrombogenic potential and resistance to clot lysis observed in Behçet syndrome[14,29]. ROS also oxidize lipids, among which oxidized low-density lipoprotein (oxLDL)[30] directly leads to an atherogenic state and endothelial damage and indirectly via the production of anti-oxLDL antibodies[31,32].

Concomitantly, ROS stimulate neutrophils, particularly low-density granulocytes, to extrude neutrophil extracellular traps (NETs)[33], which are structures consisting of cell-free DNA, histones, microbicidal proteins and proteases[34]. Patients with Behçet syndrome have an increased abundance of low-density granulocytes[35] and NET levels (particularly in case of vascular involvement)[36,37], which is correlated with increased production of thrombin[37] and ROS[38]. Indeed, NETs not only activate macrophages to produce pro-inflammatory cytokines[39,40] but also directly activate the intrinsic and extrinsic coagulation pathways and induce thrombin production[41].

Crosstalk between the gut microbiota and the ROS–thrombosis axis has also been suggested. Patients with Behçet syndrome have a specific gut microbiota fingerprint, with impaired production of short-chain fatty acids, especially butyrate[42], which, based on preclinical data, exerts cardiovascular protective effects[43]. Accordingly, tailored dietary interventions reduce ROS production and fibrinogen alterations in patients with Behçet syndrome[44,45], confirming the complex regulation of the thrombotic diathesis associated with Behçet syndrome.

Endothelial dysfunction and platelet activation. In active Behçet syndrome, immunological and inflammatory factors induce endothelial cell dysfunction[46], characterized by decreased production of nitric oxide (NO), an endothelial-derived vasorelaxant that inhibits platelet adhesion[47], and increased levels of asymmetric dimethylarginine (ADMA), an endogenous inhibitor of NO synthase[48]. Accordingly,

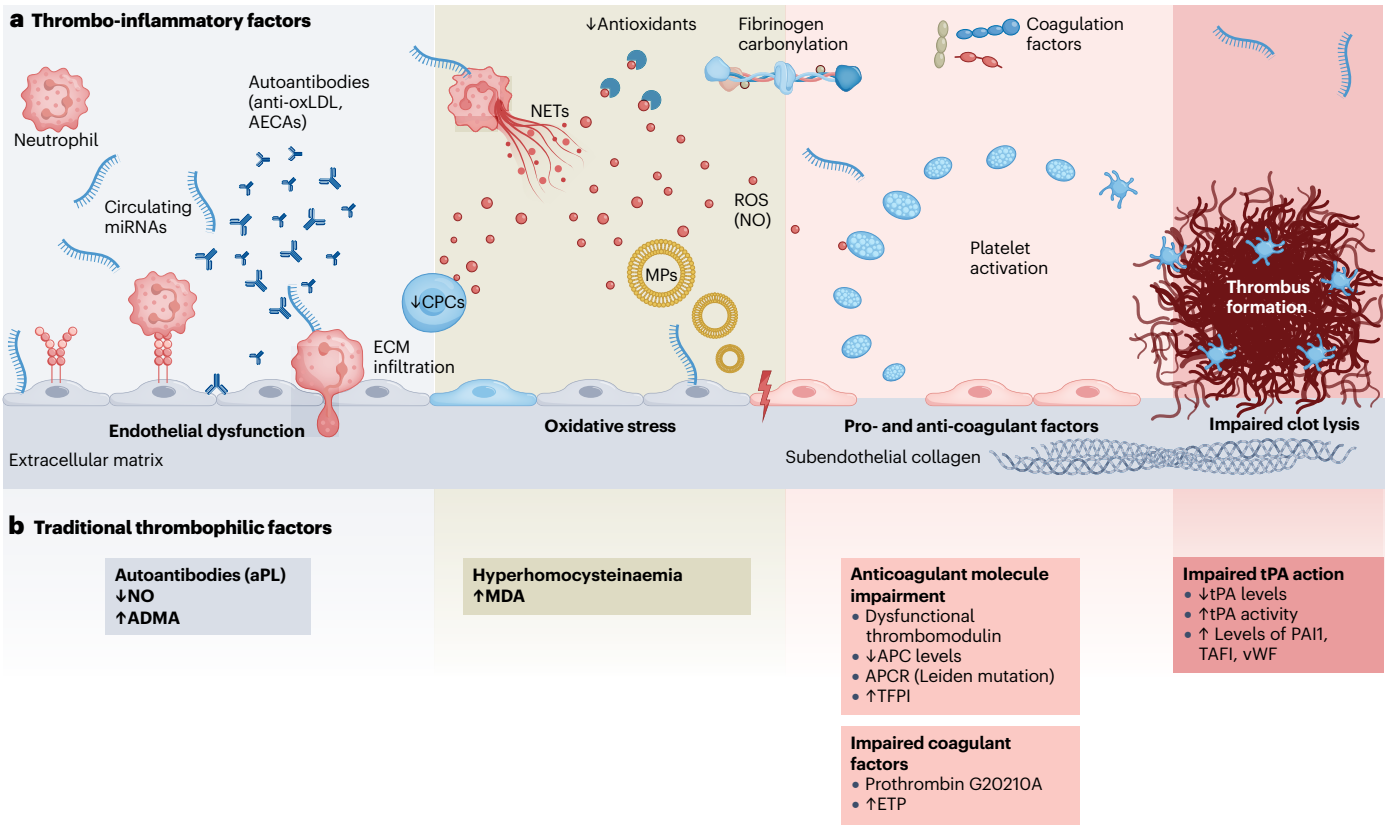

Fig. 1 | The main pathogenetic mechanisms in vascular Behçet syndrome. **a**, Thrombo-inflammatory mechanisms. It has been speculated that dysregulated circulating microRNAs (miRNAs) promote granulocyte infiltration, thereby inducing endothelial dysfunction. Concomitantly, miRNAs can also stimulate granulocytes (particularly neutrophils) to release reactive oxygen species (ROS) and neutrophil extracellular traps (NETs), which ultimately lead to platelet activation, rupture of the atherosclerotic plaque, endothelial dysfunction and impaired fibrinolysis. In addition, ROS can reduce the number and activity of circulating progenitor cells (CPCs), resulting in impaired CPC-mediated vascular repair. Hyperactivated platelets also release microparticles (MPs), which can contribute to vascular damage and thrombus formation. **b**, Thrombophilic factors. Hereditary and acquired changes in thrombophilic factors can sustain thrombo-inflammatory mechanisms in Behçet syndrome. Decreased nitric oxide (NO) production, increased plasma levels of asymmetric dimethylarginine (ADMA; the endogenous inhibitor of NO synthase) and the presence of antiphospholipid (aPL) antibodies contribute to endothelial dysfunction in Behçet syndrome. Concomitantly, increased homocysteine levels correlate with reduced activity of the antioxidant enzyme serum paraoxonase 1, resulting in increased levels of malondialdehyde (MDA), a marker of oxidative stress. In addition, abnormal function or levels of some anticoagulant factors (dysfunctional thrombomodulin, reduced activated protein C (APC) levels, APC resistance (APCR) and increased tissue factor pathway inhibitor (TFPI) levels), as well as procoagulant factors (prothrombin-G20210A mutation and increased endogenous thrombin potential (ETP)), have been reported, although conflicting results mean that the role of these factors in Behçet syndrome thrombogenesis is unclear. 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.

increased levels of endothelial injury markers (including circulating von Willebrand factor (vWF)[49] and thrombomodulin[50]) and angiogenesis markers (such as vascular endothelial growth factor) have been described in Behçet syndrome[20]. In addition, stimulated monocytes and endothelial cells display the coagulation receptor tissue factor (TF), which acts as a link between inflammation and thrombosis[51]. Furthermore, similar to in other cardiovascular and thrombotic diseases, circulating haematopoietic progenitor cells (CPCs), which are involved in vascular repair, are reduced in number and their function is impaired in patients with Behçet syndrome[52]. Of note, CPC levels and functional parameters are significantly inversely correlated ($P < 0.0001$) with oxidative stress levels, suggesting that ROS-mediated CPC dysfunction might result in impaired vascular repair in Behçet syndrome[52].

