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Research Article

Neurological Manifestation of Behçet's Disease in a Tunisian Cohort

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Abstract

Behçet's disease (BD) is a multi-systemic vasculitis characterized by attacks of acute inflammation, which can affect multiple area of the body. Neurological involvement known as "neuro-Behcet's" (NB) is rare and is one of the main causes of long-term morbidity and mortality. The aim of our work was to study the epidemiological, clinical, paraclinical and therapeutic characteristics of patients with BD with neurological involvement. We conducted a retrospective study of NB patients in the Neurology and Internal Medicine departments of the Military Instruction Hospital of Tunis. We collected 35 patients from a population of 150 patients with BD. Neurological manifestations had inaugurated the BD in 55% of the cases. Ninety-four percent of patients had central nervous system involvement and 6% had peripheral polyradiculoneuritis. Parenchymal involvement occurred in 85% of cases and non-parenchymal NB in 3% of cases. Brain magnetic resonance imaging (MRI) showed predominant demyelinating lesions in periventricular and brain stem in 15 patients, a pseudo-tumor appearance in 3 patients, and vascular lesions in 2 patients. All patients received corticosteroid and 30 patients were treated with immunosuppressive therapy. Three patients had received an immunomodulatory treatment by anti-TNF alpha. The outcome was unfavorable in patients with diffuse disease, brain stem damage, spinal cord injury, polyradiculoneuropathy and mixed impairment. Neurological manifestations of BD are various and are typically of poor outcomes with a high mortality and heavy sequelae. The prognosis depends on parenchymal involvement and time to initiate treatment.

Keywords: Behçet's disease; Neuro-Behcet's; Central nervous system; Parenchymal involvement

Introduction

Behçet's disease (BD) is a multisystem inflammatory disorder of unclear etiology [1] affecting young people of male sex [2]. It is characterized by recurrent oral and genital ulcers, skin lesions and uveitis. Other manifestations include arthritis, gastrointestinal ulcerations, thrombophlebitis and central nervous system disease [1].

Clinical diagnosis is based on the criteria of the international Behçet's disease study group of 1990 [3] and those of the International Criteria for Behçet's disease (ICBD) [4].

In the absence of sufficient clinical criteria and additional paraclinical examinations, diagnostic confirmation remains difficult.

Neurological manifestation in BD varies from 5, 4 to 59% of cases [5] and they are characterized by their clinical polymorphism, affecting the central nervous system (CNS) in 98% of cases [6].

Neurological disorders can precede other systemic manifestations in more than 3% of cases [4], causing diagnostic and therapeutic delay and constitute an element of the severity of the disease [7,8].

Considering that Tunisia is an endemic country of this pathology [9], a study of the neurological manifestations would be interesting.

The objective of our work was to analyze epidemiological, clinical and paraclinical characteristics of Tunisian BD patients with neurological involvement based on the new classifications.

Patients and Methods

We performed a retrospective study of 150 patients diagnosed as BD monitored in the Neurology and Internal Medicine departments of the Military Instruction Hospital of Tunis over a period of 23 years, from January 1997 to December 2019.

Diagnosis of BD was made according to the criteria of the international study group (ISG) of 1990 and those of the International Criteria for Behçet's disease (ICBD).

Neuro-Behcet's (NB) diagnosis was retained according to international consensus recommendation (ICR) criteria.

Patients without any evidence of objective neurological involvement including those with isolated headache, those who did not show any abnormality upon neurological examination, cerebro-spinal fluid (CSF) analysis or neuro-radiological examinations, were excluded, as well patients affected by diseases known to induce neurological involvement.

Epidemiological parameters (age, gender), family history of BD, clinical presentation, diagnostic criteria, investigations, complications and treatment were analyzed.

The onset of NB was defined as the time when the first neurological

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symptoms attributed to the disease occurred.

Neurological symptoms were subdivided into central and peripheral involvement.

Magnetic resonance imaging (MRI) was performed on all of our patients to explore different regions of the brain, spinal cord and cerebral vessels. A lumbar puncture was done with chemical and cytological study of the CSF. Electro-neuro-myogram (ENMG) was performed in front of signs of peripheral involvement. The typing of the specificity of HLA-B51 was carried out by the serological technique of micro-lymphotoxicity.

