Neurological manifestations of Behçet's disease

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Summary

Wechsler B, Sbaï A, Du-Boutin LTH, Piette J-C. Neurological manifestations of Behçet's disease. Schweiz Arch Neurol Psychiatr 2003;154:186–90.

Behçet's disease is a vasculitis of unknown origin characterised as a triad consisting of recurrent aphthous oral and genital ulcerations and uveitis. Articular, vascular and neurological manifestations may occur.

Neurological manifestations are observed in 5 to 20% of patients, particularly in males during the third decade and may be classified in:

– *Vascular involvement:* cerebral venous thrombosis with intracranial hypertension and/or cerebral arteries thrombosis or aneurysms. With anticoagulation, prognosis of cerebral venous thrombosis is usually good. Prognosis of arterial manifestations is unknown due to the rarity of cases.
– *Central nervous system involvement:* meningitis, meningoencephalitis eventually with psychic disturbance. Medullar and peripheral involvement are rare. Prognosis is generally severe due to a remitting/relapsing course and functional disability.

Delay in diagnosis is still too long, in part due to the rarity of the disease and in part due to inaugural neurological form. In such cases, extra-neurological inflammatory manifestations are of great clinical help. Extensive clinical examination is necessary, searching for cutaneous, articular, ocular and rarely digestive or renal manifestations. Neurological manifestations should be regarded as an emergency requiring urgent therapy. As for other vasculitides, corticosteroids in association with immunosuppressive agents (mostly cyclophosphamide or imuran) are used. In our experience prognosis is correlated with the localisation of the vasculitis and with therapeutic observance. Among treated patients relapses dropped from 71 to 21% and sequelae observed in 44% of cases, severe in 20% of cases.

Keywords: Behçet's disease; cerebral venous thrombosis; cerebral arteritis; meningoencephalitis

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Introduction

Behçet's disease is a vasculitis of unknown origin, characterised as a triad consisting of recurrent aphthous oral ulceration, recurrent genital ulcerations and uveitis. Behçet's disease has a worldwide distribution, although most cases are reported from Japan, the Middle East and the Mediterranean area. The prevalence in Northern Europe is 0.6 of 100 000. The observed increase in prevalence may be related to a better awareness of the disease and in some countries to migration. Our experience is founded on a series of 650 patients followed, for some of them, since 1974.

Neurological manifestations occurred in 35% of cases due to a selection bias. In the literature neurological involvement occurred in 5 to 20% of patients with Behçet's disease [1], particularly in male patients during the third decade. Prognosis of neurological manifestations is usually severe due to functional disability. In our series, central nervous system (CNS) manifestations occurred in 78 males and 31 females, mostly during the five years after diagnosis of Behçet's disease and concomitantly in 7.5% of cases. Nevertheless, in 3% of cases, neurological involvement was inaugural. Delay in diagnosis was long (mean 14.5 months). Meningoencephalitis is the most common manifestation. Medullar involvement, isolated meningitis and peripheral neurological involvement are rarely observed. Apart from CNS vasculitis, arterial and venous involvement are also observed, mainly the so-called *pseudotumour cerebri* due to cerebral venous thrombosis.

Cerebral venous thrombosis

In our experience cerebral venous thrombosis is observed in 8% of patients with Behçet's disease [2] and it accounts for one third of the neurological manifestations. It is characterised by intracranial hypertension, headache and papilloedema symptoms may also include fever, seizures, sixth nerve palsy and focal deficits in case of venous infarction. Onset of cerebral venous thrombosis is acute (less than 48 hours) or subacute (less than one month). Altered level of consciousness is possible in case of deep vein thrombosis. Cerebral fluid is always abnormal when studies have associated measurement of open lumbar pressure, cytology and level of proteins. Meningoencephalitis is rarely associated with cerebral venous thrombosis [3]. In our experience, only 4 patients out of 54 cases of cerebral venous thrombosis also had meningoencephalitis, always following steroids discontinuation.

Diagnosis of cerebral venous thrombosis is actually easy to establish with magnetic resonance imaging (MRI), much more sensitive than tomodensitometry. MRI and magnetic resonance angiography (MRA) are regarded the gold standard [4], but require rigorous interpretation [5]. MRI is also useful to diagnose venous infarcts and to look during follow-up for repermeabilisation of the occluded vessel that may be total (20% of cases) or partial (60% of cases). Classical cerebral angiography, sometimes complicated by arterial aneurysms on the site of arterial punction, is now rarely performed, except when deep vein thrombosis is suspected.