Interestingly, endothelial damage in Behçet syndrome seems to be mediated, at least in part, by anti-endothelial cell antibodies that target RalA-binding protein 1 (RALBP1; also known as RLIP76), a protein that is expressed on various cell types, including endothelial cells[53], and that contributes to endothelial activation and leukocyte (particularly neutrophil) recruitment.

Adhesion molecules (including P-selectin, also known as CD62P) are also upregulated in Behçet syndrome[54,55], particularly in patients with previous thrombosis. P-selectin is released during platelet activation and promotes leukocyte recruitment[55,56]. Accordingly, hyperactivated platelet function, probably owing to a genetic predisposition[57], has been reported in Behçet syndrome, accompanied by increased in vitro platelet aggregation in response to ADP[58,59] and by reduced platelet sensitivity to prostacyclin[60].

Cellular crosstalk: microparticles and microRNAs. Growing evidence also suggests that cell–cell signalling mechanisms contribute to thrombogenesis in Behçet syndrome. Among these are microparticles, which are irregularly shaped small vesicles that are released from the cell membrane after cell activation, apoptosis or mechanical stress[61]. Platelets from patients with Behçet syndrome are more prone to releasing microparticles[62] than those from healthy individuals, and these microparticles exert pro-inflammatory and procoagulant effects and can lead to the formation of platelet-rich thrombi, as observed in other immune-mediated diseases[20]. A reduced ratio of TF^+ microparticles to TF pathway inhibitor (TFPI)-positive microparticles has been described in Behçet syndrome, particularly in patients with a history of thrombosis[63].

Furthermore, a specific profile of differentially expressed circulating microRNAs (miRNAs; small non-coding RNAs that act as post-transcriptional regulators of gene expression) has been described in Behçet syndrome, which functional annotation analysis revealed affect pathways related to cell–matrix interaction, oxidative stress and blood coagulation[64]. Of note, a positive correlation between miRNA levels and leukocyte ROS production has been reported[64,65], further suggesting epigenetic regulation of thrombo-inflammatory mechanisms in Behçet syndrome (Fig. 1b).

Thrombophilic factors

Acquired and inherited abnormal levels of different thrombophilic factors have been reported in patients with Behçet syndrome[66] and are discussed below.

Inherited changes in thrombophilic factors: fibrinolysis. Alterations in fibrinolytic pathways have been reported in Behçet syndrome[50,67], including reduced levels of tissue-type plasminogen activator (tPA) antigen[68], enhanced tPA activity[67] and increased levels of plasminogen activator inhibitor 1 (PAI1)[49,67,69], thrombin-activatable fibrinolysis inhibitor (TAFI; also known as carboxypeptidase B2) and fibrinogen[70]. However, no strong association has been found between these parameters and Behçet syndrome-related thrombosis[67–69,71]. It has been speculated that the increased release of PAI1 from endothelial cells and the hypofibrinolysis in Behçet syndrome are mediated by lipoprotein(a), an LDL with atherogenic and anti-fibrinolytic effects[72,73]. However, lipoprotein(a) levels are comparable in patients with Behçet syndrome with or without thrombotic complications[73] and, accordingly, an association between hyperlipidaemia, particularly hypertriglyceridaemia, and thrombogenesis in Behçet syndrome seems to be weak[74,75].

Inherited changes in thrombophilic factors: anticoagulant factors. Most studies have described normal levels of the anticoagulant factors protein C, protein S and antithrombin in Behçet syndrome[50,76–78], although altered levels have been reported[79,80]. The role of thrombomodulin (an endothelial activator of protein C) in vascular Behçet syndrome is also debated[78,81]. It has been speculated that a massive release of fragmented, dysfunctional thrombomodulin from damaged endothelial cells might occur in Behçet syndrome, which might, in turn, reduce the production of non-fragmented, functional thrombomodulin, resulting in an impaired ability to activate the protein C anticoagulation pathway[82,83]. Reduced activated protein C (APC) levels have been associated with a high incidence of venous thromboembolism (VTE) in Behçet syndrome[84], although conflicting findings have been reported[70]. In addition, APC resistance (APCR) seems to be common in Behçet syndrome (29% versus 5% in the general population)[85], particularly in patients with thrombosis (65%). Accordingly, there is an increased prevalence of the factor V-G1691A variant (also known as the Leiden mutation; the major cause of APCR) in Behçet syndrome[86], occurring in up to 37% of patients with thrombotic complications and positively associated with cases of retinal vaso-occlusion[87,88] although these findings have not been confirmed in other studies[78,89].

Finally, increased levels of the anticoagulant molecule TFPI have been reported in Behçet syndrome, particularly in patients with active disease, although an association with thrombotic events has not been clearly shown[90].

Inherited changes in thrombophilic factors: procoagulant factors. An increased frequency of the prothrombin G20210A variant (a mutation that might stabilize the prothrombin mRNA and thereby result in hyperthrombinaemia) has been reported in Behçet syndrome[91,92], particularly in patients with a history of thrombosis (31%, compared with 3% in patients without a history of thrombosis)[91]. Furthermore, an increased endogenous thrombin potential (ETP; a measure of plasma-based hypercoagulability) has been reported, particularly in patients with a history of thrombosis[93]. However, other studies failed to confirm an association between the prothrombin-G20210A variant and Behçet syndrome thrombosis in various ethnic groups[78,89,94].

Acquired changes in thrombophilic factors. Antiphospholipid (aPL) antibodies are known to induce arterial and venous thromboses, as occurs in antiphospholipid syndrome[95]. A meta-analysis showed a significantly higher prevalence of aPL antibodies in patients with Behçet syndrome than in healthy controls[96], although whether this increased prevalence is associated with thrombotic manifestations in Behçet syndrome is uncertain[97,98]. Another meta-analysis revealed an increased prevalence of hyperhomocysteinaemia in patients with Behçet syndrome with thrombosis compared with those without thrombosis,

particularly in people from the Middle East, Mediterranean regions and Central and Far Eastern Asia[99], although this increased prevalence was not observed in other studies[100,101].

In patients with Behçet syndrome with thrombosis, plasma homocysteine levels correlate positively with plasma vWF concentrations, suggesting a role of endothelial injury in mediating thrombotic events[70]. It is known that increased homocysteine levels can have prothombrotic effects, including stimulating the expression of adhesion molecules (VCAM-1 and ICAM-1), cytokines, matrix metalloproteinase 9 (MMP9), TF and blood coagulation factors (factor V), and inhibiting fibrinolysis, disrupting NO metabolism, and increasing platelet reactivity and lipid peroxidation[51]. Of note, increased homocysteine levels correlate with reduced activity of serum paraoxonase 1 (PON1)[102], an antioxidant enzyme that physiologically inhibits the oxidation of plasma lipoproteins. Consistent with this finding, serum PON1 activity correlates negatively with levels of malondialdehyde (MDA)[102], a marker of oxidative stress that is increased in active Behçet syndrome[103], suggesting an indirect role of hyperhomocysteinaemia in promoting both endothelial damage and oxidative stress in Behçet syndrome. However, the reason why homocysteine levels are increased in Behçet syndrome remains unclear, as the prevalence of the hyperhomocysteinaemia risk factors folate deficiency and the *MTHFR* C677T variant in Behçet syndrome seems to be comparable with that in the general population[104].

