J Neurol (2001) 248:95–103

ORIGINAL COMMUNICATION

Aksel Siva
Orhun H. Kantarci
Sabahattin Saip
Ayse Altintas
Vedat Hamuryudan
Civan Islak
Naci Koçer
Hasan Yazici

Behçet's disease: diagnostic and prognostic aspects of neurological involvement

Received: 16 March 2000
Received in revised form: 12 June 2000
Accepted: 21 July 2000

A. Siva · O. H. Kantarci · S. Saip
A. Altintas
Department of Neurology
Istanbul University
Cerrahpasa Medical School
Istanbul, Turkey
Tel.: +90-212-247 00 22
Fax: +90-212-240 21 06
e-mail: asiva@turk.net

V. Hamuryudan · H. Yazici
Department of Rheumatology
Istanbul University
Cerrahpasa Medical School
Istanbul, Turkey

C. Islak · N. Koçer
Department of Radiology
Istanbul University
Cerrahpasa Medical School
Istanbul, Turkey

Address for correspondence:
A. Siva (✉)
Hacı Emin Sok. 20/7
Nisantası 80200, Istanbul, Turkey

Present address:
O. H. Kantarci
Department of Neurology
Mayo Clinic and Foundation
200 First Street, SW
Rochester, MN 55905, USA

A. Siva and O. H. Kantarci contributed equally to this manuscript.

Abstract This study was conducted to describe clinical and prognostic aspects of neurological involvement in Behçet's disease (BD). Patients referred for neurological evaluation fulfilled the criteria of the International Study Group for Behçet's Disease. We analyzed disability and survival by the Kaplan-Meier method, using Kurtzke's Extended Disability Status Scale (modified for BD) and the prognostic effect of demographic and clinical factors by Cox regression analysis. We studied 164 patients; of the 107 diagnostic neuroimaging studies: 72.1% showed parenchymal involvement, 11.7% venous sinus thrombosis (VST) and the others were normal. CSF studies were performed in 47 patients; all with inflammatory CSF findings (n=18) had parenchymal involvement. An isolated increase in pressure was compatible with either VST or normal imaging. The final diagnoses were VST (12.2%), neuro-Behçet syndrome (NBS) (75.6%), isolated optic neuritis (0.6%), psycho-Behçet syndrome (0.6%), and indefinite (11%). VST and NBS were never diagnosed together. Ten years from onset of BD 45.1% (all NBS) reached a disability level of EDSS 6 or higher, and 95.7±2.1% of the patients were still alive. Having accompanying cerebellar symptoms at onset or a progressive course is unfavorable. Onset with headache or a diagnosis of VST is favorable. Two major neurological diagnoses in BD are NBS and VST. These are distinct in clinical, radiological, and prognostic aspects, hence suggesting a difference in pathogenesis.

Key words Behçet's disease · Neuro-Behçet syndrome · Prognosis · Disability · Cerebral venous sinus thrombosis

Introduction and background

Behçet's disease (BD), originally described in 1937 by Behçet [7] as a distinct disease with orogenital ulceration and uveitis, is an idiopathic chronic relapsing multisystem vasculitis. Although previously various different criteria [8, 14, 26, 30] have been used for the diagnosis, the International Criteria for Classification of Behçet's disease are now accepted [17, 18]. Attacks of BD become less frequent and less severe over time. Male patients whose disease began at a young age have the worst prognosis

[43]. Despite being originally described as a dermatological disease, the major causes of morbidity and mortality result from ocular, vascular, or neurological involvement [9, 15, 36]. Acute panuveitis occurs in 42–74 % of patients [17, 18]. Optic nerve involvement has also been rarely reported [20, 22]. Arterial and venous large vessel complications are seen in 25–30 % of the cases while a possibly higher proportion may have small vessel involvement including postcapillary venules [12, 19, 23, 31, 34]. Venous vascular involvement is more common then arterial lesions in Turkish patients [23].

