

Silent neurological involvement in Behçet's disease

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ABSTRACT

Objective. The aim of this study was to determine the long term clinical course and prognosis of subclinical ('silent') neurological involvement in Behçet's disease (BD).

Methods. We included patients with BD who did not have any neurological complaints other than headache, dizziness or other non-specific complaints, that showed abnormal neurological findings (Silent Group). We compared these patients with the patients with overt parenchymal neuro-Behçet's disease (Overt Group). Cases with at least 8 years of follow-up were included.

Results. There were 22 patients in the Silent Group (15M, 7F), with a mean follow-up of 12.8 ± 4 years. Magnetic resonance imaging was abnormal in 8 of 21 patients, while neuropsychological testing revealed mild abnormalities in 15 of 20 patients. During the follow up period, 3 patients of the Silent Group had 4 overt neurological attacks. In the last visit, 21 patients were independent, while one that had previously developed overt neurological attack was deceased. The Overt Group consisted of 51 patients (45M, 6F). In the Overt Group the ratio of males was higher, nearing a marginal significance ($p = 0.051$); whereas age at onset of BD, and frequency of other organ manifestations of BD were not different. In the Overt Group at the final visit, 19 patients were independent (37%), while the remaining were either dependent to others, or deceased, which was significantly higher when compared to the Silent Group ($p = 0.005$).

Conclusion. Silent neurological involvement in BD seems to represent a milder form of the disease, since the mortality and disability rate in this group is significantly low.

Introduction

Behçet's disease (BD), first described in 1937 as a disease characterized by recurrent uveitis, oral aphthae and genital

ulcers (1), is a multisystemic inflammatory disorder with unknown etiology. It is more common among males, and this male predominance becomes further pronounced when there is any serious organ involvement (2, 3).

Neurological manifestations may occur in about 5% of BD patients (4), which is generally confined to central nervous system (CNS). Mainly two patterns of CNS involvement may be seen. Parenchymal CNS involvement is the more common form usually involving brainstem, or occasionally spinal cord. Although motor and cognitive signs predominate the clinical picture, brainstem signs, sphincteric dysfunction, pyramidocerebellar syndrome and sensory findings may also be found (5). Onset is usually with a subacutely evolving attack followed by remission with or without sequelae. After the attack(s) some of the cases show a slow progression (secondary progressive course). In a minority of the cases, there is an insidious onset without any clear-cut attack, showing a slow but continuous progression (primary progressive course) (5-7). An attack of parenchymal involvement is usually accompanied by cerebrospinal fluid (CSF) pleocytosis, and shows a typical magnetic resonance imaging (MRI) finding with a brainstem lesion extending to diencephalic structures, or to basal ganglia region (8). The large lesion seen during an attack tends to become smaller or may disappear during follow-up (8). Although less frequently, subcortical and periventricular white matter lesions may also be seen (9). On the other hand, non-parenchymal CNS involvement mainly represents CNS findings due to major vascular involvement. More commonly, increased intracranial pressure is encountered due to venous sinus thrombosis. In this setting cranial MRI usually does not reveal any parenchymal abnormalities, and CSF is usually normal other than high pressure. Less frequently,

stroke-like syndromes related to cerebral arterial involvement, or aseptic meningitis may be seen (5, 10-12). Parenchymal involvement implies significantly worse prognosis when compared to non-parenchymal involvement (5). Other poor prognostic signs include abnormal CSF findings during an attack, as well as repeated neurological attacks, incomplete recovery, or progressive course (5-7).

An autopsy series in Japan revealed 34% neurological involvement (13), which is almost 3.5 times higher than the clinical involvement reported in that area which is around 10% (14); this may imply that some patients with BD might have subclinical neurological involvement. In fact, there have been several studies mentioning 'silent' neurologic involvement in Behçet's disease (4, 5, 14). In these reports the patients with "silent" involvement do not have any specific neurological complaints, but neurological examination reveals abnormal findings. However, clinical significance and implications of 'silent' neurological involvement in BD are not yet established. Since neurological involvement of BD is important due to its devastating manifestations, which urge the clinician to institute relevant treatment as early as possible, the clinical importance of silent neurological involvement needs to be elucidated. Therefore we conducted this study to determine the long term clinical course and outcome of the patients with silent neurological involvement within our neuro-Behçet's disease series in comparison to those with overt parenchymal neurological involvement.

