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ORIGINAL ARTICLE

Neurological involvement in North Italian patients with Behçet disease

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Abstract The aim of this study was to evaluate neurological involvement in a series of 110 North Italian patients with Behçet disease (BD), a multisystemic vasculitis of unknown origin, followed up for a period of 5 years. During this time, 27 (24.5%) patients with neuro-BD were identified. Twenty out of 27 showed at least one acute attack in their clinical course. In 14 of them, a neurological evaluation was carried out during the attack. The other 13 patients were evaluated during a remission phase. The onset of neuro-BD was usually characterized by an acute attack with motor symptoms (66.6%) and behavioural/cognitive changes (47.6%), while headache was more frequent in the remission phase (76.9%). On magnetic resonance imaging, large brain-stem/diencephalon lesions were usually seen during the attack. In the remission phase, they were often located in the white-matter. Aspecific cerebrospinal fluid abnormalities were usually seen during the attacks. Cerebrospinal fluid analysis together with radiological and clinical features seems to be useful for the differential diagnosis in these patients.

Keywords Behçet disease · Neurological involvement · MRI · Behavioural changes · CSF analysis

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Introduction

Behçet disease (BD) is a multisystemic vasculitis of unknown origin, characterized by oral and genital ulcerations, uveitis and skin lesions whose clinical spectrum may include articular, gastrointestinal and neurological involvement [1, 2]. The disease typically affects young adults with a male/female ratio ranging from 11:1 to 1:1 in different countries [3].

Nervous system involvement represents an important morbidity and mortality factor. Although the exact prevalence is difficult to establish due to the wide range of reported frequency (from 4.8 to over 60%), the most representative clinical series describe a prevalence between 4.8 and 6.7%, while in autopsy studies it is found in about 20% of patients [4–6]. Recently, a prospective 20 years follow-up study showed a frequency, respectively, of 13% among men and 5.6% among women [7].

Two patterns of central nervous system (CNS) involvement have been described:

(a) the *parenchymal* involvement, or ''neuro-Behçet,'' in which the CNS damage is primarily due

to venulitis leading to a large peri-lesional oedema. This process involves preferentially brainstem, basal ganglia, diencephalic structures and internal capsules inducing pyramidal or motor symptoms, cognitive alterations, ataxia and sphincteric disturbances;

(b) the *non-parenchymal* one, or ''vascular-Behçet,'' in which the parenchymal damage is secondary to a pathological process localized in the large venous or, more rarely, arterial vessels [8].

Although BD is considered a ubiquitous disease, it occurs mostly along the ancient ''silk road,'' from East Asia to the Mediterranean Sea. Turkey has the highest prevalence (80–420 cases per 100,000 inhabitants), whereas it is lower in western countries (0.64 per 100,000 in UK and from 0.12 to 0.33 in USA) [1, 2, 9–13].

In Italy, BD is considered a rare disease. Genetic and environmental factors can account for the differences in the development and clinical expression of the disease [12]. The purpose of this study is to describe a series of North Italian BD patients with neurological involvement and to evaluate the instrumental and neuro-imaging correlations with the clinical features.

Patients and methods

All the cases (110 patients: 63 females, 47 males) fulfilling criteria of International Study Group for BD [14], observed between 1999 and 2004 at Unit for BD of our department, underwent a complete and accurate neurological evaluation. The BD unit includes rheumatology, neurology, neuro-radiology, ophthalmology, dermatology and genetic specialists. All the observed cases were Caucasian and were from the northern part of Italy.

During this time, 27 cases with neurological manifestations related to BD were identified. For each patient, the neurologist indicated the appropriate diagnostic protocol according to clinical picture. Instrumental evaluation included magnetic resonance imaging (MRI) in all patients and single-photon emission tomography, electroencephalogram, visual evoked potentials, somato-sensitive evoked potentials (SSEP) and cerebrospinal fluid (CSF) examination (when authorized after informed consent). For the cognitive evaluation, the Wechsler memory scale was used [15]. In patients whose neurological manifestations occurred before the first evaluation, previous clinical and instrumental investigations were reviewed thoroughly.

Apart from routine haematological and biochemical tests, laboratory evaluation comprised antinuclear antibodies (ANA), lupus anticoagulant test (LAC) and anticardiolipin antibodies (aCL) determination.