The treatment modalities consisted of immunosuppressive agents in combination with oral high doses or intravenous pulses of glucocorticosteroids.

The course of treatment was described using the modified Rankin score (MRs).

Our data were analyzed using the Statistical Package for the Social Sciences (SPSS version 20). Results in all groups and subgroups were compared by Pearson's chi-squared test. A value of $p < 0.05$ was regarded as statistically significant.

Results

We collected 35 patients of NB from a population of 150 patients with BD. They were 30 males and 5 females (M/F ratio = 6). The mean age at diagnosis was de 34±1, 92 (range 27-71 years). Average diagnostic duration was 2.9 years with extremes ranging from one week to 13 years. Two of our patients had a family history of BD.

The distribution of the extra-neurological manifestations: cutaneous-mucous, articular, ocular and vascular is summarized in Table 1.

Neurological involvement was observed in 23% and had inaugurated the BD in 55% of the cases (n=19).

Average disease duration of BD before neurological manifestations onset was 2.1 years.

The main signs are given in Table 2.

Headache was the most common neurological symptom found in 32 patients. Visual disturbances were reported by 37% of patients (n=13) and consisted of diplopia, blindness and strabismus. Motor disorders were present in 69% of patients (n=24), presented by weakness in 51% of cases and unsteadiness in 49% of cases. Sensitive disorders were reported in 34% of cases (n=12) and there were numbness, tingling and burning sensation in 26%, 9% and 3%, respectively. Six patients presented with seizure which are revealing in 1 patient. Psychiatric disorders were present in 15% of patients and consisted of delusions (n=2), hypomania in two cases and a recurrent episodes of depression in one case. Cognitive impairment was reported in 11% of patients (n=4). Isolated antegrade memory impairment without impact on daily life was observed in three patients. A subcortical dementia associating attentional disorders and executive function disorders was observed in the fourth patient. Sphincter disturbances were described in 12% of patients (n=4). Urine leakage and dysuria were reported in 6% of cases and erectile dysfunction in 12%.

Table 1: Extra-neurological signs in patients with Neuro-Behcet's.

Extra-neurological manifestations	Number of patients	Percentage %
Cutaneous-mucous symptoms		
Oral ulcer	35	100
Genital ulcer	22	63
Pseudofolliculitis	22	63
Erythema nodosum	4	11
Positive pathergy test	9	26
Articular symptoms	10	28.5
Ocular involvement		
Retinal vasculitis	7	20
Intermediate uveitis	2	6
Anterior uveitis	1	3
Posterior uveitis	1	3
Vascular involvement		
Deep vein thrombosis	7	20
Arterial thrombosis	1	3
Arterial aneurysms	1	3
Intestinal involvement	1	3

Table 2: Neurological symptoms in patients with Neuro-Behcet's.

Neurological manifestations	n (%)
Visual disturbances	n=13 (37%)
Motor disorders	n=24 (69 %)
Sensitive disorders	n=12 (34%)
Unsteady gait	n=17 (49%)
Swallowing disorders	n=4 (11%)
Language disorders	n=3 (9%)
Headache	n=12 (34%)
dizziness	n=1 (3%)
seizure	n=6 (17%)
Psychiatric disorders	n=5 (14%)
Cognitive impairment	n=4 (11%)
Sphincter disturbances	n=3 (9 %)

Patients were classified according to criteria of Neuro-Behçet defined proposed by the international consensus of experts of 2014 [10].

The CNS was affected in 94% of cases (n=33). Two patients had peripheral polyradiculoneuritis as shown in Table 3.

Central involvement was parenchymal in 85% of cases (n=30), non parenchymatous in 3% of cases (n=1) and mixed in 6% of cases (n=2).

Parenchymal involvement occurred in 30 patients (85%). Among them 4 (13%) presented with brainstem involvement clinically defined by involvement of the cranial nerves, ophthalmoparesis, cerebellar syndrome or pyramidal dysfunction. Ten patients (34%) presented with hemispheric involvement and one patient (3 %) with spinal cord involvement. Retrobulbar optic neuropathy was found in

Table 3: Distribution of patients by type of neurological involvement.

