

# Cerebral venous thrombosis revealing Behçet's disease in a Moroccan patient: A case report and literature review

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## Abstract

Behçet's disease is an inflammatory disease, the origin of which still remains unclear, and it has multiple *manifestations*, one of them being thrombosis. In this report, we describe the case of a 24-year-old Moroccan patient who presented with headache persisting for more than 2 weeks, which was found to be caused by cerebral venous sinus thrombosis. His medical history of recurrent oral and genital ulcerations, epididymitis and one episode of pericarditis led to the diagnosis of Behçet's disease. We could observe an almost complete relief of symptoms with colchicine therapy, and anticoagulation with warfarin was started for secondary prevention of thrombosis.

## Keywords

Cerebral venous thrombosis, Behçet's disease

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## Introduction

Behçet's disease (BD) is an inflammatory disease of unknown origin with auto-inflammatory features<sup>1</sup> and vasculitis as the main lesion, occurring in blood vessels of all types and sizes and therefore classified as a variable vessel vasculitis.<sup>2</sup> Its clinical manifestations—typically of self-limiting character—are manifold and consist of oral and genital ulcers, other cutaneous lesions such as erythema nodosum and pseudofolliculitis, ocular and neurological disease, positive pathergy reaction, as well as vascular disease<sup>3</sup> including arterial or deep venous thrombosis, (pseudo-)aneurysms and superficial thrombophlebitis.<sup>4</sup> One peculiarity of this pathology lies in its geographical distribution: prevalence of BD is particularly high along the Silk Road extending from the Far East to the Mediterranean Basin.<sup>5</sup> Here, we report the case of a young Moroccan patient in which BD was revealed by cerebral venous thrombosis.

## Case presentation

A 24-year-old man of Moroccan origin experienced progressive headache and left-sided neck pain for 18 days before hospitalization in our institution.

The patient had already received analgesic medication and antibiotics by several physicians assuming migraine, sinusitis, or poorly adapted glasses, without significant relief. Four days prior to admission, a contrastless cranial computed tomography (CT) scan revealed no abnormalities. However, due to persisting headache and inflammatory syndrome (C-reactive protein (CRP), 139 mg/L; erythrocyte sedimentation rate (ESR), 44 mm/h; white blood cell (WBC) count, 13,400/μL<sup>3</sup>), the patient was admitted to our emergency department. On admission, he set his Visual Analogue Score at 8–9 out of 10 and described the headache as throbbing,

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localized in the left frontal area with occipital irradiation. The patient did not experience any nausea, vomiting, or photophobia. He was in a good overall condition, aside from the debilitating headache and a subfebrile state.

His medical history comprised eight episodes of epididymitis since 2013; an episode of pericarditis in 2015, treated with aspirin and colchicine; an episode of sinusitis; and aphthosis. The latter occurred initially at the age of 6 and remained mainly oral, with some lesions on the scrotum reappearing from time to time.

Physical examination showed a wide-based and jerky gait, as well as a slightly unstable Romberg's test. There were no other neurological abnormalities. Furthermore, multiple red-purplish and indurated skin lesions that were hot and painful to the touch were found on both arms and the left leg. According to the patient, those nodules had been present for 4 years on the legs, whereas the lesions on his arms had appeared 6 days before admission, along with nocturnal hyperhidrosis. Moreover, folliculitis could be found on the lower extremity and the perineum, as well as two pustules on the scrotum. Our patient also complained about intermittent and migrating arthralgia.

A blood test on admission showed persisting inflammation (C-reactive protein, 173 mg/L) and elevated liver enzymes (aspartate transaminase (AST), 73 IU/L; alanine transaminase (ALT), 74 IU/L; gamma-glutamyltransferase (GGT), 151 IU/L). In order to exclude an infectious disease, blood and urine cultures were made but grew no microorganisms.

Because cerebral venous thrombosis (CVT) was suspected, the patient underwent a CT scan with contrast, which revealed thrombosis of the left transverse and sigmoid sinuses and of the left internal jugular vein. Thus, the patient was therapeutically anticoagulated with nadroparin (7600 UI twice daily) and hospitalized in our neurology department. CVT was confirmed 1 day later by magnetic resonance imaging (MRI), exhibiting only minimal parenchymal sequelae.