Magnetic resonance imaging was performed using 1-T General Electric Signa Horizon unit with standard T2-weighted FLAIR sequences (8,002 ms TR, 104 ms TE, 2,000 ms TI, 6.0 mm thickness, 1.0 mm gap, 256×192 matrix). If suggested by clinical picture, MRI sequences of cervical spine were also done.

SPECT was done after intravenous injection of a flow tracer (99 m Tc-HMPAO 740 MBq). The images were acquired with a dual-headed gamma-camera (Vertex; ADAC, Milpitas, CA, USA) with fan-beam collimators (FWHM 8 mm), 128×28 matrix; axial 3.2 mm thick were subsequently reconstructed. Visual interpretation of the images was performed as previously described [16].

Based on the proposal of Akman-Demir et al. [17], clinical courses and phases were classified as follows: (a) the *primary progressive course*, a progressive worsening of neurological manifestation without any identifiable acute attack; (b) the *secondary progressive course*, a continuous worsening of neurological condition after one or more attacks and, finally, (c) the *silent neurological involvement*, the presence of neurological signs without clinical symptoms except for tension headache or dizziness.

Concerning the clinical phases, an *acute attack* was defined as an acute neurological disturbance lasting more than 24 h. Otherwise, the patients were considered as observed in the *acute phase* if evaluated within a month of the onset of the neurological symptoms, or in the *remission phase*, when evaluation was performed at least 1 month after an acute attack without any progression of neurological symptoms.

Results

Twenty-seven patients (7 males, 20 females) with neurological complaints out of 110 patients (24.5% of the cases) with BD observed from 1999 to 2004 at our BD unit were evaluated. The mean follow-up time was 23 months (range 6–36 months). The mean age at onset of BD was 27.7 ± 2.08 years; the mean duration of the disease at the time of assessment was 13.7 years (range 4–38 years). The mean age at the first neurological presentation was 34.7 ± 1.7 years. Five patients had neurological symptoms as first manifestation of BD. During the study period, no patient died.

From the therapeutic point of view, all the patients with an acute CNS involvement underwent cyclophosphamide pulse therapy associated with high-dose glucocorticoids (1 mg/kg/day). One patient received anti-TNFα therapy (Infliximab 5 mg/kg every 6 weeks), due to poor response to cyclophosphamide.

Clinical and laboratory picture

Concerning the pattern of neurological manifestations, 26 had a neuro-Behçet and only 1 was associated with vascular-Behçet/neuro-Behçet. During the period of observation, the disease course may be classified as showed in Table 1.

Twenty out of 27 patients showed at least 1 acute attack in their clinical course (3 patients had 2 attacks and 3 suffered 3 attacks), with a total of 29 attacks. A complete neurological evaluation during the attack was carried out in 14 patients (10 patients with 1 attack, 1 patient with 2 attacks and 3 patients with 3 attacks) with a total of 21 acute attacks observed. The remaining 13 patients were evaluated during a remission phase.

In order of frequency, symptoms/signs were as reported in Table 2. The major cognitive disturbance was mild memory impairment. Isolated behavioural changes, observed in four patients, were characterized by excessive daytime sleeping and/or hyperphagia, sexopathy and anxiety disorders (agoraphobia). Two patients had both behavioural and cognitive impairment. In the great majority, the clinical picture was characterized by an association of several symptoms/signs. As to sensitive disturbances, only one patient had significant neurological symptoms. SSEP alterations were found in ten patients. Among these, five showed lesions in the postero-lateral columns of the spinal cord. None of them showed a peripheral neuropathy. All the patients, except one, had sensitive alterations associated with pyramidal signs.

Haematological and biochemical analyses (data not showed) did not reveal any significant alteration nor correlations to the clinical pictures. ANA, aCL and LAC were absent in all the patients with neurological involvement.

Cerebrospinal fluid evaluation was performed in 14 patients (7 during an attack, 7 in the remission phase). During the acute phase, five out seven CSF samples found an abnormally raised protein and/or cell count (mixed lymphocyte/neutrophil pleocytosis) while two were negative. In the remission phase, only one out of seven showed this alteration. Oligoclonal bands associated with an intrathecal synthesis of immunoglobulins were observed in one patient with acute neurological picture.

Four patients (three males/one female) presented high degree of disability due to a locked-in syndrome, a right emiparesis associated with extra-pyramidal symptoms, a pseudo-bulbar syndrome (dysarthria, dysphagia and emotional incontinence) and a severe cognitive and behavioural disturbance.