Type of neurological involvement	Number of patients	Percentage
Central nervous system (n=33)		
Parenchymal	30	85%
Non-parenchymal	1	1%
Mixed	2	6%
Peripheral nervous system (n=2)		
Chronic polyradiculoneuropathy	2	6%

Table 4: Distribution of patients according to Sites of involvement of the nervous system.

Sites of involvement	n (%)
Parenchymal CNS involvement	
Brainstem involvement	4 (13)
Hemispheric involvement	10 (34)
Isolated spinal cord involvement	1 (3)
Multifocal involvement	11 (37)
Retrobulbar optic neuropathy	4 (13)
Non parenchymal involvement	
Cerebral vein thrombosis	1(3)
Mixed involvement	
Intracranial hypertension	2 (6)

four patients (13%).

Multifocal or diffuse involvement defined by a combination of signs of brainstem involvement, hemispherical involvement and/or spinal cord involvement was diagnosed in 37% of cases (n=11). Non-parenchymal NBD consisting of cerebral vein thrombosis (CVT) found in one case (3 %). Mixed involvement including a combination of parenchymal and non-parenchymal involvement was noted in 2 patients who had Intracranial hypertension syndrome Table 4.

Radiologically, brain MRI was performed in all patients. Radiological abnormalities were objectified in 54% of cases. Four types of lesions were objectified in our patients: demyelinating lesions in periventricular and brain stem in 13 patients, a pseudotumor appearance in 3 patients, and vascular lesions with arterial aneurysm and cerebral trombophlebitis in 2 patients and cerebral atrophy in four patients.

The lesions were supratentorial in 43% (n=15): periventricular (n=10), subcortical (n=8), juxtacortical (n=6) and central gray nuclei (n=6). Twenty-nine percent (n=10) of patients had lesions in the brainstem. The involvement was mesencephalic and bulbar in 20% of cases (n=7). Spinal cord involvement was observed in 12% of cases (n=2).

The CSF study conducted in 51% of patients (n=18) was abnormal in 16 cases. Hyperproteinorachia was found in 16 patients (89%). Lymphocytic meningitis in 22% of cases, with a predominance of Polymorphonuclear neutrophils (PMN) in 6% of cases and variegated formula in 6% of cases.

Table 5 summarizes all the biological and radiological signs of central neurological involvement.

Table 5: Biological and radiological signs during NB.

CSF study	
Hyperproteinorachia + hypercellularity	
Lymphocytic meningitis	22%(n=4)
PMN meningitis	6%(n=1)
Variegated meningitis	6%(n=1)
No formula	6%(n=1)
Hyperproteinorachia + No hypercellularity	22%(n=8)
Normal CSF analysis	11%(n=2)
Brain MRI	
Demyelinating lesions	37%(n=13)
Pseudotumor	8,6%(n=3)
Cerebral atrophy	12%(n=4)
Vascular lesions	6%(n=2)

An Electromyography (EMG) was performed in 14% of patients (n=5) with clinical neurogenic syndrome. He was in favor of axonal polyradiculoneuropathy in two cases.

HLA typing was performed in 14 patients (40%) of which 6 had a positive HLA B51 typing.

All patients were treated. Time to treatment was on average 7.4 months. Oral corticosteroid therapy at a high dose (1mg/kg/day) for 6 weeks was used in all cases. In 25 patients, pulses of methylprednisolone were administered at a dose of 1 gram/day for 5 days and in 5 patients for 3 days. Corticosteroid was associated with immunosuppressive therapy in 30 cases: cyclophosphamide (15 patients) and azathioprine (15 patients). Methotrexate was used as a second-line treatment in 2 patients. Three patients had received intravenous inflimiximab (anti-TNF α) at a dose of 5mg/kg.

Anticoagulant therapy was prescribed in the patient who had presented with cerebral venous thrombosis.

Our patients have been followed-up for a median of 7 years. The evolution was by push in 60% of cases, primary progressive in 20% of cases and secondarily progressive in the rest of the cases. Three patients recovered well without significant residual disability, with a modified Rankin score (MRs=1). Twelve patients had a minimal to moderate disability (MRs between 2 and 3), 15 patients had moderately severe disability (MRs=4) and 5 patients made no improvement with a severe neurological impairments (MRs=5).