Neurological involvement most commonly is reported to manifest as brainstem or corticospinal tract syndromes (neuro-Behçet syndrome, NBS), increased intracranial pressure mostly related to venous sinus thrombosis (VST) or aseptic meningitis, isolated behavioral symptoms (psycho-Behçet syndrome, PBS), or isolated headache [1, 2, 11, 13, 33, 36–39, 43]. Rare presentations include intracerebral hemorrhage due to ruptured aneurysms, peripheral neuropathy, isolated optic neuritis, and a parkinsonian syndrome [6, 10, 20, 35]. Magnetic resonance imaging (MRI) is more sensitive than computed tomography (CT) in visualizing reversible inflammatory parenchymal lesions, which are generally located within the brainstem, occasionally with extension to the diencephalon, or within the periventricular and subcortical white matters [3–5, 16, 24, 27, 29, 39, 42]. A limited number of series describing neurological involvement in BD have been published [1, 2, 22, 37, 43]. The present study describes demographic, clinical, and diagnostic features of a hospital-based series of patients seen at a single center with BD and neurological involvement, to study the prognostic effects of associated variables and to describe differences among major clinical patterns of presentation.

Material and methods

Patient source and collection

The Behçet's Disease Research Center at Istanbul University Cerrahpasa Medical School has been in existence since 1978. It is a weekly multidisciplinary outpatient clinic in which rheumatologists, dermatologists, and ophthalmologists participate. Neurological and other consultations are obtained as indicated by patients' symptoms and signs. While the outpatient clinic for patients with NBS in the Neurology Department was officially established only in 1987, earlier neurological consultations were carried out on individual basis, and patient records date back to 1983.

A database was formed in 1994 to study the demographic, clinical, radiological, and prognostic aspects of the patients with BD and neurological involvement. Records of patients who had been seen and followed before 1994 were retrospectively evaluated. Between April 1994 and January 1998 entries were prospectively updated. Retrospective and prospective data were pooled. The final status of patients who had not been seen on follow-up visits within the past 2 years of the study was assessed by telephone interviews. In the case of any new complaint, patients were scheduled for follow-up visits. The inclusion criteria were as follows:

a) Fulfilling the international diagnostic criteria for BD [17, 18]
b) Onset of neurological symptoms otherwise not explained by any other known systemic or neurological disease or treatment
c) Presence of at least one of the following:
   – Objective abnormalities on neurological examination (clinically definite)
   – Abnormal neuroimaging findings suggestive of CNS parenchymal involvement [24] or VST due to BD (radiologically supported–definite)
   – Cerebrospinal fluid findings of aseptic inflammation or increased pressure suggestive of CNS parenchymal involvement or VST due to BD (CSF-supported, definite)
d) In the case of isolated chronic headache syndromes which do not fulfill the previous criterion; onset or change in character (e. g., increased attack rate or intensity) of the syndrome within 6 months of the onset of BD

Headache is a very common symptom in the general population. Unless other CNS signs or symptoms were present, only cases with a change in character of an existing headache or an onset of headache within 6 months of the BD onset, where imaging and CSF studies are justified, were included in the study.

Data classification and statistical analysis

Independent factors studied were; demographics (gender, age at onset of BD, age at onset of neurological involvement), clinical aspects at disease onset, disease course (single episode, relapsing-remitting or chronic-progressive), diagnostic studies (CSF, CT and MRI) and the final diagnoses. The outcome variable considered for survival analysis was time to the final level of disability reached due to neurological involvement.

Patients who fulfilled the inclusion criteria were categorized into three groups according to clinical characteristics at onset: headache with or without papilledema (HA^+), localizing CNS symptoms and signs with or without headache (CNS Sx), other symptoms or signs (i. e., isolated optic neuritis, nonlocalizing CNS symptoms such as generalized seizures, or peripheral nervous system involvement) with or without headache (other Sx). Imaging findings were grouped into three categories: normal MRI, VST, and CNS parenchymal lesions (CNS-p). In cases in which MRI was not performed, CT demonstrating a lesion was considered diagnostic, while normal CT finding was not, due to the relatively low sensitivity in detection of parenchymal lesions. Similarly, CSF studies were grouped into three broad categories: normal, increased CSF pressure (> 180 mmHg) alone, inflammatory findings (white blood cell counts > 5 cells/ml or an elevated protein level) with or without increased pressure.