Patients and methods

We included cases with BD, fulfilling International Study Group Criteria for BD (15), that were diagnosed with "silent neurological involvement" at our department. Silent neurological involvement was defined as patients without any complaints other than primary headache disorders such as migraine or tension type headache, and non-specific complaints such as dizziness, fatigue, or mood changes, but who showed abnormal findings in initial neurological

Table I. Clinical characteristics.

	Silent Group	Overt Group	P
Male: Female	15:7	45:6	= 0.051
Mean age at referral	31.7 ± 7.4	34.2 ± 8.9	NS
Mean age at n-BD diagnosis	33.9 ± 8.7	33.1 ± 8.7	NS
Mean n-BD duration (month)	137.8 ± 46.9	114.2 ± 2.8	NS
Number of visits during follow-up	9.0 ± 8.5	12.2 ± 7.1	NS
Final disability status			
Independent	21 (95%)	19 (37%)	< 0.01*
Dependent	0	13 (26%)	
Dead	1 (5%)	19 (37%)	
MRI			
Normal	13	7	< 0.01**
Periventricular WM	6	5	<0.01***
Brainstem/and/or basal ganglia	2	19	
NPT			
Normal	2	1	
Mild	12	4	
Moderate/severe	6	22	< 0.01****

n-BD: neuro Behçet's disease, MRI: magnetic resonance imaging, WM: white matter, PT: neuropsychological testing.

*Independent versus dead or dependent; **normal versus abnormal; ***periventricular white matter versus brainstem/and/or basal ganglia; ****normal/mild versus moderate/severe.

examination (such as, slight/asymmetric weakness, sensorial deficits, asymmetric and/or enhanced DTR's, Babinski's or Hoffmann's sign, sphincteric abnormalities), and/or abnormal findings in at least two evaluations including MRI, neuropsychological testing (NPT), evoked potential (EP) studies and CSF analysis. Any overt neurological disturbance lasting more than 24 h. is defined as an attack (8).

This study is a partly retrospective, and partly a case control study. In 1997, our neuro-Behçet's database was screened retrospectively to identify patients qualifying for the definition of silent neurological involvement with at least 3 years of follow-up, and 28 patients were found. Patients with any history of perinatal brain injury, previous head trauma or any other disease that could have caused abnormal findings on neurological examination were excluded. Among those 28 patients, 6 could not be reached or refused to participate; therefore 22 patients were evaluated. Besides neurological examination, all patients were sent for a cranial MRI scan (in various scanners with different magnetic power, with axial T1, T2, and proton weighted sequences), and NPT with an extensive

battery, as defined in a previous study (17). Additionally EP and CSF analysis were performed whenever possible. All patients continued their routine outpatient visits, and were called and invited for a final neurological examination in May 2004, and those who declined that visit were interviewed by phone concerning their final health status. Among the initial 22 patients, 8 patients were reexamined in 2004 and 13 patients were interviewed by phone; only one patient could not be contacted, but had 14 years of follow-up. Therefore, only those cases with at least 8 years of follow up were included.

Data of the Silent Group were compared to the data of patient group with overt parenchymal neurological involvement (Overt Group) who also had been followed up for at least 8 years. Those patients who died within this period were also included. For statistical analysis, for non parametric-comparisons chi square or Fisher's exact test, and for parametric comparisons Student's t test were used.

Results

There were 774 patients with BD registered at Istanbul Faculty of Medicine

Neurology Department since 1984 until May 2004, and 270 of these patients had neuro-Behçet's disease. Of these 270 neuro-Behçet's patients 28 fulfilled the above-mentioned criteria for silent neurological involvement. Amongst these 28 patients 22 (15 males, 7 females) patients accepted to attend the study in 1997, and were called back in 2004. Of the 248 remaining cases 191 had parenchymal CNS involvement, among which 32 had more than 8 years of follow up and 19 that were deceased adding up to 51 (45 males, 6 females) which consisted the Overt Group.