Contrarily to ancient data, prognosis of cerebral venous thrombosis is good with anticoagulation and steroids. Neurological symptoms disappear within 4 weeks and blindness due to optic atrophy becomes very uncommon (less than 2%). Relapses of cerebral venous thrombosis are rare and shunt derivation is exceptionally required by the persistence of papilloedema despite therapy. Duration of anticoagulation is not codified but we recommend a long-term administration, due to the chronicity of the disease.

Involvement of cerebral arteries

Arterial involvement is observed in 4% of cases of Behçet's disease and more frequently in patients with cerebral venous thrombosis (15%), thus suggesting the existence of a peculiar subset of Behçet's disease, called "vasculo-Behçet". Involvement of cerebral arteries is exceptional but there are now some reports on cerebral artery aneurysms and/or thrombosis leading either to strokes or to meningeal or intracerebral haemorrhagia [6–8]. Development of MRA will probably allow to determine the true incidence of such events in Behçet's disease.

Central nervous system involvement

CNS involvement has a poor prognosis. In the few cases reports with neuropathologic examination, the most significant neuropathological changes are small foci of complete or incomplete necrosis with a predilection for the brain stem, hypothalamus, internal capsule and basal ganglia. In the acute stage, oedema is observed, sometimes with pseudotumoural clinical manifestation, and this could explain the prompt efficacy of steroids.

Onset of CNS involvement is acute or subacute, sometimes associated with fever.

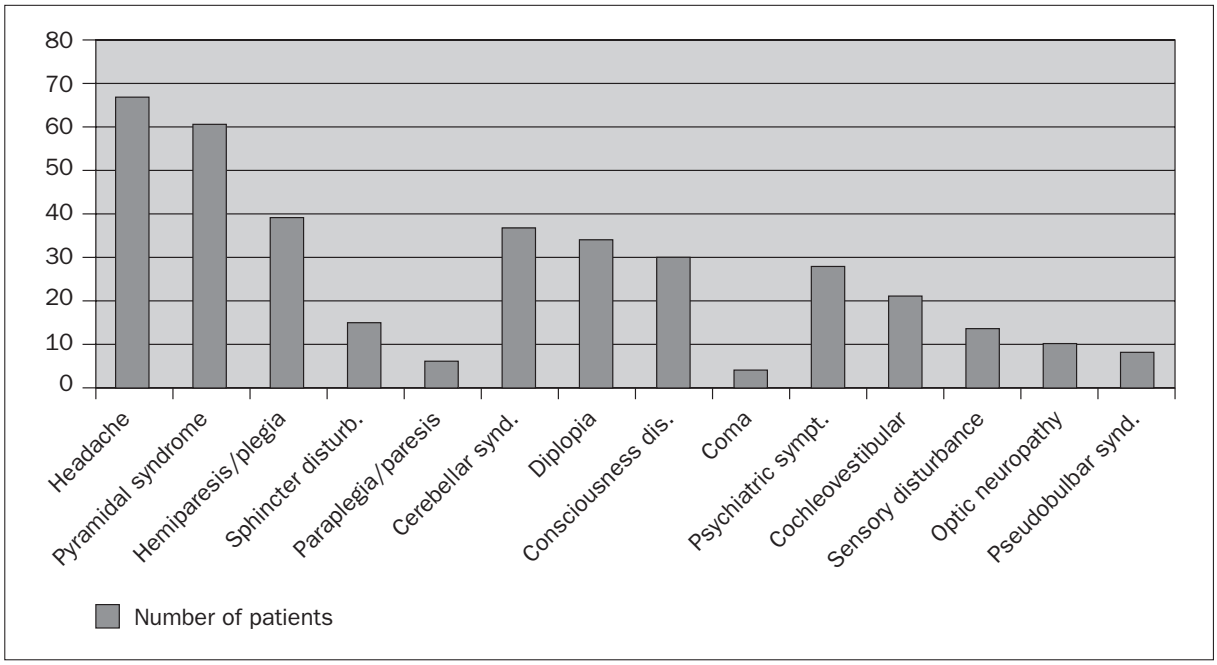
Acute isolated aseptic meningitis is possible and may announce a more severe attack. There is no specific aspect of Behçet's disease, but there is a predominance for brain stem and diencephalic involvement [6, 9–11]. The clinical manifestations are diverse with hemiplegia or paraplegia, ataxia and pyramidal syndrome. Headache is frequent. Figure 1 describes the neurological symptoms in our series of 109 patients with CNS involvement.