Vascular events in Behçet syndrome

General features

Vascular involvement in Behçet syndrome has unique features when compared with other primary vasculitides or vascular diseases associated with autoimmune or inflammatory rheumatic diseases:[105] it is more frequent and runs a severe course in the young population (individuals <50 years of age), particularly among males[6,106]. The tremendous tendency towards thrombosis has the greatest discriminative power to distinguish vascular involvement in Behçet syndrome from other inflammatory vascular conditions[107]. Almost any vessel can be affected, although veins are more commonly affected than arteries[4]. Arterial disease manifests commonly with aneurysms and less frequently with in situ thrombosis[108]. Vascular involvement occurs early in the disease course, with three quarters of patients experiencing their first event within 5 years of disease onset[4]. Importantly, vascular involvement can develop before or simultaneously with the skin–mucosa lesions characteristic of Behçet syndrome in about one-third of patients[4]. Vascular disease is invariably relapsing[109,110], with relapses occurring at the primary site or at another vascular territory, resulting in extensive involvement very early in the disease course. The vascular phenotype almost always includes fever, a high acute phase response and constitutional symptoms[111]. Whereas DVT is by no means specific to Behçet syndrome, arterial aneurysms, especially pulmonary artery aneurysms (PAAs), are important in the differential diagnosis[112]. The prevalence of vascular involvement in Behçet syndrome also varies by ethnicity[113–116]. Although DVT and PAA are the most common vascular events in Behçet syndrome, these events are relatively rare in some geographic areas, such as Japan[113–115], whereas aortic valvular insufficiency is more prevalent in the Far East than in the Middle East[4,117].

Clinical features

The organ manifestations in Behçet syndrome rarely occur in isolation but instead are often clustered in clinical phenotypes, which also have different demographic characteristics and treatment responses and outcomes, and thus probably have different disease mechanisms[1,18,112,118–123]. These clinical phenotypes can basically be described as only mucocutaneous manifestations, eye, joint, Crohn's-like or vascular disease[121], although manifestations overlapping different phenotypes can occur in the same patient[124,125].

Peripheral vascular involvement is significantly associated with extra-parenchymal neurological involvement, specifically, cerebral venous sinus thrombosis (CVST)[126]. In addition, the co-existence of different vascular events, mostly SVT and DVT, in the same patients is not rare in Behçet syndrome[118,120]. Conversely, vascular involvement has been negatively associated with the presence of ocular manifestations[127], although another study did not confirm this inverse correlation[128]. The Behçet vascular phenotype is characterized by an increased risk of vascular flares, profound venous and arterial collateral formation that sustains thrombotic occlusions, and increased mortality risk[122,129,130]. In particular, the mortality rate for arterial manifestations can reach 26%[131,132], with up to 2.5-fold higher risk of death in patients with arterial involvement than in those without[133]. Moreover, vascular manifestations exhibit significant cross associations, including between CVST and pulmonary artery involvement (PAI), intracardiac thrombi and PAI, Budd–Chiari syndrome and IVC thrombosis, and between Budd–Chiari syndrome, IVC thrombosis, SVC thrombosis, CVST and PAI[4,121,122,132,134]. Of note, lower-extremity DVT is often present in these associations, usually being the prime event and perhaps acting as a catalyst[1,4,121]. The most common types of vascular involvement (Fig. 2), their clinical features (Figs. 3,4) and their characteristics and long-term complications (Table 1) are discussed below.

Venous involvement

Lower-extremity venous thrombosis. The deep and superficial veins of the lower limbs are the most commonly affected vascular districts in Behçet syndrome, comprising about 70–80% of all involved vessels[4,107,135]. Although venous thrombosis in the lower extremities is not specific to Behçet syndrome, young age, male sex and a relapsing disease course eventually resulting in thrombotic occlusion are pathognomonic of Behçet syndrome[107]. In prospective studies, the cumulative relapse rate may reach up to 45% at 1-year follow up[109,136,137]. A comparative study showed a higher relapse risk in patients from France than in those from Turkey, suggesting an association with ethnicity[137]. Venous involvement tends to be bilateral and diffuse, extending from the popliteal vein to the IVC[107,138]. Complete or partial recanalization is much less frequent and collateral formation tends to be abundant in patients with vascular Behçet syndrome than in those without[107]. Poor recanalization and lack of immunosuppressant use are the major predictors of relapse[109,110]. Severe PTS (Fig. 3h) may develop in half of cases and claudication (the main element responsible for walking disability) in one-third of cases[107,138–140]. PTS is associated with varying combinations of leg pain, swelling, hyper-pigmentation, varicose collateral veins and, in severe cases, venous ulcers[109]. Successful control of Behçet syndrome disease activity with immunosuppressants may decrease the development of PTS, improve venous disease-specific quality of life and prevent relapses in vascular Behçet syndrome[138].

Budd–Chiari syndrome. Budd–Chiari syndrome is an uncommon, serious, potentially life-threatening disorder[4,122,134,141–143] involving hepatic outflow tract obstruction due to hepatic or supra-hepatic IVC involvement[144]. Budd–Chiari syndrome can occur in isolation or be associated with thrombosis in the hepatic veins[134]. Asymptomatic presentation without ascites has also been reported, and these patients have a better prognosis (mortality rate <10%) than those with

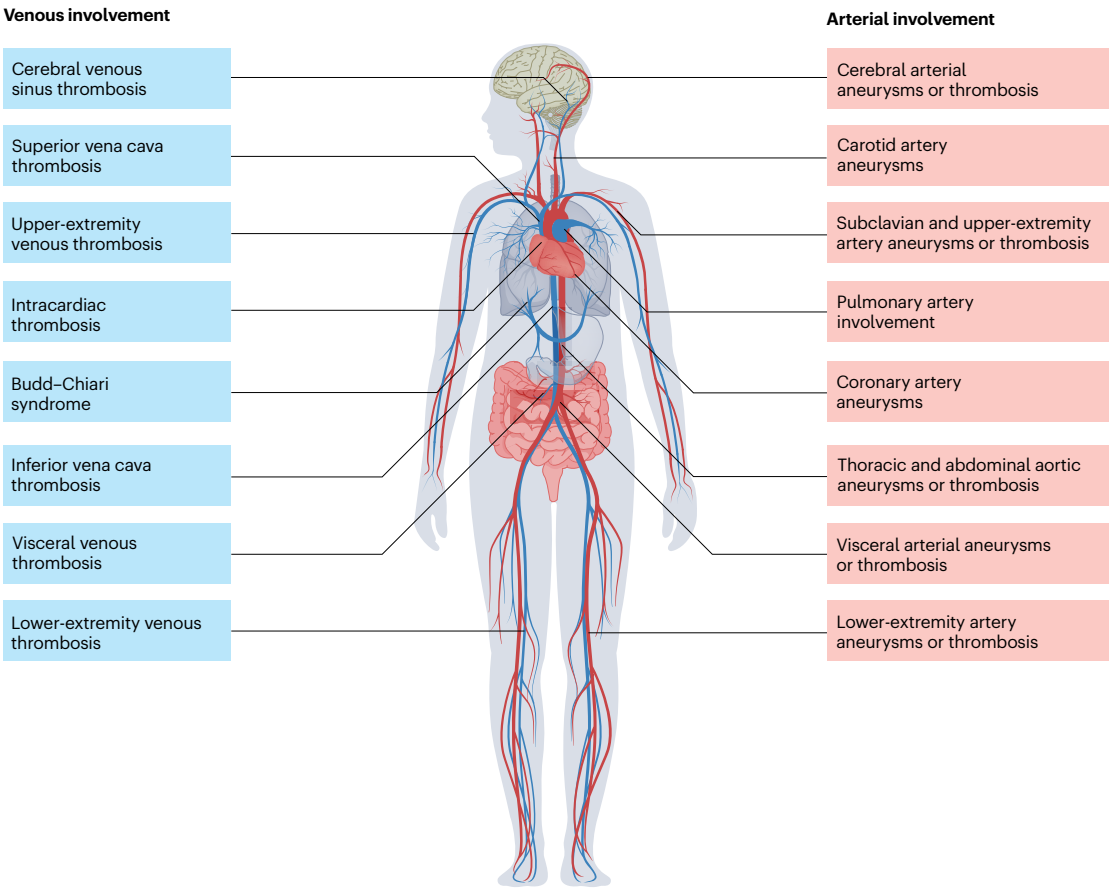

Fig. 2 | Vascular involvement in Behçet syndrome. Superficial and deep venous thrombosis, mainly affecting the upper or lower extremities, are the most common manifestations of vascular Behçet syndrome. Venous thromboses of atypical sites, including the inferior and superior vena cava, Budd–Chiari syndrome, cerebral venous sinus or intracardiac thrombosis, are also a specific feature of Behçet syndrome. Arterial involvement is not infrequent and presents with specific features, most commonly in situ thrombosis and aneurysms of pulmonary arteries but also aneurysms of thoracic and abdominal aorta, peripheral and visceral arteries, lower- and upper-extremity arteries, carotid and cerebral artery aneurysms or thromboses.

