

Methotrexate Therapy in Deep Venous Thrombosis in Behcet Disease in Children

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Abstract

Behcet disease is a chronic condition, systemic disease, with etiopathology still incomplete known but in which are involved immune and genetic factors who may lead to inflammation and coagulation conditions. Authors present the case of a patient, masculine sex, 14 years old, diagnosed with Behcet disease, who had the vascular manifestation, with deep and superficial lower extremity vein thrombosis, that appeared at more than five years after first signs of disease (recurrent oral ulcerations). The patient had not presented positive markers for primary thrombophilia. Methotrexate therapy led to complete disappearance of lower extremity vein thrombosis, after about one year of treatment (as shown in Doppler vascular ultrasound). No side effect was observed related to Methotrexate therapy.

Conclusions: Methotrexate therapy may be a very efficient alternative treatment in deep lower extremity vein thrombosis in Behcet disease, without anticoagulants association.

Keywords Behcet disease; Venous thrombosis; Methotrexate

Introduction

Behcet disease is a chronic condition, systemic disease, with etiopathology still incomplete known but in which are involved immune and genetic factors who may lead to inflammation and thrombotic tendency [1,2]. The important manifestations of disease are determined by vasculitis process [3]. The disease has unpredictable reactivations and remissions. Behcet disease appears usually in young adults, between 20 and 40 years, but there were reported children cases also [4-6]. First pediatric case report was published in 1978 by Mundy and Miller [7]. Behcet's disease tends to be more common in the 'silk road' countries: Far East, Middle East and Mediterranean countries [8], with high prevalence in Turkey.

In time, there were proposed more diagnostic criteria sets, with a consensus in 1990 when, International Study Group for Behcet's Disease [9] elaborated five criteria: 1. oral ulcerations (aphthous or herpetiform) at least three times in one year; 2. recurrent genital ulcerations; 3. eye lesions, bilateral in most cases (uveitis or retinal vasculitis); 4. skin lesions (erythema nodosum, pseudofolliculitis, papulo-pustular lesions, acneiform nodules); 5. positive "pathergy test" (hyper-reactivity of the skin that occurs in response to minimal trauma, occurrence of a small red bump or pustule at the site of needle insertion of at least 2 mm, after 24-48 hours). For positive diagnostic was binding oral ulceration and two more positive criteria.

For increasing sensitivity, specificity and accuracy of those diagnosis criteria, in 2004 it was brought together an international work team from 27 countries, that in 2006, at International Conference of Behcet's Disease in Lisbon-Portugal, elaborated the

International Criteria for Behcet's disease (ICBD) [10-12]. These international criteria for diagnosis added a sixth one at those five already existing: vascular implication, one of the disease characteristics. For each criterion it is given a score: oral ulceration and eye lesions it points 2 for each and the rest of 4 criteria, 1 point each. A positive diagnosis it needs at least 3 points.

Others manifestations of the disease include: neurological issues (hemiplegia/hemiparesis, ataxia, cranial nerves palsy, sphincter dysfunction); cognitive dysfunction; movement disorder; gastrointestinal manifestations (ulcers that may appear anywhere along the gastrointestinal tract and may lead to abdominal pain, nausea, bleeding, intestinal perforation); renal manifestations (proteinuria, microscopic haematuria, and rarely glomerulonephritis [13,14], amyloidosis and renal vein thrombosis [15]); cardiac involvement (pericarditis, cardiomyopathy, endocarditis with valvular insufficiency, endomyocardial fibrosis, intracavitary thrombosis, and coronary artery disease) [16-22]. There are no pathognomonic tests for Behcet disease.

Case Report

A 17 year old patient, masculine sex, was admitted to the 2nd Pediatric Clinic, Cluj-Napoca, in August 2010 for pain and swelling in left lower extremity. The symptoms started two weeks before, with a week free interval after a tonsillectomy made in a territorially hospital; the patient received Ceftriaxonum and Clindamycinum, local therapy with Heparin, but because the evolution was unchanged the patient was transferred in our hospital. At initial presentation to our clinic, physical examination shown malaise, important asthenia, fever (38.3°C), pallor, skin pseudo folliculitis to sterile needle puncture,