Psychiatric symptoms including personality changes are frequently observed in up to 54% of cases for Akman-Demir [6]. In some series, on late stage, dementia becomes evident in about 30% of affected patients [12]. Impotence and sphincter disturbances are also reported. Peripheral neuropathy or myopathy is exceptional. Focal muscle involvement has been described which may mimick thrombophlebitis [13]. Serum level of creatine phosphokinase is normal, and elevated values imply to rule out colchicine toxicity [14]. Medullar involvement, sometimes isolated is rarely observed and it responds well to corticosteroids. Parkinsonian syndrome, movement disorders, mutism, paroxysmal dysarthria-ataxia and deafness with labyrinthis have also been reported.

In our experience, cerebrospinal fluid is abnormal in 85% of cases, with pleocytosis and/or elevated protein content. Lymphocytic predominance was observed in 62% of cases, neutrophilic predominance in 22% and a mixed pattern in 12% of cases.

Progress in imaging has been important in the past years. MRI is actually the best imaging technique for diagnosis and follow-up. In the acute phase MRI is always abnormal and fairly correlating with clinical data [9, 15–18]. Lesions are usually

Figure 1 Neurological symptoms in a personal series of 109 patients with CNS involvement.



nonhaemorrhagic, multiple, extensive and confluent without predilection for the periventricular regions. They predominate within the white matter (70%), the brain stem (60%), the basal ganglia and the thalamus (40%) (fig. 2). However, the MRI findings are not specific for Behçet's disease and similar aspects may be observed in other CNS vasculitides and systemic lupus erythematosus though the brain stem is rarely affected in the latter. For Koçer et al. [17] Behçet's disease lesions extend along long fibre tracts and spare red nucleus suggesting that the downward extension is due to oedema. Lesions are generally not compatible with arterial territories. The disappearance of perilesional oedema is consistent with a probable inflammatory-venous pathogenesis. Effectively, hypersignals can regress or eventually disappear with therapy, but generally they persist in T_2-weighted or FLAIR sequences, helping a retrospective diagnosis. During follow-up, it is possible to observe new signals without clinical neurological symptoms evoking silent disease activity [15].

Diagnosis

When neurological manifestations occur at the same time or after typical mucocutaneous manifestations, diagnosis of Behçet's disease is unquestionable. The international criteria of classification

Figure 2 Localisation of hypersignals on MRI.

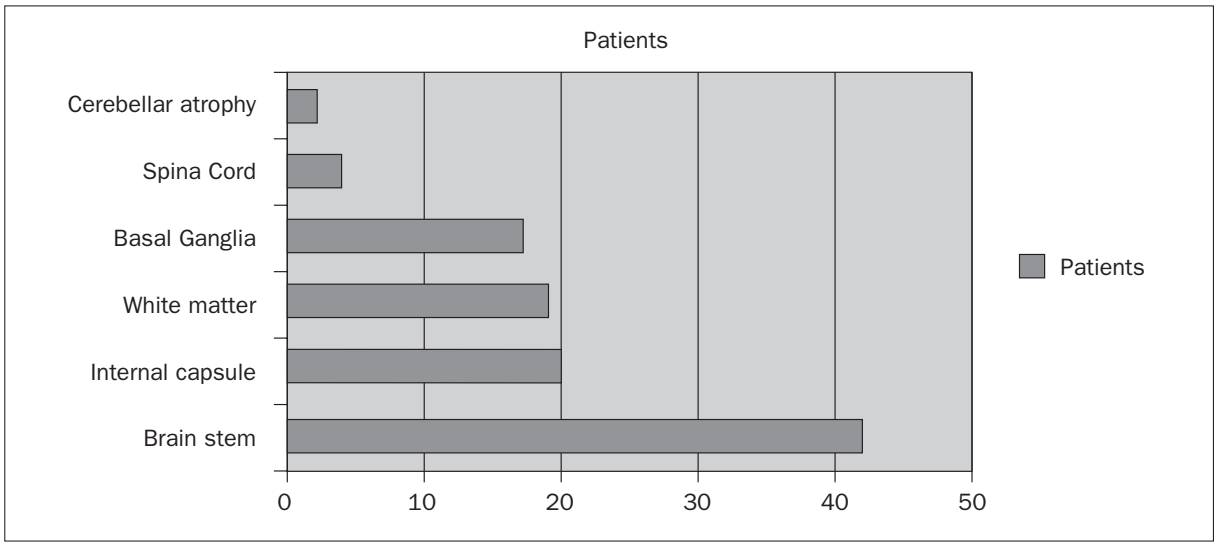


Table 1 Classification criteria (International Study Group for Behçet's disease [19]) with a sensitivity of 91% and a specificity of 96%.