Given this clinical pattern, suspicion of BD arose and was reinforced by biopsies of the cutaneous lesions whose analysis revealed erythema nodosum, pseudofolliculitis and vasculitis. However, no hypermetabolic spots in large vessel walls could be visualized in the positron emission tomography (PET) CT images. Ophthalmological examination was normal and there was no pathergy reaction.

During his hospitalization, the patient was started on warfarin. One month later, colchicine therapy was added to his drug regimen at a dose of 1 mg per day. During this time, the headache was nearly no longer present, and 2 months later, the erythema nodosum had disappeared, with other cutaneous lesions having greatly diminished. Arthralgia still persisted nonetheless. To date, the symptoms of our patient have been stable for over 12 months.

On follow-up, we experienced difficulties in equilibrating our patient's anticoagulation treatment at first, requiring regular surveillance in our hemostasis and thrombosis unit. In light

of progressive improvement in our patient's international normalized ratio (INR) values, we now aim to maintain a lifelong anticoagulation treatment in order to prevent any further thrombotic events. Screening for thrombophilia (activated protein C resistance, antithrombin III deficiency, prothrombin G20210A mutation, anti-cardiolipin antibodies, lupus anticoagulant) was negative. We did not test protein C and/or S deficiency because of the ongoing warfarin treatment.

## Discussion

CVT is one of many possible manifestations of BD and is considered as a type of non-parenchymal neuro-Behçet's disease (NBD).<sup>6</sup> Our patient met both the International Study Group diagnostic criteria for Behçet's disease (ISGBD)<sup>7</sup> and International Criteria for Behçet's disease (ICBD),<sup>8</sup> as well as the criteria for definite NBD.<sup>6</sup>

CVT occurs in 8%–12% of patients, although reported frequencies differ between studies.<sup>9</sup> The association of those two conditions appears to be particularly frequent in young men.<sup>9,10</sup> Furthermore, CVT might be revealing BD in 30% of patients.<sup>11</sup> Diagnosis of CVT is ideally based on MRI and magnetic resonance venography as performed in our patient.<sup>12</sup>

The manifestations of CVT that we observed are typical, as CVT in BD mainly affects the superior sagittal, transverse, sigmoid and straight sinuses, causing intracranial hypertension and persisting headache in most patients. Other possible manifestations are papilloedema, facial palsy, nausea and focal deficits.<sup>11</sup> Another characteristic of CVT in BD that we could also observe is a higher frequency of progressive onset and less focal lesions and deficits compared to CVT due to other etiologies.

A possible explanation of these findings could be a difference in thrombogenesis between Behçet-associated CVT and non-Behçet CVT.<sup>10</sup>

In fact, thrombosis in BD is mainly caused by chronic inflammation and the resulting endothelial damage, but other hemostatic anomalies have recently been taken into account.<sup>5</sup> Endothelial damage is the consequence of an inflammatory process in BD, involving oxidative stress, reduced antioxidant activity and formation of auto-antibodies such as anti-oxidized low-density lipoprotein (LDL) and anti-endothelium antibodies. The resulting expression of tissue factor by endothelial cells and monocytes and exposure of subendothelial collagen then stimulate the coagulation cascade.<sup>13</sup> The endothelium also secretes pro-coagulant molecules such as von Willebrand Factor (vWF), thromboxane A2 (TxA2), platelet activator factor (PAF), E-selectin, P-selectin and type 1 inhibitor of plasminogen activators (PAI-1).<sup>14</sup> In addition, it reduces the activity of anti-thrombotic agents like prostacyclin (PGI-2), nitric oxide (NO), thrombomodulin (TM), tissue plasminogen activator (t-PA), urokinase-type plasminogen activator (u-PA) and tissue factor pathway inhibitor (TFP-1).<sup>14</sup>

BD patients—with or without thrombosis—show increased thrombin generation compared to thrombosis patients without thrombophilia or healthy controls.<sup>15</sup> This might be the consequence of increased fibrinogen levels, which we could also observe in our patient, that lead to increased protection of thrombin from inhibition by antithrombin. Moreover, thrombin stimulates platelet synthesis and secretion of PAI-1 and transforming growth factor- $\beta$  (TGF- $\beta$ ), leading to hypofibrinolysis.

