
Behçet's disease: features of neurological involvement in a dedicated centre in Italy

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ABSTRACT

Objective. The aim of the present study was to retrospectively assess the prevalence of neurological involvement and the clinical patterns of presentation in a monocentric cohort of patients with BD, who have been followed in the last twenty years at our centre.

Methods. One hundred and seventeen patients were retrospectively studied. The male/female ratio was 1.6:1, with a mean disease duration of 11 ± 5 years. Their mean age was 42 ± 9 years (min:18, max:77), while the mean age at disease onset was 25 ± 4 years (min:10, max:58). The mean \pm SD duration of follow-up at our centre was 7 ± 2 (min:1, max:11) years.

Results. Neurological involvement was observed in 38% (44 patients, 36 males and 8 females; mean age at onset 25 ± 4 years). Organic brain involvement, demonstrated by MRI was due to ischaemic pons-mesencephalon lesions in 19 patients and to meningoencephalitis with brainstem involvement in 16. Peripheral nervous system involvement was confirmed by electroneuromyographic study in 4 patients, and consisted of peripheral neuropathy prominent in the lower extremities in all cases; we have also observed only 2 cases of endocranial hypertension and 3 BD patients suffering from pulsatile, severe headache, without abnormal neurological examination, responding only to medium-high doses of steroids. Excluding peripheral neuropathy and isolated headache, the onset of CNS involvement (total prevalence: 32% of the cohort) was observed in 2 patients within the first year from the onset of BD, in 4 cases between the first and the third year, in 24 between the third and the fifth year, 7 between the fifth and the tenth year; none presented a CNS involvement after the first 10 years of disease.

Conclusions. Neuro-BD is more frequent in young males and it never represents a presenting feature of the disease. The most frequent time of onset of neurological involvement seems to be within the first 10 years of disease. Since neurological involvement may result in severe functional disability or be a life-threatening disease, a careful follow-up during the first years after onset is recommended.

Introduction

Behçet's disease (BD) is a systemic, chronic-relapsing vasculitis, typically characterised by recurrent oro-genital ulcers, ocular inflammation and skin manifestations; articular, vascular, gastro-enteric and neurological involvement may also occur (1, 2). The onset of disease typically occurs in patients in the late third and early fourth decades of life. Despite BD has a worldwide distribution, it is most commonly seen in the Middle East, Far East and the Mediterranean basin, a particular trend that reminds of the ancient Silk Road (3, 4). Moreover, the prevalence rates of BD in the endemic areas is strongly correlated to the prevalence of human leukocyte antigen (HLA)-B51. It is believed that a complex background with both genetic and environmental factors contributes to the disease development. Since there are no established laboratory findings to define BD, the diagnosis remains mainly dependent on the identification of the typical clinical pictures. In 1990 the International Study Group (ISG) for BD has proposed the validated classification criteria; to fulfill these criteria a *conditio sine qua non* for the diagnosis must be the presence of recurrent oral ulcers, together with two or more of the following: recurrent genital ulcerations, eye lesions, skin lesions or a positive pathergy test (5). Globally, the

Competing interests: none declared.

clinical profile of BD is extremely variable; while prevalent muco-cutaneous involvement and arthritis represent the only clinical features in patients with a benign disease subset; there are other patients who develop potentially sight- or life-threatening manifestations, due to ocular, neurological or major vascular involvement. Although not included in the ISG criteria for BD, neurological involvement represents the second main cause of mortality, preceded by large vessel disease (6). The presence of neurological involvement is well described in BD (neuro-BD), with a prevalence that varies from 2% to 50% (7-10). Despite immunosuppressant therapy, neurological involvement is still considered a worrying complication of the disease, representing an important cause of morbidity and mortality. The aim of the present study was to retrospectively assess the prevalence of neurological involvement and the clinical patterns of presentation in a mono-centric cohort of patients with BD, who have been followed in the last twenty years at our centre.