symptoms, probably because of the subacute onset, less extensive disease and efficient collateral formation[134]. By contrast, presentation with ascites, liver failure and liver function test abnormalities is associated with increased mortality (up to 60%). Budd–Chiari syndrome due to Behçet syndrome is characterized by a younger age at onset and male predominance, and patients are more likely to have DVT, intra-hepatic collaterals, a severe prognosis and a poor response to anticoagulants or vascular interventions than patients with Budd–Chiari syndrome of other causes[134,142].

Inferior vena cava thrombosis. The IVC can be divided into three anatomical portions, namely infrahepatic, hepatic and suprahepatic tracts[122]. Thrombosis occurs most commonly in the infrahepatic tract, owing to an extension of lower-extremity DVT. In the case of bilateral common femoral vein (CFV) thrombosis, iliac vein thrombosis can occur in around 50% of cases and IVC thrombosis in 20% of cases[122]. IVC thrombosis often develops insidiously except in the presence of Budd–Chiari syndrome[122]. Typical symptoms and signs of IVC thrombosis include lower back or abdominal pain in acute and venous collaterals in chronic vena cava obstruction (Fig. 3e,f,g).

Superior vena cava thrombosis. SVC thrombosis can occur in the jugular and subclavian veins and may extend to the upper-extremity veins. Relapse is seemingly rare; however, complete recanalization is seldom observed. Long-term complications of SVC thrombosis include recurrent haemoptysis[145], sleep apnoea disorder, larynx or pharynx oedema and refractory pleural effusions that can sometimes be chylous[122,146].

Cerebral venous sinus thrombosis. CVST mostly involves the superior sagittal and transverse sinuses[147,148] (Fig. 3a,b) and may occur as the sole manifestation of Behçet syndrome in juvenile patients[149]. CVST due to Behçet syndrome can be differentiated from that of other causes by the rare occurrence of venous infarction, infrequent neurological symptoms and multiple sinus involvement in Behçet syndrome[147]. Relapses are occasionally observed[147,148]; however, the outcome is generally favourable. In a retrospective study, 90% of patients responded well to the treatment within 1 month[147,150]. In a systematic review, a good response was achieved in more than half of the patients, whereas sequelae developed in 20% of patients. However, partial visual impairment or total visual loss due to optic atrophy may be observed[122,151,152].

Arterial involvement

Pulmonary artery involvement. PAI is characterized by aneurysms (in 72% of cases) (Fig. 4b,c) and in situ thrombosis (in 28% of cases)[132]. PAI is typically bilateral, multiple and mostly located on the lower-lobe arteries[132]. Thoracic CT imaging can disclose several pulmonary parenchymal lesions such as ground-glass lesions, subpleural nodules, cavities and consolidations, as well as pleural effusions and reactive mediastinal lymph nodes[132]. Aneurysms may disappear and thrombotic lesions may heal with either recanalization or occlusion. However, total occlusion leads to bronchial artery hyperplasia[130,132], which can result in recurrent haemoptysis and mild exertional dyspnoea[130,132,153]. Estimated systolic pulmonary artery pressure may be increased mildly or moderately, and rare cases with chronic thromboembolic pulmonary hypertension (CTEPH) have been reported[154]. Large aneurysms (>3 cm) have a poor prognosis with risk of rupture and pose a great challenge for medical and surgical management[132,155]. Mortality rate is ~25% in patients with PAI[6,156]. In a French series of patients with arterial disease, relapse occurred in 28% of patients and complete remission was achieved in 39% of patients, but mortality was high (73% survival at 20-year follow up)[157].

Non-pulmonary artery involvement. In contrast to other types of vascular disease in Behçet syndrome, non-PAI is a late event that develops on average 10 years after disease onset[4,108]. Aneurysms (Fig. 4d–f) are the most common vascular lesion (47%), followed by thrombotic occlusions (36%), stenosis (14%) and, rarely, aortitis (3%)[132]. Common sites include the abdominal aorta and iliac, femoral, popliteal and carotid arteries[108,132]. Besides a strong association with lower-extremity DVT, adjacent veins may also be involved[108]. Presentation is usually acute with pain, pulsatile mass, claudication and digital necrosis[108,157]. Patients generally have intense inflammation manifested with fever, weight loss and elevated acute phase response[108,157]. Aneurysms in Behçet syndrome are often surrounded by a thick inflammatory fibrotic tissue (thought to prevent catastrophic free rupture) and hyperplastic lymph nodes that are different from those seen in atherosclerosis[108].

Cardiac involvement

Cardiac involvement is rare in Behçet syndrome, can involve both venous and arterial structures[158], and includes pericarditis, endocarditis with valvular regurgitation, intracardiac thrombosis (Fig. 3c), myocarditis and coronary artery aneurysms (Fig. 4e). Importantly, cardiac involvement may be the first manifestation of Behçet syndrome[158]. Patients may present with sudden heart failure or with serious complications in the aftermath of cardiac valve surgery[117]. Intracardiac thrombosis, invariably involving the right side of the heart, is strongly associated with PAI and is at risk of transforming into endomyocardial fibrosis[159]. Data on the prognosis of cardiac involvement in Behçet syndrome are limited[136]. Mortality was 15% at 3 years in a French cohort[158], whereas intracardiac thrombosis resolved in most cases in a Turkish series[117,160].

Coronary artery involvement is rare (occurring in 0.5% of cases)[161]. Although the available data are limited, an invasive treatment strategy should be preferred owing to high mortality from coronary artery bypass. Surgery should only be performed after inflammation has been brought under control with immunosuppressive treatments to decrease postoperative complications[162].