Levels of protein C, S and antithrombin in BD do not seem to be lower than in healthy subjects.<sup>13</sup> Activated protein C resistance (APCR) was shown to be more frequent in BD than in the general population, but without an increase in thrombophlebitis in those patients.<sup>16</sup> However, testing for APCR in this case was negative.

Concerning genetically predetermined prothrombotic states, several studies demonstrated an association between a higher prevalence of factor V Leiden and thrombosis in Turkish BD patients, but this association could not be confirmed in non-Turkish BD patients with factor V Leiden.<sup>17</sup> For methylenetetrahydrofolate reductase (MTHFR) C677T polymorphism, no such association could be demonstrated either. On the contrary, an association between prothrombin G20210A mutation and thrombosis in BD is likely.<sup>17</sup> The same seems to be true for platelet glycoprotein Ia C807T/G873A polymorphism.<sup>18</sup> Increased homocysteine levels, platelet activation and NO levels and their role in thrombogenesis in BD patients are still controversially discussed.<sup>13</sup>

Screening for prothrombotic risk factors cannot yet be recommended for all BD patients with CVT, and further studies are necessary to determine their usefulness and impact on treatment choices and duration. To date, there is no consensus on whether a combined treatment of immunosuppressive agents and anticoagulation should be preferred over anticoagulation or immunosuppressive therapy alone in BD-associated CVT. Some authors argue that anticoagulation treatment might be dangerous in BD patients, given the risk of bleeding aneurysms, and that immunosuppressive agents are a more adapted treatment considering the etiopathology of thrombosis in BD.<sup>11,19</sup> In 2009, Saadoun et al.<sup>9</sup> concluded in a case series of 64 patients that adding immunosuppressive therapy does not influence either the neurological outcome or the risk of thrombosis relapse compared to anticoagulation alone in BD-associated CVT. A systematic review by Aguiar de Sousa et al.<sup>11</sup> in 2011 showed that immunosuppressive therapy is broadly used in BD-associated CVT, although we are still lacking evidence provided by a randomized controlled trial comparing different treatment options for CVT in BD. In their international consensus recommendations, Kalra et al.<sup>6</sup> suggest a temporary corticosteroid therapy in (sub)acute CVT and treatment with other immunosuppressive agents in case of antecedent CVT, active systemic disease or parenchymal NBD. In the

present case, we chose not to start immunosuppressive therapy as our patient responded very well to colchicine and we did not want to encounter the risk of adverse effects caused by immunosuppressants. Use of corticosteroids in this indication is also suggested by the European Stroke Organisation.<sup>20</sup> However, the strength of the latter's recommendations is described as “weak” by their authors.

There are no recommendations on necessity and duration of anticoagulation therapy, but systemic aneurysms should always be excluded before initiating this kind of treatment. Reported treatment duration ranges from 3 to 6 months to a long-term anticoagulation, especially if there is evidence for an underlying prothrombotic condition.<sup>6</sup> We opted for a long-term anticoagulation therapy in order to prevent an extension of the existing blood clot and to reduce the risk of thrombosis relapse, given the relatively high risk for this kind of event in BD.<sup>9</sup> In fact, most practitioners in non-endemic countries still tend to prescribe anticoagulation therapy in this indication.<sup>21,22</sup> In Turkey, where BD is highly prevalent,<sup>3</sup> there is no consensus on this issue either.<sup>23</sup>

## Conclusion

BD patients are more at risk of thrombotic events than the general population due to endothelial damage and a general prothrombotic state. It is crucial not to overlook the possibility of this diagnosis in order to be able to prevent thrombotic events. Nevertheless, there is still not enough evidence to determine which BD patients should undergo screening for other prothrombotic risk factors. There is also not enough data on whether immunosuppressive agents should be used and whether they should be combined with anticoagulation treatment for secondary prevention of thrombosis in BD patients. In the present case, our patient was set on coumarinic anticoagulation as there are only few reports about the use of novel oral anticoagulants in CVT.

Finally, we want to emphasize that CVT should not be omitted in the differential diagnosis of uncommon and persisting headache, which lasted more than 2 weeks until diagnosis in the case of our patient, with luckily only minimal sequelae.

## Declaration of conflicting interests

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## Ethics approval

Our institution does not require ethical approval for reporting individual cases or case series.

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## Informed consent

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