Demographic parameters of the two groups are listed in Table I. The mean age at referral, mean age at neuro-Behçet's disease diagnosis, neuro-Behçet's disease duration were not significantly different between the two groups, as well as the distribution of other organ involvements. In the Overt Group the ratio of males to females was higher (7.5:1 versus 2:1), nearing a marginal significance ($p = 0.051$).

During the follow up period 3 patients in the Silent Group experienced 4 overt neurological attacks, 1 to 12 years after the recognition of silent neurological involvement. Among these, 2 patients had a brainstem attack, and one patient had two attacks involving the spinal cord. In the overt group 47 patients had 101 overt neurological attacks, 30 of which showed secondary progressive course, while 4 had primary progressive course from the onset.

Initial neurological examination findings revealed mostly pyramidal signs in the Silent Group such as deep tendon reflex asymmetry or hyperactivity in 14 patients, mild hemiparesis in 10 patients, posturing in 11 patients, Babinski's or Hoffman's sign in 6 patients, sphincteric dysfunction in 1 patient. During follow-up, two patients without overt disease, developed mild sphincteric dysfunction, and one patient complained of impotence. Of the 3 patients who experienced overt attacks, one had mild gait ataxia evident on tandem walking and impotence, one had mild paraparesis with sensory level, and the last one had dysarthria, V1th cranial nerve paresis,

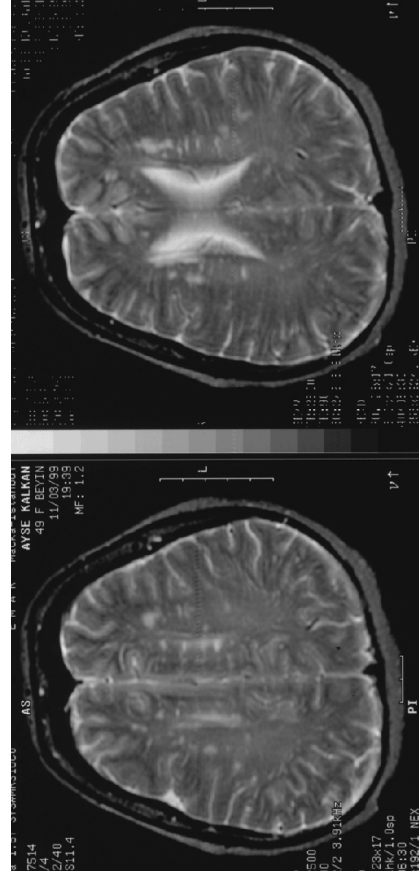


Fig. 1. MRI shows bilateral periventricular white matter lesions, in a patient from the Silent Group who has not had any overt n-BD attacks.

dysphagia and ataxia. Of the patients in the Overt Group 49 had pyramidal signs, 31 had hemi-/quadriparesis, 24 had brain stem signs and 22 had pyramidal midcerebellar signs.

At the final visit, 21 patients in the Silent Group (95%) were independent concerning both motor and cognitive functions according to our disability scale (5). Only one patient who had an overt brainstem attack 12 years after his admission was deceased due to severe disease course and infection after a further 2 years. In the Overt Group 19 patients were independent (37%), 13 patients were dependent concerning motor and/or cognitive function and 19 patients were deceased. The ratio of dependent or deceased patients was significantly higher in the Overt Group ($P < 0.0001$) (Table I). The only deceased patient in the Silent Group had 179.5 months of neuro-Behçet's disease duration. This was much longer than the mean neuro-

Behçet's disease duration which was 66.5 months in the deceased patients of the Overt Group.