Discussion

We aimed to describe in this retrospective study the frequency and the characteristics of neurological involvement in a cohort of BD patients of Tunisian origin.

The prevalence of neurological manifestations in BD ranges from 5.3 to over 50%, depending on diagnostic criteria and ethnic populations [11,12]. The frequency of NBD in our series was 23%.

The average age of our population was 34 ± 1.92 years. A few cases have been reported in children [13]. The male predominance observed in our series was reported in the different series in the

literature [2,13,14].

Two of our patients had a family history of BD in its non-neurological form. Family forms reported in the Tunisian series are estimated between 2% and 7.7% [3,15]

The systemic manifestations most discussed in the literature in association with neurological disorders were cutaneous-mucous, ocular, vascular and intestinal involvement [2,16,17].

Neurological involvement often occurs during the course of the disease with an average time to diagnosis of 6.4 years [17]. In our study, neurological manifestations appeared after a delay of 2.9 years and they were inaugural in 54% of cases.

Neurological symptoms are polymorphic, they are subdivided into two main subtypes: parenchymal, linked to a direct inflammatory disease of the central nervous system, and non parenchymal that occurs secondary to vascular involvement [13].

The parenchymal central nervous system (CNS) involvement was the most common form of NB in our study (85%) as well as in most large series of NB (70 and 80% of cases) [81]. The most common presentation of these cases was pyramidal signs and signs of brainstem damage [13].

In our study, the most reported symptoms were pyramidal signs (49%) and cerebellar syndrome (20%). Cranial nerve involvement was found in 9% of our population.

Non-parenchymal NB usually involves the main vascular structures of the CNS [17]. In our study it was found in 3% of cases.

Peripheral neuropathy, found in 2 of our patients, remains uncommon finding in BD [17]. Al Araji et al. found a frequency of 0.8% in a review focused in NB characteristics [19].

On neuroradiology imaging, cerebral CT scan is not very specific. It showed capsulo-thalamic, insular and lenticular hypodensities in 4 patients and parenchymal atrophy in 3 of our patients.

Brain MRI is more sensitive, it shows Hyperintensities in T2 and flair sequences. The most frequently affected areas are the brainstem, basal ganglia, deep white matter, subcortical white matter and cerebellum [20]. In our series, brain MRI performed in all our patients was pathological in 54% of cases. The lesions observed involved the brainstem in 29%, the central gray nuclei in 17%, and periventricular white matter in 29%. Superior sagittal sinus thrombosis was found in 1 case.

HLA-B51 is a genetic marker of BD, but is less frequent in NBD patients [21,22], found in 6 of our cases.

The clinical course can be that one of a single acute attack, an attack-remission course or a primarily progressive course [23]. This requires early therapeutic management. There is no consensus on the best treatment of NB [24]. The treatment is based on the use of glucocorticoids in doses that change according to the severity of the presentation; generally, it starts with prednisone 1mg/kg per day for one month, followed by withdrawal in a gradual form depending of the patient´s tolerance [25]. In serious cases it is useful a treatment with corticoids pulses, as intravenous methylprednisolone 1g, administered every 24 hours during one to five days [25]. In case of nervous compromise, the treatment includes the use of azathioprine as a first line agent; alternatives include mycophenolate, methotrexate, and cyclophosphamide. [25-27]. All of our patients had received corticosteroid therapy. Of the immunosuppressants, Azathioprine and cyclophosphamide are the most widely used.

Our study confirmed data from the literature on the severity of neurological damage, with a poor prognosis of NB with parenchymal involvement compared to non parenchymal NB [28,29].

The outcome was unfavorable in all patients with diffuse disease, brain stem damage, spinal cord injury, polyradiculoneuropathy and mixed impairment.

Conclusion

Neurological manifestations of BD are various and are typically of poor outcomes with a high mortality and heavy sequelae. The prognosis depends on parenchymal involvement and time to initiate treatment.

Declaration

Availability of data and material: Data transparency.

Author contributions: All authors contributed to the study conception and design.

Ethics approval: Approval was obtained from the ethics committee.

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