Table 1 Distribution of the cases of neuro-Behçet disease according to clinical course and phase of the neurological involvement

	Patients no.
Acute attack	5 (18.5%)
Primary progressive course	0
Secondary progressive course	13 (48.1%)
Silent neurological involvement	3 (11.1%)
Remission phase	6 (22.2%)
Total	27

Table 2 Major neurological clinical features observed in acute attack and in remission phase

Neurological findings	Acute attack (14 patients/ 21 events)	Remission phase (13 patients)
Motor symptoms/ pyramidal signs	14 (66.6%)	7 (53.8%)
Headache	9 (42.8%)	10 (76.9%)
Behavioural/cognitive symptoms	10 (47.6%)	6 (46.1%)
Sensory symptoms	10 (47.6%)	0
Cranial nerves involvement	4 (19.1%)	1 (7.7%)
Optic neuropathy	1 (4.8%)	0
Cerebellar symptoms	0	2 (15.4%)
Dysarthria	2 (9.5%)	0
Ophthalmoplegia	2 (9.5%)	0
Sphincter/impotence	4 (19.1%)	0
Other	5 (23.8%)	5 (38.5%)

MRI findings

In *acute phase* (21 MRI studies in 14 patients), MRI lesions were located in eight examinations (38.1%) in the brain-stem and/or in diencephalon (Figs. 1, 2, 3). In five (23.8%) studies, the lesions were noted in the spinal cord, involving the postero-lateral part (Fig. 4), in four (14.8%), lesions were seen in the cerebellum, in eight (38.1%), they were found in white-matter (periventricular and/or subcortical), three of which were isolated. Three MRI studies performed in acute phase were negative. Spinal cord and cerebellum involvement were always associated with brain-stem and/or diencephalon lesions.

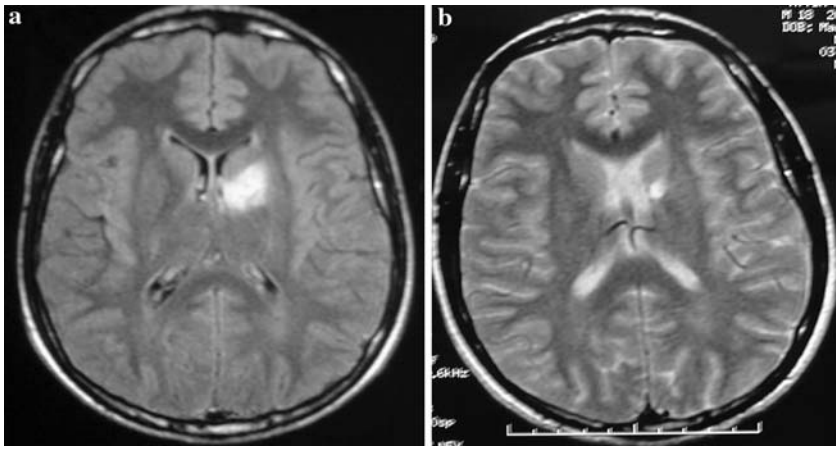

Fig. 1 **a** Axial FLAIR MR image, obtained during an attack, showing a large (2 cm) high-signal lesion involving internal capsula and caudate nucleus in an 18-year-old man. This patient had acute onset of BD characterized by spastic paraparesis, bilateral hypo-pallestaesia and severe hypo-estaesia involving lower right leg. **b** Axial T2-weighted SE MR image showing a partial regression of the lesion, after Infliximab therapy 1 month later

In *remission phase* (13 MRI studies in 13 patients), 9 MRI studies (69.2%) showed lesions in the white-matter, while no lesions were seen in the brain-stem or in the basal ganglia, one case (long-standing neuro-BD) being associated with a brain-stem atrophy without cerebral atrophy. Four MRI studies were negative.

Hemispheric MRI lesions were located in the subcortical and in deep peri-ventricular white-matter without cortical involvement. Most of them, observed especially in the chronic phase, were not associated with any others lesions (Table 3).

Six patients underwent a SPECT evaluation, coupled with MRI study. In the *acute phase*, all the six patients had SPECT studies positive, while only three of them showed MRI lesions. Otherwise, during a *remission phase*, four out of six SPECT studies were still positive, while another two patients, previously negative, became positive at MRI study. Concerning the anatomic correlation between SPECT/MRI studies, the results were consistent in only one case.