MRI

At least one MRI scan was available in 21 of the Silent Group, while 12 patients had more than one MRI scans. There were abnormal findings in 8 patients (38%), whereas 13 patients (62%) had normal MRI scans. Seven of the 8 abnormal MRI's were performed before any neurological attack. Lesions were predominantly in the hemispheric white matter in 6 of the 8 abnormal scans (75%) (Fig. 1). In 1 patient who later had overt neurological attacks there were brainstem lesions (Figs. 2) in the scans before any neurological attack, while in the second patient there were only white matter lesions and the third patient did not have an MRI scan performed before experiencing an overt attack. In those 3 patients who later had an attack, control MRI's after the

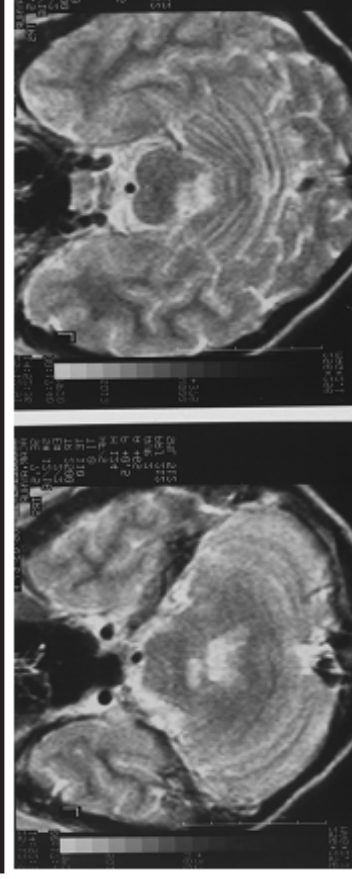


Fig. 2. MRI scan of a patient who subsequently developed a spinal cord attack, at the initial neurological involvement period, that shows a T2 hyperintense lesion in the right pontobulbar region.

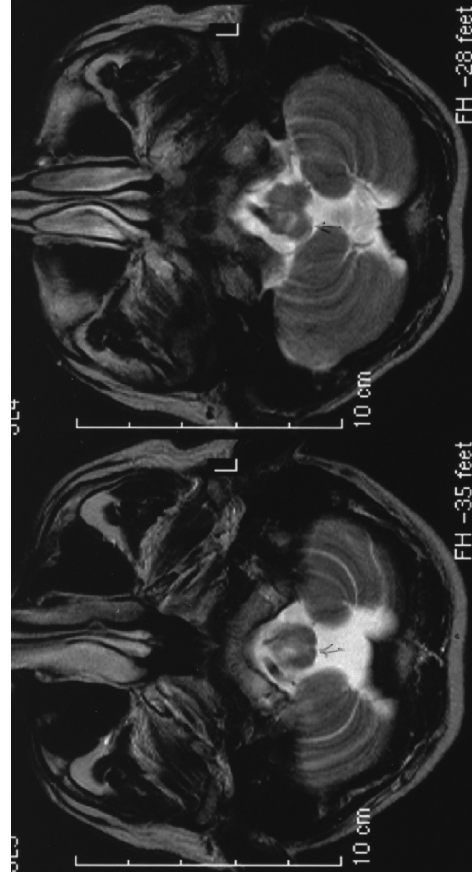


Fig. 3. MRI scan of a patient from the Silent Group at the time of a brain stem attack he had 1.5 years after the recognition of silent neurological involvement.

resolution of the attack showed that the lesion had regressed, with brainstem atrophy and enlargement of the IIIrd ventricle in one. Two other patients, who never had any neurological attacks, disclosed additional white matter lesions in their repeat MRI's. On the other hand, the patients in the Overt Group mostly had brainstem lesions (48%) extending to the diencephalic structures, isolated brainstem or basal ganglia lesions (13%) and periventricular white matter lesions (16%). Seven patients in this group had normal MRI's (23%). Three of these latter cases had their MRI at follow-up when MRI became available years after their attacks, while 4 of them were patients with spinal cord involvement (Table I).

NPT

In the Silent Group at least one NPT was performed in 20 patients. There was mild impairment in 12 of these patients; moderate to severe abnormalities in 6, while in 2 the tests were normal. The most frequently and predominantly involved system was the frontal executive system (14 patients), followed by impairment in memory (8 patients) and in attention (5 patients). Twelve patients had repeat NPT. There was no change in 8 patients, fluctuations in 1 (memory was better, while frontal executive functions were impaired), progression in 1 (memory deficit increased) and improvement in 2 patients. In the Overt Group NPT was performed in 27 patients. One patient

had normal findings, 4 patients revealed mild and 22 patients showed moderate to severe abnormalities. The most affected system was memory (25 patients), followed by attention (20 patients) and frontal executive system (10 patients). The ratio of the patients with moderate to severe impairment were significantly higher in the Overt Group ($p = 0.001$) (Table I).