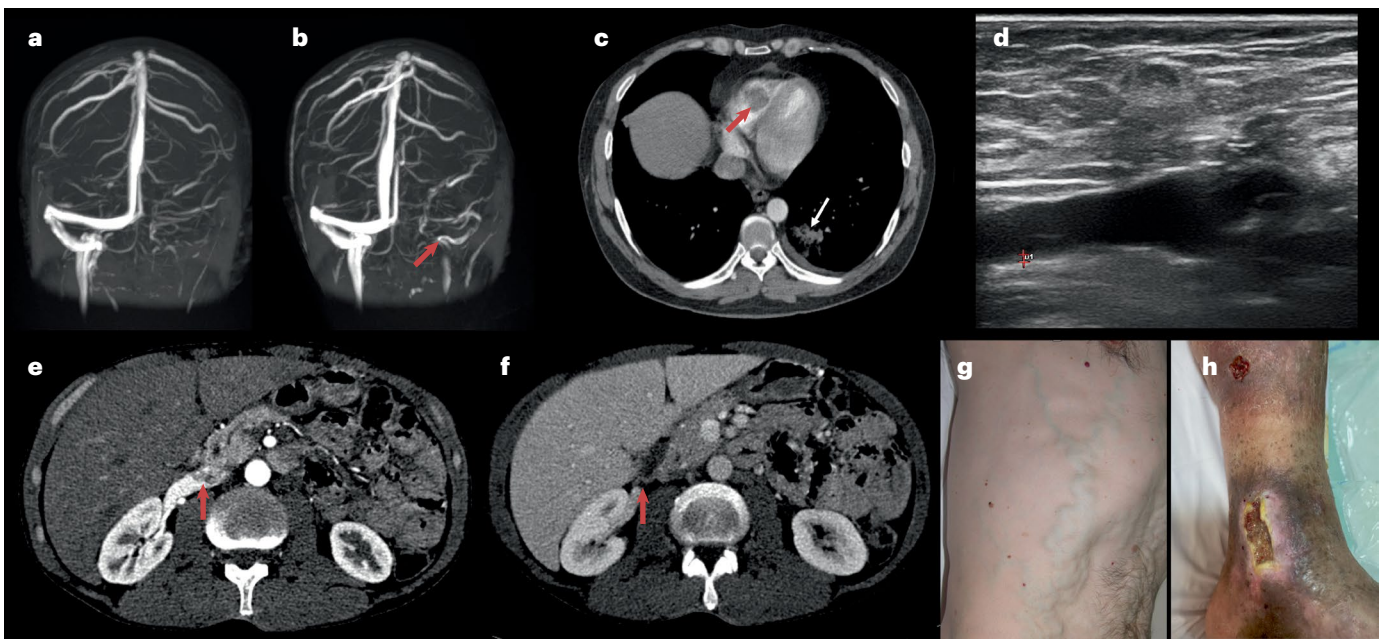

Fig. 3 | Imaging of venous involvement in Behçet syndrome. a, Cerebral MRI showing left transverse–sigmoid sinus thrombosis. **b**, Cerebral MRI showing partial recanalization (red arrow) of the left transverse–sigmoid sinus thrombosis after 3 months of oral anticoagulant and azathioprine therapy. **c**, Thoracic CT-angiography showing right ventricle filling defect consistent with intracardiac thrombus (red arrow) and subpleural haemorrhagic infarct area adjacent to mild pleural effusion (white arrow). **d**, Doppler ultrasonography showing common femoral vein wall thickness (red crosses). **e**,**f**, Contrast-enhanced abdominal CT scan showing thrombosis (red arrows) of the subrenal tract of the inferior vena cava, both in the arterial (part **e**) and the portal venous phase (part **f**). **g**, Abdominal collaterals in a patient with inferior vena cava thrombosis. **h**, Stasis ulcers on the left malleolus and proximal medial surface of the tibia, oedema and hyperpigmentation indicating severe post-thrombotic syndrome in a patient with lower-extremity vein thrombosis.

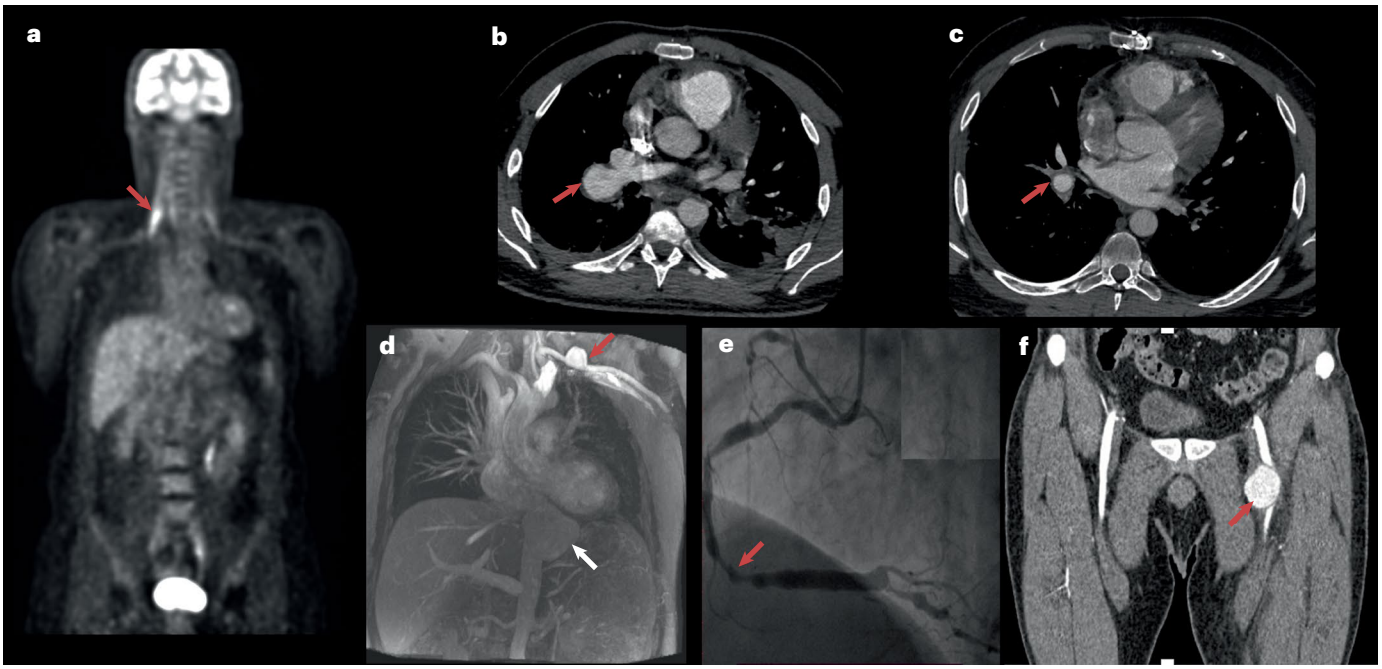

Fig. 4 | Imaging of arterial involvement in Behçet syndrome. **a**, ^{18}F-fluorodeoxyglucose (FDG)-PET showing enhanced contrast medium uptake of the right common carotid artery, compatible with an active phlogistic process (red arrow). **b**,**c**, Thoracic CT-angiography showing pulmonary artery aneurysm (red arrows), before (part **b**) and after 6 months of anti-TNF therapy (part **c**). **d**, MR-angiography showing saccular aneurysm of the descending thoracic aorta in the thoracoabdominal tract (white arrow) and aneurysm of the left subclavian artery in the postvertebral tract (red arrow). **e**, Coronary angiography showing a number of diffuse fusiform aneurysms on the right coronary artery (red arrow indicates one example). **f**, MR-angiography showing left femoral artery aneurysm (red arrow).

Imaging vascular involvement

Venous Doppler ultrasonography is the most commonly used imaging tool to detect venous involvement in Behçet syndrome, including thrombosis of lower extremities or hepatic veins. In a study comparing Doppler ultrasonography and MR venography in patients with Behçet syndrome with chronic DVT, Doppler ultrasonography detected chronic findings in all patients whereas MR venography was positive in 93% of patients. However, collateral veins were detected more frequently with MR venography than with Doppler ultrasonography, suggesting that MR venography might be an alternative or additional method to detect chronic thrombosis in the lower extremities[129]. Contrast-enhanced CT scans and MR angiography as non-invasive radiological methods are the preferred imaging methods to diagnose vena cava thrombosis[163]. For CVST, both contrast-enhanced CT and MR angiography may be used for the diagnosis, but MR angiography is superior to contrast-enhanced CT for detecting a clot in the cortical or deep veins. MR angiography also easily shows the ischaemic damage (even haemorrhagic) in the cerebral parenchyma in patients with CVST[164] (Fig. 3a).

Invasive procedures are not preferred for imaging of the arterial system in vascular Behçet syndrome owing to the risk of aneurysm formation at the insertion site[165]. Conventional angiography should therefore be avoided unless endovascular interventions are planned. For the diagnosis of pulmonary arterial involvement, contrast-enhanced CT is the best option as it shows small aneurysms better than MR angiography[130,166,167]. For imaging of peripheral arterial involvement in Behçet syndrome, both contrast-enhanced CT and MR angiography can be used. The development of multidetector CT has enabled reconstructions of three-dimensional, high-resolution images within a very short time.