Patients and methods

We carried out an analysis by reviewing the medical documentation of all patients with a diagnosis of BD consecutively seen in our centre from 1989 to 2009. One hundred and seventeen patients were retrospectively studied. The male/female ratio was 1.6:1, with a mean disease duration of 11 ± 5 years; their mean age was 42 ± 9 years (min:18, max:77), while the mean age at disease onset was 25 ± 4 years (min:10, max:58). The primary aims of the study were to assess the profile of neurological involvement in a cohort of patients with BD, who have been followed in the last twenty years in our Institution. The secondary aim was to explore any potential demographic and/or clinical difference between the subset of patients with neuro-BD and the other patients of the cohort. Therefore, we retrospectively assessed the prevalence of all documented neurological signs and symptoms reported during the follow-up in our cohort; moreover we evaluated the timing of the onset of central nervous system (CNS) involvement,

Table I. Demographic profile.

| | |
|--|---|
| Number of patients | 117 |
| M/F | 72/45 |
| Mean \pm SD age (min-max) (years) | 42 ± 9 (18-77) |
| Mean \pm SD age at disease onset (min-max) (years) | 25 ± 4 years (10-58) |
| Mean \pm SD disease duration (min-max) (years) | 11 ± 5 (1-31) |
| Mean \pm SD follow-up duration (min-max) (years) | 7 ± 2 (1-11) |
| ISG criteria for BD | 94/117 (80%) |
| HLA B51 positivity | 66% (77/117) |
| Geographical origin | Italy 112 Morocco 2 Turkey 1 Greece 1 Albania 1 |

Table II. Clinical manifestations other than neurological reported during the follow-up.

| Clinical manifestations | Number (%) |
|-------------------------------|------------|
| Oral ulcers | 94 (80%) |
| Genital ulcers | 84 (72%) |
| Joint involvement | 57 (49%) |
| - knees arthritis | 43 |
| - wrist | 6 |
| - elbow | 5 |
| metatarsophalangeal joints | 3 |
| Skin lesions | 55 (47%) |
| - Erythema nodosum | 45 |
| - Papulopustular lesions | 27 |
| Skin pathergy reaction | 34 (29%) |
| Ocular involvement | 47 (40%) |
| - Posterior uveitis | 32 |
| - Anterior uveitis | 27 |
| - Retinal vasculitis | 21 |
| Panuveitis | 17 |
| Vascular thrombotic events | 26 (22%) |
| - deep vein thrombosis | 17 |
| - superficial vein thrombosis | 4 |
| - arterial thrombosis | 4 |
| arterial aneurysm | 1 |
| Intestinal involvement | |
| - multiple ulcers | 14 (16%) |

defining it as the timing of the clinical and magnetic resonance imaging (MRI) documented diagnosis. The mean \pm SD duration of follow-up at our centre was 7 ± 2 (min:1, max: 11) years. Finally, we compared the prevalence of each main clinical finding other than neurological in neuro-BD patients with the other patients of the cohort. The demographic profile of the cohort studied is summarised in Table I.

Statistical analysis

All the results are expressed in mean \pm standard deviation (SD). Chi-square test was used to evaluate the differences among the subgroups. A *p* value <0.05 was considered statistically significant.

Results

One hundred and seventeen patients were retrospectively studied. Cumulative clinical manifestations other than neurological reported during the follow-up are shown in Table II. Neurological involvement was observed in 38% (44 patients, 36 males and 8 females; mean age at onset 25 ± 4 years). Organic brain involvement, demonstrated by MRI, was due to ischaemic pons-mesencephalon lesions in 19 patients and to meningoencephalitis with brainstem involvement in the other 16. Peripheral nervous system involvement was confirmed by electroneuromyographic study in 4 patients, and consisted of peripheral neuropathy prominent

in the lower extremities in all cases; we have also observed only 2 cases of endocranial hypertension due to cerebral venous thrombosis. Moreover, we included in the group of neurological involvement 3 BD patients suffering from pulsatile, severe headache, without abnormal neurological examination, responding only to medium-high doses of steroids; these patients were characterised by the presence of non-specific MRI lesions and the onset of headache seemed to be associated with signs and symptoms of disease relapses other than CNS (*i.e.* mucocutaneous, articular features). The most common presenting symptoms among patients who experienced central nervous system involvement are shown in Fig. 1. Comparison of the prevalence of the neurological involvement according to the gender showed that about 50% (36/72) of the males of the cohort developed it, in contrast with 18% (8/45) of the females ($p < 0.0005$).