Other tests

CSF analysis was performed in 5 cases. Two of these were performed during an attack and showed pleocytosis. On the other hand, only one out of the remaining 3 revealed a mild mononuclear pleocytosis. Visual EP's (VEP) were performed in 8 patients and showed abnormal findings in 4. Brainstem auditory (BAEP), sensory (SEP) and motor EP's (MEP) were performed in 5 patients. One patient had abnormal BAEP findings, 1 patient had abnormal SEP findings and 2 patients had abnormal MEP findings.

Treatment

None of the Silent Group patients received immunosuppressant therapy for neurological reasons except for those who had overt neuro-Behçet's attacks. Three patients with overt neurological attacks received pulsed steroid therapy while one of them received pulsed cyclophosphamide for recurrent attacks. However, for systemic involvement including mucocutaneous manifestations, or other organ involvements,

such as uveitis, arthritis, or vascular involvement, oral steroids were used in 21 patients, azathioprine in 11, cyclophosphamide in 5, cyclosporine A in 2, chlorambucil in one patient, whereas 18 patients received colchicine and 3 patients received nonsteroid anti-inflammatory drugs.

Discussion

In a previous study of long-term follow-up of cases with BD and headache, we had noted that a small subgroup of these patients had developed minor abnormalities on neurological examination, without any overt neurological attacks (17). And although subclinical neurological involvement in BD has been reported in studies involving neuroimaging (18-22), neuropsychology (23, 24), and, neuropsychology (25, 26) such cases have not been reported as a distinct group in comparison with patients with overt neuro-Behçet's disease. It is not known if these cases represent a milder form of neurological involvement, or an early phase of primary progressive neurological involvement since long-term outcome of these patients has not been investigated. Therefore, in this study we evaluated 22 patients with BD and silent neurological involvement (who did not have a specific neurological complaint, but showed minor abnormalities on neurological examination or had abnormal findings in at least two evaluations including MRI, NPT, EPs or CSF) who had a follow-up period of over 8 years, and compared them with the patients having overt neurological involvement. Demographic characteristics, such as age, mean neuro-Behçet's duration and other organ involvements of the Silent Group were similar to the Overt Group, except the ratio of male to female patients. Although showing a marginal significance, the ratio of female patients was higher in the Silent Group, which is an unexpected finding in any serious organ involvement of BD (3). However, it is a fact that BD has a milder course in female patients (27); hence this difference might be reflecting a similarly mild CNS involvement in females compared to severe neurological involvement in males.

Among the patients in the Silent Group, 3 patients (13.6%) developed 4 overt neurological attacks later in the course of the disease. In a previously published series from our department (4), prevalence of overt neurological involvement was around 5% among BD cases seen in one year. Therefore, neurological attacks seemed to occur at a slightly higher rate than the expected neurological involvement incidence in general BD series. On the other hand, in studies with long-term follow up, the ratio of neurological involvement increase with time. In a recent study from Istanbul, 20-year prevalence of neurological involvement among male BD cases is around 13%, which is very similar to our ratio (28).

Cranial MRI was performed in 21 of our patients with silent neurological involvement, and 13 of them were normal. There were 8 abnormal MRI scans in the Silent Group; 6 of them were showing hemispheric white matter lesions and 2 of them revealed brainstem lesions. In large series with neuro-Behçet's disease, as well as the Overt Group in our study, brainstem, diencephalon and basal ganglia regions are more commonly involved, whereas hemispheric white matter lesions are seen in approximately 10-15% of the cases (5, 9); however most of the cases with hemispheric white matter lesions have silent neurological involvement (8). Therefore, MRI findings seem to be a distinctive feature between patients with silent versus overt neurological involvement. There are other neuroimaging studies implying silent neurological involvement in BD. In a cranial MRI study, small cerebral white matter lesions were described in 1 of 10 neurologically asymptomatic BD patients, while in another study similar MRI appearances were reported in 2 out of 4 patients (18, 19). Similarly, T2-weighted hyper signal foci were reported in parietal, frontal, subcortical and periventricular white matter in 6 subjects with ocular Behçet's disease without neurological symptoms (20). However, caution should be exerted when dealing with small deep hyperintense foci, since many neurologically healthy individuals, especially those over 40,