^{18}Fluorodeoxyglucose (FDG)-PET–CT has been the most widely used imaging tool for large-vessel vasculitis in recent years (Fig. 4a) and can also be an option in Behçet cases with suspected isolated aortic involvement with vessel wall thickening and mural thrombus. However, there are limited data with PET–CT imaging to show inflammatory activity in pulmonary arteries, aorta and intracardiac thrombosis in Behçet syndrome[168–170].

Monitoring subclinical involvement

Asymptomatic vascular involvement is a major concern, especially for patients with a previous venous vascular event. Subclinical lower-extremity thrombosis is present in 0–6% of the patients, whereas venous insufficiency is frequent (32.3–74%), suggesting the presence of subclinical venous vascular disease[171–173].

MRI has been used to detect increased vein wall thickness in popliteal veins of patients with Behçet syndrome[174]. A controlled Doppler ultrasonography study showed an increased vein wall thickness of lower-extremity veins in male patients with Behçet syndrome compared with healthy males or male patients with ankylosing spondylitis. Doppler ultrasonography assessment of the CFV, the largest lower-extremity vein, using cut-off values for right and left CFV ≥0.5 mm had high area under the receiver operating characteristic curve values (>0.8) with sensitivities of 81–82.8% and specificities of 78.4–81.1%[175] (Fig. 3d).

A study assessed vein wall thickness in patients with Behçet syndrome with or without vascular involvement and in healthy individuals

and observed increased vein wall thickness in both groups of patients with Behçet syndrome compared with healthy controls[176]. Among patients with Behçet syndrome, those with vascular involvement have the greatest vein wall thickness[176,177]. Further studies have confirmed the presence of increased vein wall thickness in Behçet syndrome, including in other vessels such as the portal and jugular veins[177,178]. Increased vessel wall thickness is also observed in pulmonary arteries, which have a similar structure to systemic veins in patients with Behçet syndrome[179].

When the diagnostic performance of CFV thickness measurement was assessed in multiple inflammatory diseases, increased CFV thickness was a distinctive feature of Behçet syndrome[180] that discriminated this disease from other inflammatory disorders (including ankylosing spondylitis, other systemic vasculitides and Crohn's disease) as well as non-Behçet-syndrome-related vascular diseases except for antiphospholipid syndrome[180,181]. The cut-off value of ≥0.5 mm performed quite well against all control diseases, with sensitivity and specificity (except for anti-phospholipid syndrome) higher than >80%; in particular, CFV thickness values >0.75 mm seem to indicate a very high probability of Behçet syndrome.

Diagnosing Behçet syndrome can be challenging, especially in patients presenting with involvement of one major organ, defined as 'incomplete' Behçet syndrome in some series[182]. Early diagnosis is of the utmost importance, especially in patients presenting with only venous or arterial thrombosis, as management of these thromboses differs from that of non-inflammatory DVT, requiring immunosuppressants and anticoagulants rather than anticoagulant therapy alone. New observations suggest that CFV thickness measurement might be a valuable additional diagnostic tool in single-organ, incomplete disease, including in the paediatric population with Behçet syndrome[183], although its diagnostic value needs to be confirmed in other clinical and geographical settings.

Outcome measures

Disease assessment in Behçet syndrome is complicated by the heterogeneity of clinical findings and variation in the frequency and severity of relapses of different organ manifestations. Several outcome measures are validated for use in daily practice and in clinical trials for the assessment of Behçet syndrome and the subset of patients with vascular disease; however, these measures are not widely used. Vascular remission in Behçet syndrome is usually defined as the absence of new vascular lesions (in previously unaffected vascular territories) and the absence of progression of pre-existing vascular lesions detected in serial imaging studies (that is, Doppler ultrasonography and/or CT-angiography and/or MR-angiography).

Behçet's Disease Current Activity Index[184], Behçet's Syndrome Activity Scale[185], Clinical Manifestation Index[186] and the Iranian Behçet's Disease Dynamic Activity Measure[187] are indices for the overall assessment of Behçet syndrome disease activity. However, in a survey among Behçet syndrome experts, fewer than half agreed that any of these scales are reliable and valid[188].

Table 1 | Features and complications of venous and arterial involvement in Behçet syndrome

Feature or complication	Prevalence	Common signs and symptoms at presentation	Long-term complications	Associated features
Venous involvement				
Lower-extremity venous thrombosis	~70–80%	Swelling, pain and claudication	Post-thrombotic syndrome and claudication	Young age at onset, increased relapse rate and involvement of both deep and superficial veins, continuous segments of vessel wall and both legs
Budd–Chiari syndrome	~<5%	Abdominal pain, ascites and collateral formation on the abdomen and back	Mild liver insufficiency symptoms, hypersplenism and upper gastrointestinal bleeding due to oesophageal varices	Strong association with DVT and IVC thrombosis, abundant intra-hepatic collaterals, severe prognosis and poor response to anticoagulants or vascular interventions
Superior vena cava thrombosis	~10%	Dyspnoea, swelling on the face, neck and/or upper extremities, hoarse voice, conjunctival suffusion, and collateral formations on the upper torso and around the neck	Sleep apnoea syndrome, pleural effusions (eventually chylous), recurrent haemoptysis and oedema of the pharynx and larynx	Young age at onset, subacute insidious onset and strong association with DVT, IVC or CVST
Cerebral venous sinus thrombosis	~10%	Intracranial pressure symptoms (severe headache, vomiting, diplopia and blurred vision) and cranial nerve palsies	Optic atrophy and visual field and hearing defects	Rare venous infarction, infrequent neurological symptoms and multiple sinus involvement
Arterial involvement				
Pulmonary arteries	~10%	Haemoptysis (often abundant), chest pain, cough, dyspnoea, fever and weight loss	Recurrent haemoptysis (small quantity), dyspnoea, pulmonary hypertension, CTEPH, and pneumothorax (subpleural cavities)	Strong association with thrombosis, multiple bilateral and lower lobe involvement, and absence of features ascribed to large-vessel vasculitis
Non-pulmonary arteries	~<5%	Abdominal or back pain, extremity pain, pulsatile mass, claudication, extremity pallor, digital cyanosis, fever and weight loss	Claudication, peripheral arterial disease, and digital ischaemia	Young age, high acute phase reactants, few atherosclerotic risk factors, false aneurysm, recurrence at the same site, thick inflammatory fibrotic tissue surrounding the aneurysm, enlarged lymph nodes and thrombosed adjacent veins

CTEPH, chronic thromboembolic pulmonary hypertension; CVST, central venous sinus thrombosis; DVT, deep vein thrombosis; IVC, inferior vena cava.

A Behçet syndrome-specific tool to measure quality of life has been developed but is not used widely[189]. The Villalta scale is a widely used and validated tool[190] to diagnose and assess the severity of PTS, including in vascular Behçet syndrome[140]. The Venous Insufficiency Epidemiological and Economic Study Quality of Life/Symptom questionnaire was developed to assess venous disease-specific quality of life in vascular Behçet syndrome[190].

The Outcome Measures in Rheumatology Clinical Trials Behçet Syndrome Working Group developed a core set of five mandatory domains (overall disease activity, new organ involvement, quality of life, adverse events and death) to be used in all clinical trials of Behçet syndrome and also defined organ-specific subdomains[191]. For trials of vascular involvement, the vascular subdomain assesses vascular lesions, SVT and PTS, with recanalization included as an 'optional' subdomain. Assessing these subdomains in all trials on vascular Behçet syndrome is helpful to avoid missing any relevant information on new or worsening manifestations, to assess the potential impact of an agent in treating or preventing these events, and when the efficacy of a treatment on vascular involvement is not the primary outcome of the trial[191].

Treatment strategies

General aspects

Patients with vascular involvement need to be managed early and aggressively because of the increased mortality risk and associated severe morbidities such as walking disability, PTS and CTEPH[6,107,108,132–134,139–143,153,154,157]. Moreover, vascular involvement has a socio-economic impact, including a high rate of unemployment[107], increased cost of illness[192] and considerably impaired quality of life[138].