Excluding peripheral neuropathy and isolated headache, the onset of CNS involvement (total prevalence: 32% of the cohort) was observed in 2 patients within the first year from the onset of BD, in 4 cases between the first and the third year, in 24 between the third and the fifth year, 7 between the fifth and the tenth year; none presented a CNS involvement after the first 10 years of disease (Fig. 2).

Comparing neuro-BD with other patients who did not experience neurological involvement, the only significant difference in the prevalence of the typical features of disease was in the frequency of ocular involvement, which was 25% (11/44) and 49% (36/73), respectively ($p < 0.001$). Additionally, when ocular involvement was present, the most frequent ocular lesion in patients with neuro-BD was represented by anterior uveitis (8/11), versus a prominent prevalence of posterior uveitis and/or retinal vasculitis (30/36) in patients without neurological involvement.

Discussion

This study was aimed at assessing the profile of neurological involvement in a mono-centric Italian cohort of BD. Although not included in the com-

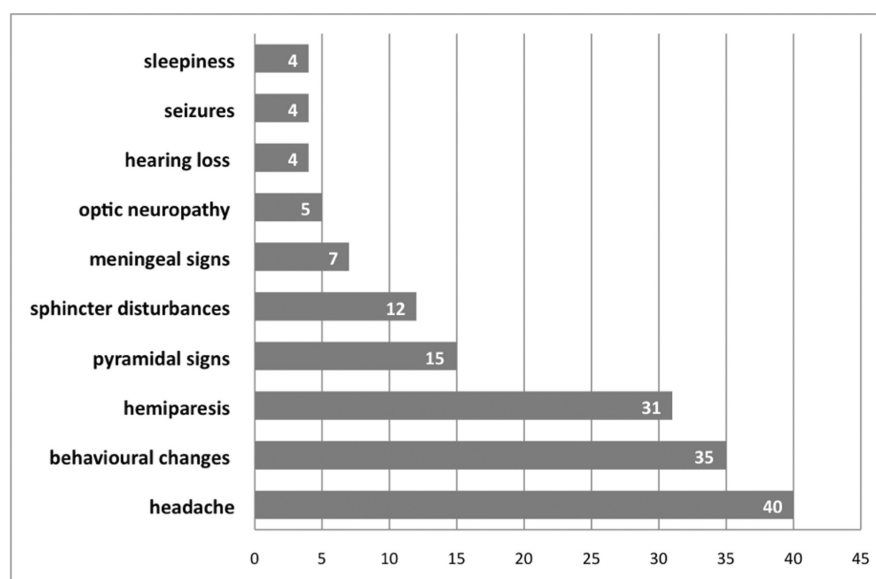


Fig. 1. The most common presenting neurological symptoms.