may harbor such punctate lesions (29-32). Therefore in our study, we did not include cases with only such MRI findings, if they did not have any additional clinical or neuropsychological findings. Another point of interest is the high number of normal MRIs in these patients, which is highly unexpected in overt neuro-Behçet's disease.

It is interesting to note that two patients in our Silent Group who later had an overt neurological attack, had an abnormal MRI scan initially at the silent stage (Figs. 1, 2). Furthermore, one out of 2 patients that developed a neurological attack, had a brainstem lesion at the silent stage (Fig. 2). Although the numbers are too small to draw any definite conclusions, it might be suggested that any brainstem lesion in a patient with silent neurological findings should prompt a closer follow-up of the neurological status.

Other than MRI studies, SPECT and MRS have also been studied in BD. A SPECT study suggested subclinical involvement in BD patients who had normal MRI; 35% of them showed decreased and asymmetrical tracer uptakes (21). An MRS study conducted in a mixed group of BD patients with and without neurological involvement revealed significant difference of choline/creatinine ratio between BD patients without neurological involvement and controls, concluding that MRS may be used to assess subclinical involvement in neuro-Behçet's disease (22). However, since the roles of SPECT or MRS in the diagnosis of BD have not been established yet, the importance of these findings needs to be further confirmed. Our study did not include either of these investigation procedures.

Evoked potentials have also been extensively used in defining subclinical neurological involvement. In one study, 38% of the patients without neurological symptoms had abnormalities of one or more EP modality (25). In another study, BD patients without neurological involvement had significantly prolonged latencies of P300 and showed a significantly delayed motor response time compared to normal controls (26), suggesting subclinical invol-

vement. A transcranial magnetic stimulation study in patients with BD revealed delayed central motor conduction time or increased motor evoked potential latency in 55.5 % of the patients without overt neurological involvement showing only pyramidal signs on neurological examination (33). Although evoked potentials may be useful in detecting silent cases, in our cohort they were not routinely performed, but were used only as an adjunct to clinical evaluation where needed.

Neuropsychological testing of the Silent Group showed 12 mildly affected patients in addition to two normal patients and (70%), 6 moderate to severe involvement (30%); whereas in the Overt Group 5 patients revealed normal or mild (19%) and 22 patients showed moderate to severe abnormalities (82%). This difference of severity in favor of the Silent Group was notable. Furthermore, our cohort reveals a difference between the Silent Group and the Overt Group in terms of the predominantly affected cognitive domain being the frontal executive system in the former and memory in the latter. There are other studies where neuropsychological testing has been used to define asymptomatic neuro-Behçet's cases. In one study cognitive impairment was evident in 46% of BD patients without overt neurological involvement, and memory was the most affected cognitive domain (24).

The Silent Group was also different from the Overt Group in terms of outcome; only one patient died due to severe disease course and infection whereas all the other patients including the patients having overt neuro-Behçet's disease attacks were independent after about 12 years. The only deceased patient had an overt attack much later in disease course. Mortality rate in the patients with overt neurological involvement in this cohort is around 37% (19/51), and in a previously published general BD series it was 9.8% (28); whereas in the Silent Group mortality rate was much lower (1/22, 4.6%).

Our findings imply that cases with BD and silent neurological involvement were different from the cases with overt neurological involvement in

terms of outcome, neuropsychological and neuroradiological evaluations. Therefore, these cases do not seem to represent an earlier stage of primary progressive neurological involvement in BD, which usually has a grave outcome (5). Rather, these cases seem to have a milder form of neurological involvement. We conclude that, although these cases may require a closer neurological follow up to detect any overt neurological transformation, they do not seem to require any specific treatment at this stage.

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