Despite the importance of effective treatment, research on primary and secondary prevention of vascular events in Behçet syndrome is lacking. The EULAR recommendations for the management of Behçet syndrome with vascular involvements were updated in 2018 (ref. 193) and recommend immunosuppressants as the cornerstone of treatment for vascular Behçet syndrome, whereas the role of anticoagulants in this clinical setting is the subject of debate (Table 2). As in other vascular diseases, protecting the integrity of the arterial wall can be achieved with statin therapy, anti-platelet drugs, smoking cessation and diet interventions such as butyrate-rich anti-inflammatory diets[44]. A simple but effective method for treating venous disease is the use of stockings that reduce the risk of PTS development in early disease and decrease symptoms such as swelling and pain[193].

Treatment of venous events

Thrombosis at typical sites and PTS. The treatment goals for venous thrombosis of the extremities are to prevent recurrence of thrombotic events and to provide a good recanalization to prevent PTS development. Management of venous involvement requires immunosuppressants to reduce vessel wall inflammation, which is considered the main pathological condition underlying thrombotic complications of Behçet syndrome (Table 2). Depending on the type of veins that are involved and whether the patient presents with an acute or chronic thrombus, treatment options include corticosteroids, conventional immunosuppressants such as cyclophosphamide, azathioprine, cyclosporine A and mycophenolate, as well as biologic DMARDs including monoclonal antibodies targeting TNF (anti-TNF) and interferon-α (IFNα)[109,193–197].

The role of anticoagulants for the treatment of venous thrombosis in patients with Behçet syndrome is controversial. Anticoagulant

Table 2 | Treatment strategies according to vascular clinical involvement in Behçet syndrome

Feature or complication	Treatment		
	Immunosuppressants	Anticoagulants	Non-pharmacological treatment
Venous involvement			
Lower-extremity venous thrombosis	Oral glucocorticoids alone or with traditional immunosuppressants (azathioprine, cyclosporine A and mycophenolate), or biologic DMARDs (anti-TNF and IFNα)	Controversial (vitamin K antagonists and direct oral anticoagulants)	Compression stockings or Unna bandages
Budd–Chiari syndrome or vena cava thrombosis	High-dose intravenous methylprednisolone pulses, followed by oral glucocorticoids and traditional immunosuppressants (cyclophosphamide), or biologic DMARDs (anti-TNF); azathioprine for remission maintenance	Recommended (vitamin K antagonists)	Endovascular interventions might be considered
Cerebral venous sinus thrombosis	Short-term glucocorticoids and traditional immunosuppressants (cyclophosphamide or azathioprine), or biologic DMARDs (anti-TNF)	Recommended (vitamin K antagonists)	Lumboperitoneal shunts
Arterial involvement			
Pulmonary artery aneurysms	High-dose intravenous methylprednisolone pulses followed by oral glucocorticoids and traditional immunosuppressants (cyclophosphamide); in refractory patients, use biologic DMARDs (anti-TNF)	NA	Consider only in life-threatening situations; embolization in patients at a high risk of major bleeding; surgery (lobectomy or segmentectomy) in patients with a giant aneurysm
Aortic aneurysms	Oral glucocorticoids and traditional immunosuppressants (cyclophosphamide), or biologic DMARDs (anti-TNF)	NA	Endovascular or surgical treatment if the aneurysm is life-threatening
Peripheral artery aneurysms	Oral glucocorticoids and traditional immunosuppressants (cyclophosphamide or azathioprine)	NA	Surgery or stenting (endovascular graft, bypass surgery, ligation and graft interposition) in symptomatic patients

NA, not applicable.

treatment does not seem to affect the relapse rate, presence or severity of PTS or decrease residual thrombosis[138,140,194]. However, according to local clinical practice, anticoagulation is prescribed in addition to immunosuppressants in some centres, whereas in others anticoagulants are administered only in selected patients with additional Behçet syndrome-unrelated cardiovascular risk factors[110,136,198].

Recurrence rates of up to 36% are reported at 5 years, regardless of whether immunosuppressants are used with or without anticoagulation[110,136,198]. A small prospective cohort study showed that IFNα may provide lower recurrence rates and better recanalization in patients with azathioprine-refractory disease[109]. Better outcomes were reported with adalimumab than with conventional immunosuppressants in a retrospective study[195], but the addition of anticoagulants did not improve outcome in either group. A meta-analysis of retrospective studies exploring the effect of treatment modalities on thrombotic relapse risk showed that immunosuppressant use is associated with reduced risk of relapse (relative risk (RR) 0.17; 95% CI 0.08–0.35), whereas anticoagulant use is not (RR 0.75; 95% CI 0.48–1.17)[194]. A retrospective study evaluating risk factors for PTS showed that immunosuppressant use was associated with a lower risk of severe PTS (odds ratio (OR) 0.10; 95% CI 0.02–0.05)[140]. A multicentre retrospective study of direct oral anticoagulants (DOAs) showed a decreased time-dependent risk of relapse with DOAs alone (hazard ratio (HR) 0.11; 95% CI 0.03–0.45) and a greater decrease with DOAs plus DMARDs (HR 0.024; 95% CI 0.004–0.14) compared with no DOAs[199].

Thrombosis at atypical sites. IVC and hepatic vein thrombosis causing Budd–Chiari syndrome, SVC thrombosis and intracardiac thrombosis are more serious types of venous involvement that must be treated promptly and aggressively (Table 2). Data on the treatment of these lesions are based on experience reported in small cohort studies and case series. High-dose intravenous methylprednisolone pulses may be the initial treatment choice during the acute phase, followed by oral prednisolone (0.5–1 mg/kg daily) tapered over 3–6 months in addition to cyclophosphamide or anti-TNF. Azathioprine (2–2.5 mg/kg daily) may be used for maintenance of remission. Anti-TNF is used for a longer duration in patients who only achieve partial remission or those who are at a high risk of relapse. The use of anticoagulants for the treatment of vena cava thrombosis and Budd–Chiari syndrome is controversial[200]. In addition to immunosuppressants, surgical and endovascular interventions have been tried in refractory patients with Budd–Chiari syndrome, with variable success[201].

CVST is usually manageable with short-term corticosteroids and immunosuppressants and the outcome is usually good[148]. However, some patients may experience severe elevation of intracranial pressure and optic nerve compression that may cause vision loss[202]. It is important to recognize such patients early, and treat them aggressively with high-dose glucocorticoids, immunosuppressants or conventional or biologic DMARDs such as cyclophosphamide or anti-TNF. If these therapies are not adequate to suppress the intracranial pressure rapidly, then interventions such as lumboperitoneal shunts may be tried. Anticoagulant therapy should be considered in these patients, not only in the acute phase[126] but also as maintenance treatment[148].

Treatment of arterial events

There is no firm evidence or randomized controlled trials that directly address the optimal induction immunosuppressive therapy for arterial lesions in Behçet syndrome, so treatment recommendations are based on consensus or observational studies[193].

Pulmonary artery aneurysms. The primary treatment for PAA is high-dose glucocorticoids and monthly intravenous cyclophosphamide pulses[193] (Table 2). Glucocorticoids are usually given as intravenous methylprednisolone pulses, followed by oral prednisolone (or prednisone) at a dose of 1 mg/kg daily[132,157,203]. Two retrospective studies evaluated the mortality rate in patients with Behçet syndrome with PAI who were treated with cyclophosphamide or other interventions (surgery or azathioprine and corticosteroids)[204,205]. In the first study, mortality occurred in 6 of 17 patients in the cyclophosphamide group and all patients (n = 5) treated with other interventions[204]. In the second study, mortality occurred in 1 of 4 patients in the cyclophosphamide group and in all patients (n = 5) in the other intervention group[205]. Although cyclophosphamide is often effective in patients with Behçet syndrome who have major vessel disease, remission may not be sustained and cyclophosphamide is associated with substantial toxicity, limiting its long-term use[132].