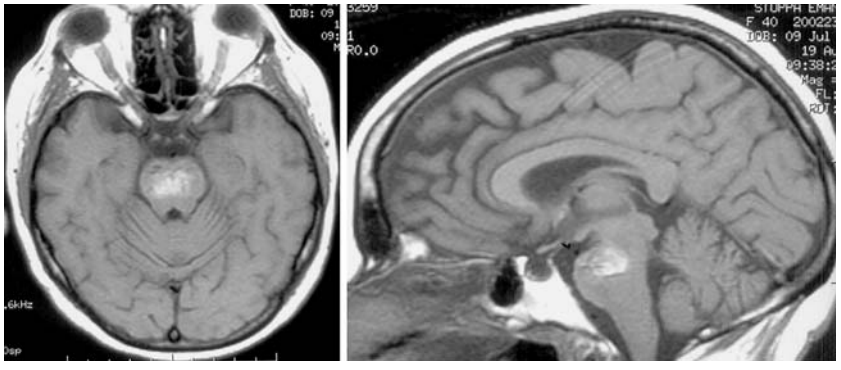

Fig. 2 Axial and sagittal T1-weighted SE MR images showing a large ponto-mesencephalic lesion in a 41-year-old woman with a locked-in syndrome 1 week after the acute onset

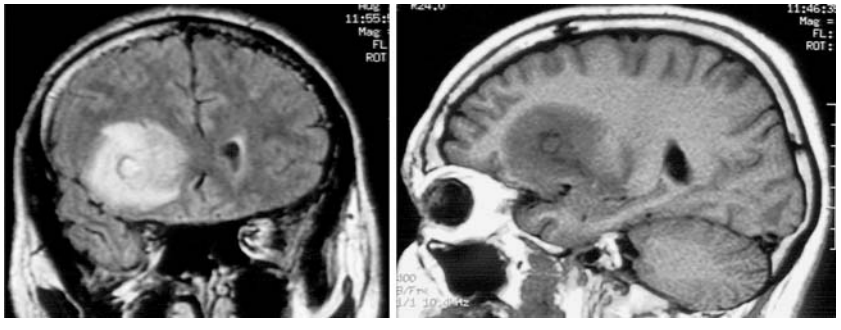

Fig. 3 Coronal FLAIR MR and sagittal T1-weighted SE MR images showing an extensive subcortical lesion in the right fronto-temporal region in a 26-year-old man with a secondary progressive course. Basal ganglia and ventricular compression are also evident

Fig. 4 Sagittal T2-weighted FSE MR image demonstrating spinal cord involvement at C3–C5 level in the same patient in Fig. 1

Discussion

Since Cavara and D'Ermo introduced the term ''neuro-Behçet disease'' [18], few large series of patients have been reported. Recently, Akman-Demir et al. described the neurological features in 200 Turkey patients with neuro-BD, and proposed a definition for the clinical course and radiological findings emphasizing the differences between the acute and remission phases of the disease [17]. To our knowledge, an Italian study on neurological involvement in BD has not been previously reported.

Table 3 Localization of MRI alterations observed in acute phase or in remission phase

Area of CNS involved	Acute phase 21(%)	Remission phase 13 (%)
Brain-stem or basal ganglia	8 (38.1)	0
Brain-stem atrophy	0	1 (7.6)
Cerebellum	4 (14.8)	0
Spinal cord	5 (23.8)	0
White-matter	8 (38.1)	9 (69.2)
No MRI alterations	3 (14.2)	4 (30.7)

In the present series, some differences have been observed in respect to other larger series. In particular, a female predominance and a higher prevalence of neurological involvement have been demonstrated. Possible explanations are the small size of the cohort considered, a referral bias due to the selection of more severe inpatients cases and the fast collaboration with neurologists of our BD unit. Significantly, recent reports from other countries also reported a significant female predominance in BD (up to 67%), and a neurological involvement in 23% of the cases [19–21]. These data seem to confirm the relevance of regional and ethnic variations in sex prevalence and clinical manifestations of BD, in particular out of the ''silk road'' area. However, despite the female predominance in our cases, most severe neurological pictures were seen in males.

The onset of the neurological involvement is frequently characterized by an acute attack with corticospinal tract symptoms, often with cerebellar disturbances, headache and associated behavioural and cognitive changes [17]. The acute attack is usually followed by a progressive secondary course.