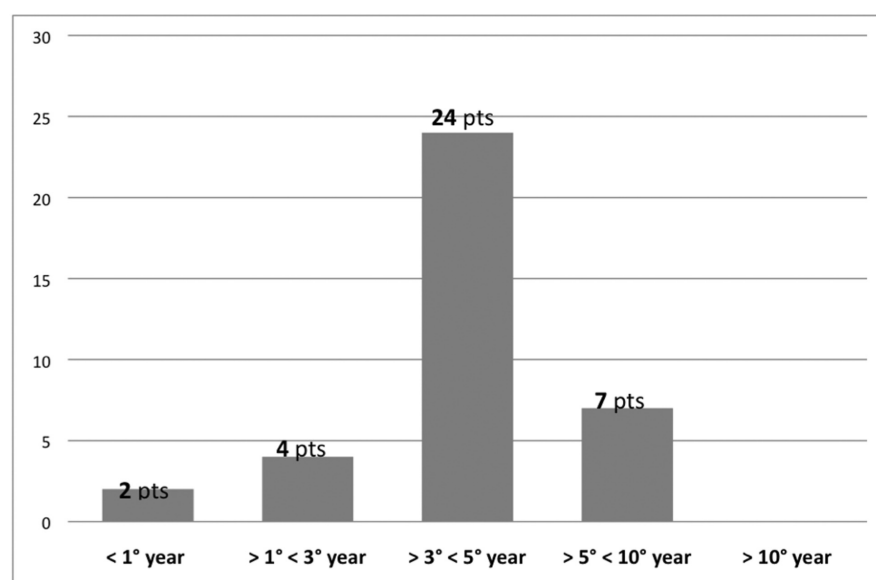


Fig. 2. Timing of the onset of CNS involvement.

monly used criteria for BD, neurological involvement may result in severe functional disability or, sometimes, be a life-threatening disease (6).

There have been many studies describing the prevalence of neuro-BD in different countries. The results of the present study indicate a high prevalence of neurological involvement compared to the literature data, and this is probably partially due to the hospital-based nature of our cohort, that may potentially create a selection bias (*i.e.* selection of patients with more severe disease); moreover, about one third of our patients were admitted to our Insti-

tution as in-patients. While another Italian retrospective multicentre study (11) reported a somewhat high prevalence of 17.5% CNS involvement throughout the course of the disease, we detected a still higher prevalence of CNS involvement of 32%, with a global frequency of neurological involvement of 38%. Therefore, the real prevalence of neurological involvement in BD patients should be better evaluated in prospective studies.

Neuro-BD is usually categorised into two main groups: parenchymal brain involvement (more frequent) and non-parenchymal or vascular disease (10, 12).

The most frequent brain lesion is represented by a parenchymal involvement, similarly to most of other cohorts so far reported (7-10); indeed, the most common neurological lesions occurred in our cohort were represented by ischemic pons-mesencephalon lesions and by meningoencephalitis with brainstem involvement. Only a few cases in our cohort experienced peripheral nervous system involvement, while endo-cranial hypertension was very uncommon. None of the patients reported a mixed pattern of neurological involvement. Headache represents one of the most common clinical manifestations of neuro-BD and was reported in our study in all patients with an evidence of CNS involvement. In addition to this kind of headache, we also reported in the group of patients with neurological involvement three cases of "non-structural headache", a relatively new entity characterised by bilateral, pulsatile, moderately severe headache, commonly associated with signs or symptoms of disease flare-ups, not associated with abnormal neurological examination (13, 14). The typical response to medium-high doses of steroids only makes this peculiar clinical feature complex, and certainly deserves further specific studies. In line with previous studies, our results have shown a more common neurological involvement in young males. It rarely is the first disease manifestation. The onset of CNS involvement in the cohort studied was localised in the first 10 years, with a higher incidence rate in the first 5 years. Notably, none of the neuro-BD patients studied presented neurological symptoms and/or signs at the onset of BD, as well as none presented a neurological involvement after the first ten years from the onset. These results are, in our opinion, important since the timing of onset of neuro-BD strongly affects the scheduling of the follow-up timing. Interestingly, we observed a less frequent ocular involvement in neuro-BD

patients compared to other subjects of the cohort, even if this is in contrast with literature data which show a higher prevalence of ocular involvement (more than 50%) (7, 10). Moreover, data from large cohorts showed that when ocular involvement is present in neuro-BD patients, it mainly involves the posterior ocular segment; in our experience, however, we observed a prominent prevalence of anterior uveitis. Indeed, neuro-BD is still related to high rates of morbidity and mortality: early recognition of severe organ involvements could certainly represent an important element to prevent irreversible damages due to the chronic-relapsing course of the disease. As suggested in other systemic autoimmune diseases, a disease-specific set of quality assessment tools should help physicians deliver a high quality of care in neuro-BD patients (15-17).

Conclusions

Among Italian patients, neuro-BD is more frequent in young males and it never occurs as a presenting feature of the disease. The most frequent time of onset of neurological involvement seems to be within the first ten years of the disease. Since neurological involvement may result in severe functional disability or may be life-threatening, a careful follow-up during the first years after onset is strongly recommended.

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