recurrent oral ulceration: Observed by physician or patient, which recurred at least 3 times in one 12-month period.
plus two of:
recurrent genital ulceration: aphthous ulceration or scarring, observed by physician or patient
eye lesions: anterior uveitis, posterior uveitis, or cells in vitreous on slit-lamp examination; or retinal vasculitis observed by an ophthalmologist
skin lesions: erythema nodosum observed by physician or patient, pseudofolliculitis, or papulopustular lesions; or acneiform nodules observed by physician in post-adolescent patients not on corticosteroid treatment
positive pathergy test read by physician at 24–48 hours

These findings are applicable only in absence of other clinical explanations.

have a specificity of 96% and a sensitivity of 91% (table 1) [19]. Clinical examination looking for oral or genital aphthae (active or scars) and/or pseudofolliculitis and precise medical history are essential. Hypersensitivity to puncture, erythema nodosa or superficial thrombophlebitis are of importance. In Western countries, pathergy test is of poor sensitivity due, in part, to the use of disposable needles. Ocular involvement had to be searched for with slit-lamp examination and retinal angiography. When neurological manifestations are isolated, infection must be ruled out. The presence of other inflammatory manifestations (arthritis, thrombophlebitis, aneurysms, colitis) is of great clinical help. In contrast, the result of typing for HLAB51 (present in 50% of cases in our experience and in 84% of cases in Turkish series) is neither a diagnostic nor an exclusion criterion. When uveitis is associated with neurological manifestations, the differential diagnosis is mainly restricted to sarcoidosis, Whipple's disease, ocular/CNS lymphomas. A "Behçet's MINUS syndrome (multifocal intermittent neurological and uveitic syndrome)" was suggested by Lueck et al. for patients without full-blown clinical features of Behçet's disease in order not to delay therapy [20].

Course and therapy

Spontaneously, Behçet's disease has a remitting/relapsing course, and its neurological manifestations gradually cause irreversible disability. After 10 years all patients had at least one relapse in the series of Siva et al. [3]. Among patients with neurological manifestations, 14% are disabled at 3 years for Kidd et al. [10] and 50% are disabled or dead after 3 years of follow-up for Akman-Demir et al. [6]. In the experience of our tertiary care centre, good prognosis is correlated with the absence of pons involvement ($p = 0.03$), neutrophilic meningitis ($p = 0.037$), and with good therapeutic observance ($p = 0.002$). Only 20 out of 109 patients (18%) did not improve with therapy and 80% of them were already physically or mentally dependent at admission. Among treated patients, with a mean follow-up of 96 months, the frequency of relapses dropped from 70 to 21%. Sequelae were observed in 48 cases (44%), mild to moderate in 26, important to severe in 22, including sphincter disturbances in 22.

In the absence of controlled trials dedicated to neurological manifestations of Behçet's disease, therapeutic guidelines are mainly experience based. We think neurological manifestations should be regarded an emergency requiring urgent therapy. The decision to treat is easy when diagnosis is established, whereas it may be difficult when Behçet's disease is only suspected, leading to the concomitant use of antibiotics. As for other vasculitides, corticosteroids are initially administered by pulsed therapy (1 g of methylprednisolone on 3 consecutive days) in association with immunosuppressive therapy (azathioprine 2.5 mg/kg/d) or cyclophosphamide (0.750 g/m^2 intravenously every 4 weeks). Duration of immunosuppression is not codified, but we generally recommend not to stop it before two years. Corticosteroids are progressively tapered and maintained on a long-term basis at a dosage of 0.1 mg/kg/d, in association with colchicine, antiplatelet agents and adequate prevention of steroid-induced osteoporosis. Colchicine withdrawal may be followed by prompt recurrences of CNS manifestations, as we have reported [21].

Diversity and severity of neurological manifestations of Behçet's disease are particular among vasculitides. Due to the lack of data on the aetiology and pathophysiology of Behçet's disease and the absence of specific biological markers, intensive and sustained symptomatic therapy with long-term follow-up remain the only tools to counteract the severe spontaneous prognosis of Behçet's disease-related neurological involvement.

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