During the acute attack, brain-stem/basal ganglia MRI lesions were the predominant findings, sometimes associated with both spinal cord and hemispheric white-matter lesions, particularly of the meso-diencephalic oedematous type. These lesions may have upward or downward extension [22, 23]. In the remission phase, brain-stem and/or cerebellum atrophy without cerebral atrophy, unusual in other neurological diseases, has been described as a hallmark of CNS involvement [22]. In the present study, this aspect was found in only one patient.

Cortical involvement is rather uncommon compared with other systemic vasculitis, allowing the higher functions to be conserved [15, 24]. We observed only one case with this involvement, in which, however, the higher cortical functions were unchanged.

In this study, patients with spinal cord lesions were frequently observed without clinically significant neurological disturbances. A thorough neurological evaluation, together with an extensive MRI study including the spinal cord, also in patients without evident symptoms, may be informative. Furthermore, in all patients with spinal cord involvement, the lesions were located in the postero-lateral part of the cord.

As described, a neuro-behavioural syndrome in neuro-BD patients may occur with a specific pattern of cognitive decline including memory loss, poor attention and ''frontal lobe dysfunction'' presenting little correlation between the area involved and the specific disturbances. The cognitive impairment or behavioural changes may occur without MRI alterations [15].

In our series, the behavioural and cognitive symptoms were observed mainly during an attack, in all cases associated with motor symptoms. As to the cognitive functions, the most frequent feature was mild memory impairment. An isolated behavioural change, observed in four patients, persisted after an acute attack. Two of these patients were negative at MRI evaluation. These unexpected pictures could be explained by the development of neurological lesions in neuro-BD, which tend to regress over a rather short period.

This supports the hypothesis that the acute lesion is due to venous infarctions, with large peri-lesional oedema, suggesting an ''inflammatory-venous'' aetiology of the CNS parenchymal involvement [23]. It is important to remember that normal MRI cannot exclude a previous neurological attack, and MRI evaluation should be carried out as soon as possible after a neurological manifestation [25, 26].

Magnetic resonance imaging findings, as well as the neurological manifestations, are fairly typical according to the size and location of CNS lesions, mainly during the acute phase of neuro-BD [22, 26]. During the acute attack, extensive MRI lesions are characteristically located within the brain-stem and basal ganglia, while in the chronic phase, some small lesions are evident in the subcortical white-matter. MRI patterns reflect the different features of the acute and chronic stages of the disease, demonstrating alterations in almost all acute cases, but in only less than 30% in the chronic stages [22]. On the other hand, MRI findings can be indicative in acute cases in which the major lesions are located in the brain-stem–diencephalon–basal ganglia regions, even in the absence of overt systemic involvement. In this way, it is necessary to remember that neurological manifestation may be the first sign/symptom of BD.

Although SPECT examination was not considered a specific end-point of the study, it could be positive in those particular subsets of neuro-BD patients without MRI lesions [16, 27]. We observed different MRI and SPECT results considering the acute or remission phase of disease. SPECT evaluation was positive in all the patients during the acute attack, while MRI studies were positive in 50% of them. However, in the remission phase, the results were almost opposite in the same patients. Besides, only one patient showed an anatomic correlation between the two imaging techniques.

Despite the low number of patients studied, these data are consistent with other reports about the role of SPECT analysis in discovering early brain functional changes. Currently, the real meaning of SPECT findings is unclear; in particular, the correlations between SPECT and MRI alterations are poor. However, similar to other connective tissue diseases, in a subset of patients with neuro-BD with no MRI lesions, SPECT together with other imaging techniques, such as MR-spectroscopy and diffusion-MRI, could have some value [28, 29].

Pleocytosis and/or elevated protein concentration was observed in 71.4% of seven patients evaluated in the acute phase, while during a chronic phase, a similar abnormality was noted in only one case. An intrathecal synthesis of immunoglobulins that disappeared after an acute attack was found in one case. This finding is not frequently observed in other neurological diseases [30–33].

As reported in other large series, CSF analysis together with MRI findings and clinical pictures could be useful in the differential diagnosis with other neurological diseases, at least for excluding other confusing conditions [34, 35].

In conclusion, BD is not such a rare disease even in a country away from the Silk Route regions and may present as a neurological disease. The male prevalence seems to be not as relevant as previously described. Only the clinical examination and a carefully recorded medical history associated with several instrumental options, such as SPECT, MRI, MR-spectroscopy and diffusion-MRI, can correctly identify the condition.

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