axillary pustules, rough surface nodules, easy painful, red or purplish on the anterior and medial regions of right shank and ankle, swelling pain at knees, ankle, dorsal shank, mostly on the right leg, multiple oral ulcerations, in evolution he presented scrotal ulcerations also, pharynx congestion with pseudo membrane, no clinical pulmonary modifications, palpable pulse in all the arteries, without any focal neurological signs. Family history was irrelevant and his personal history revealed recurrent oral ulceration (almost every month) since early childhood. Laboratory tests detected an important inflammation syndrome: ESR (erythrocyte sedimentation rate) 70 mm/h, elevated C-reactive protein 19.5 mg/dl). Throat culture revealed no evidence of infection. Antinuclear antibodies (ANA), anti-DNA, p- and c- ANCA were negative. Antistreptolysin O titer was normal. Doppler vascular ultrasound detected right femoral-popliteal venous thrombosis, superficial segmented left retromaleolar venous thrombosis, after five months he presented also superficial right small saphenous vein thrombosis. The diagnosis established was Behcet disease with predominant vascular involvement. We point out that our patient was investigated for hereditary thrombophilia: anticardiolipin antibodies, S and C protein, antithrombin III, factor V Leiden mutation- were all negative. Cervical vascular ultrasound revealed normal vertebral arteries, neck collaterals and superior vena cava. Abdominal Doppler ultrasound did not find pathological modifications. Ophthalmic artery ultrasound and the ophthalmological examination were also normal. Echocardiography discovered left ventricular hypertrophy, in time this aspect became normal (January 2011). ECG was normal. Medications included Prednisone 40 mg/day, with a fast favourable evolution, except vascular ultrasound aspect. Because symptoms got head when we tried to reduce the doses, it appeared iatrogenic Cushing syndrome and lower extremity vascular ultrasound aspect remained unchanged, after 3 months we decided to replace the Prednisone therapy with Methotrexate 12.5 mg/week (in association with folic acid 5 mg/week).

Results

By Methotrexate therapy the patient had favourable evolution. He had no lower extremity tumescence or pain. Casual he presented oral ulcerations but without pain and those oral ulcerations cured faster. After one year of treatment with Methotrexate, Doppler vascular ultrasound shown full regression of lower extremity vascular modifications, this aspect keeping up in all next evaluations. Inflammation parameters remain negative, hematologic parameters, liver and renal functions remain also normal. No side effect was observed related to Methotrexate therapy.

Discussion

The patient was followed up in our hospital for three years, and from Behcet manifestations he presented: recurrent oral ulcerations, scrotal ulcerations, skin lesions like erythema nodosum and axillary pustules, positive "pathergy test" (it is known that is more often seen in those countries where Behcet disease is frequent and it is sporadic in Europe and USA [23], arthritis and superficial and deep lower extremity vein thrombosis.

Vascular implication in this disease includes both arteries and veins with various dimensions, in variable percentage 7, 7-38% [24]. Furthermore, a superficial venous thrombosis, especially if is recurrent or it has a migratory nature it must draw attention to Behcet disease [25]. Behcet vascular inflammation leads to stenosis, thrombosis and aneurysms. Most frequent vascular process is venous thrombosis, usually at lower extremity [26-31], as in our case, and this represents

85-93% [27] from vascular Behcet disease (the term vascular disease refers to patients that mostly present large blood vessels damage, often complicated with pulmonary aneurysms that may lead to death [32]). Secondly frequent thrombosis localization is cava vein [27], often reported in Mediterranean Basin and Europe [33]. Vascular affection appears in five years interval from the disease onset [34-36]. Some authors reports vascular manifestation, in 7 to 30% from patients, before clinical diagnosis of disease [34,35]. In our patient, vascular manifestations started after five years from first disease manifestations (oral ulcerations).

Even if, recently progresses were made to understand Behcet disease etiopathology, there are still lots of unknown and lots of polemics. So, even if Yurdakul and colab. allows that one third from patients have thrombophilia [37] and recently studies shows fibrinolytic disorders [38,39], other studies that had investigated thrombosis pathology in Behcet disease did not find major abnormality to coagulation or fibrinolytic mechanisms [27,40-42] that could lead to thrombosis in Behcet disease. Current data admit that Behcet thrombosis pathology do not involve coagulation disorders [43-50]. Investigation for hereditary thrombophilia was negative to our patient.

Behcet disease treatment is still a challenge. Even if anticoagulation therapy is used in some cases (cardiac or cerebral manifestations) [22,51,52], except pulmonary aneurysm and it is encouraging even for children, most authors considers it inefficient [53-58] (thrombosis appears even if it is used anticoagulants alone). Although venous thrombosis is frequent, embolism is sporadic, which is why anticoagulants, antiplatelet and fibrinolytic therapy are not recommended [32,59,60]. Another reason to avoid these medications is high risk for bleeding, especially in symptomatic or asymptomatic pulmonary aneurysms [61].

Considering anticoagulant therapy inefficiency, thrombosis pathology in Behcet disease, low risk of embolization and absence of thrombophilia profile in our patient, we preferred, in this case, not to use anticoagulation therapy but immunosuppressive drugs, who has positive proved effect [62-65], considering also European League Against Rheumatism (EULAR) references [66,67]. EULAR recommends corticosteroids and immunosuppressive drugs and discountenances anticoagulant and antiplatelet medication [66,68]. But, if patients associate thrombophilia risk factors, we could associate anticoagulant therapy also [69]. According to EULAR guide, for major vascular implication it recommends corticosteroids, Azathioprine, Cyclosporine A or Cyclophosphamide, although there is no firm evidence to guide the treatment of vascular manifestations in Behcet disease (Methotrexate therapy is recommended especially in Behcet disease nervous implication). Methotrexate proved to be efficient in venous thrombosis also.

Conclusion

Methotrexate therapy may be a very efficient alternative treatment in deep venous thrombosis in Behcet disease, without anticoagulants association.

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