Monoclonal anti-TNF antibodies are recommended in refractory cases[193]. Observational, uncontrolled evidence showed that infliximab provides benefit in some patients with refractory disease[206–208]. Vascular remission has been achieved in up to 85% of patients with Behçet syndrome that is refractory to conventional immunosuppressants. Strikingly, unlike peripheral aneurysms, a regression and sometimes a disappearance of the PAA have been observed under treatment. However, relapses can occur after anti-TNF withdrawal[206]. Pulmonary endarterectomy is a new option in cases with CTEPH, although this procedure should be performed with caution and after effective immunosuppression[154].

As mortality rates have been high in surgically treated patients, surgery should not be undertaken except for in life-threatening situations[132,155,204,205]. Mortality from open surgery was reported in 3 studies that included 79 patients with PAA[132,204,205]. Six of eight patients who had open surgery died within the first month after surgery. However, a case series did report favourable outcome with lobectomy in patients presenting with giant aneurysms refractory to medical treatment[155]. Embolization may be necessary in patients at high risk of major bleeding[132,209,210].

Aortic aneurysms. Therapies for aortic aneurysms include corticosteroids and immunosuppressants, and often an endovascular or surgical treatment if the aneurysm is life-threatening (Table 2). A randomized, prospective trial comparing the efficacy and safety of infliximab with that of cyclophosphamide in severe Behçet syndrome with vascular involvement is ongoing (NCT 03371095). Moreover, a study of ten patients with major arterial involvement suggested that the IL-6-receptor inhibitor tocilizumab could be a safe and effective steroid- and immunosuppressant-sparing option for refractory arterial lesions in Behçet syndrome[211]. A pilot study of 13 patients with Behçet syndrome, including 5 patients with active cardiac or arterial involvement (3 with aortic aneurysm, 1 with aortic valve regurgitation and aortic root dilation, and 1 with stenosis or occlusion of multiple arteries), reported clinical and radiological disease remission after treatment with tofacitinib, a JAK1 and JAK3 inhibitor that targets T cell signalling[212]. However, prospective controlled studies are needed to confirm the therapeutic benefit of these treatments in this population.

Observational studies[128,157] reported a favourable outcome after vascular procedures in up to 70% of cases of Behçet syndrome, although relapse occurred in up to 30% of cases. Most recurrences occurred at the same arterial anatomical site[128,157]. The main causes of mortality are complications that occur in the anastomosis sites after the surgery[213].

Unlike pulmonary arteries, peripheral arterial aneurysms require surgery or stenting unless they are small, asymptomatic and are at low risk of rupture. Medical treatment with corticosteroids and immunosuppressants (that is, azathioprine) may be sufficient for small aneurysms. Surgery or stenting should not be delayed if the patient is symptomatic[193] (Table 2). Vascular surgery frequently leads to postoperative complications such as anastomotic leakage, occlusion or pseudoaneurysm[213,214]. Observational studies show that pharmacological treatment with immunosuppressants and corticosteroids is necessary in addition to surgery or stenting, as they decrease the risk of postoperative complications and recurrences compared with no medical treatment[157,213–215]. Medical treatment should ideally be started before an aneurysm repair is attempted.

Possible interventions in these patients include endovascular graft, bypass surgery, ligation, and graft interposition. In a case series, surgery was especially successful in non-pulmonary aneurysms in most patients (92%) at 7.4-year follow up[216]. For both aortic and peripheral arterial aneurysms, the choice of surgical intervention between graft insertion, ligation and by-pass surgery can be made according to the size and location of the aneurysm and the surgeon's experience. Synthetic grafts are preferred, as there is a higher risk of thrombosis with venous grafts in patients with Behçet syndrome[215].

Future perspectives

Pathogenesis and biomarkers

Despite progress in understanding the pathogenesis of Behçet syndrome, the exact mechanisms of vascular involvement in Behçet syndrome are far from being fully elucidated. Understanding the pathogenetic process and the complex interactions sustaining it is pivotal to determining the most effective treatment approach and to set up appropriate disease monitoring and risk assessment. Research is also needed to establish the contribution of epigenetic modulators (such as miRNA) in linking inflammation to thrombosis. The potential role of candidate miRNAs as biomarkers for timely monitoring of disease activity and assessment of thrombotic risk warrants investigation. Furthermore, the possibility of developing anti-miRNA molecules to inhibit circulating pro-thrombotic miRNAs should be explored. NETs are also emerging as promising biomarkers for monitoring disease activity and could represent a big step forward in the clinical approach to Behçet syndrome.

Diagnosis, monitoring and prognosis

As vascular Behçet syndrome is often incomplete (that is, not all major diagnostic symptoms are present) and patients lack other specific disease manifestations, diagnosis of Behçet syndrome can be particularly challenging. In this context, CFV thickness measurement by Doppler ultrasonography might be an additional feasible and reliable test in patients with suspected incomplete vascular Behçet syndrome. Further studies are needed to assess the diagnostic ability of CFV thickness in combination with conventional criteria to support the diagnosis of vascular Behçet syndrome.

A major challenge in monitoring disease is the lack of a tool to assess vascular Behçet syndrome activity and to estimate the risk of occurrence or recurrence of thrombotic events in patients with vascular involvement. The vascular damage index, a validated score to assess damage in systemic vasculitis, has been used in Behçet syndrome and is significantly associated with thrombosis ($P = 0.022$)[217]. However, experts agree on the need to develop a dedicated vascular activity score for Behçet syndrome, as the Outcome Measures in Rheumatology Clinical Trials group has proposed[188]. Furthermore, identifying treatment targets specific to vascular involvement that should be assessed in clinical trials and monitored during daily practice is essential for improving outcomes in patients with Behçet syndrome with vascular involvement. Efforts should also be made to develop prognostic scores to guide clinicians in tailoring an appropriate long-term cardiovascular prophylaxis in Behçet syndrome.

Treatment

Given the inflammatory nature of vascular Behçet syndrome, immunosuppressants represent the mainstay of treatment for vascular involvement; however, the risk–benefit profile of an add-on anticoagulant regimen is unclear. Randomized clinical trials are needed to clarify the efficacy and safety of long-term combination treatment with immunosuppressants and anticoagulants for the secondary prevention of thrombosis in Behçet syndrome, as well as to identify clinical subgroups of patients that might benefit most from this combined approach. Once data from clinical trials are obtained, new treatment guidelines are advocated to overcome current discrepancies among the different therapeutic approaches, and to guide the choice of the most appropriate therapeutic strategy.

Controlled trials of newer biologic DMARDs and other molecules are needed to identify treatment modalities that will decrease recurrence rates and prevent mortality, which are still high with current treatment strategies. In addition, preclinical and clinical studies are needed to elucidate the contribution of gut microbiota dysbiosis in mediating vascular involvement in Behçet syndrome, which might pave the way for new non-pharmacological approaches to the prevention of thrombo-inflammatory events based on tailored nutritional interventions.

Conclusions

Venous and arterial involvement account for a considerable burden of morbidity and mortality in Behçet syndrome. An impaired immune-inflammatory response, mostly sustained by neutrophil hyperactivation, directly mediates thrombogenesis in Behçet syndrome, in the absence of traditional cardiovascular risk factors. Accordingly, immunosuppressants represent the current mainstay of thrombosis treatment and secondary prevention, whereas the use of anticoagulants is still being debated. Of note, appropriate immunosuppressant (with or without anticoagulant) treatment should be set up after an accurate assessment of the causal relationship between the vascular event and Behçet syndrome, excluding additional causes unrelated to Behçet syndrome, which might instead require different therapeutic approaches, especially in geographic areas in which Behçet syndrome has a low prevalence. Future research addressing the diagnostic performance of vascular imaging and the pathogenetic contribution of epigenetic modulators and the gut microbiota might help to support diagnosis and to identify new therapeutic approaches to tailored cardiovascular prevention in Behçet syndrome.

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Additional information
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