The final diagnoses were classified as: VST, parenchymal NBS, isolated PBS unrelated to corticosteroid use and without any clinical or laboratory support for VST or NBS, isolated cognitive changes, isolated optic neuritis, aseptic meningitis, and peripheral neuropathy. Patients who had a clinically suspected syndrome but in whom imaging and CSF results were inadequate to establish a definite diagnosis were classified as indefinite (Fig. 1).

We rated disability using Kurtzke's [25] Expended Disability Status Scale (EDSS). This is an ordinal scale from 0 to 10, with 6 representing a moderate disability (patient requires assistance in walking and during other activities of daily life) and 10 representing death. It was originally devised for disability associated with multiple sclerosis. Although the scale has not been validated as a measure of long-term neurological disability in BD, the functional systems involved in the two disorders are similar, and we have extensive previous experience with this scale [21]. Slight modification was necessary because in BD visual disability is most commonly due to uveitis except for rare cases of optic neuritis. Hence visual problems had to be eliminated from the original scale since they do not contribute significantly to neurological burden.

To evaluate the compatibility of the retrospective and prospective data for pooling, demographic and clinical features of the group with

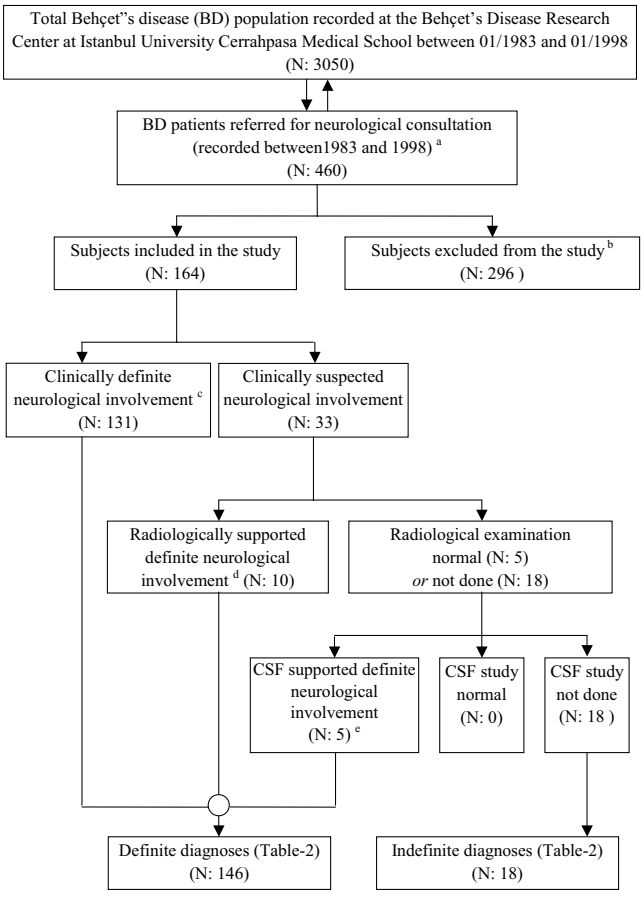

Fig. 1 Patient selection and diagnostic scheme of the study. *a* Referrals were in both directions since some patients have come to direct neurological attention by referrals from elsewhere. *b* Subjects excluded from the study are discussed in the text. *c* Symptoms supported by at least one positive neurological sign in the neurological examination, otherwise not explained by any other known systemic or neurological disease. *d* Symptoms supported by presence of suggestive CT or MRI lesions [24] in the absence of specific clinical examination findings. *e* Normal MRI with CSF results suggestive of aseptic inflammation or increased pressure in the absence of specific clinical examination findings

disease onset before the use of the standardized database and the group with disease onset after 1994 were compared with each other. To describe distinct diagnostic categories of neurological involvement, clinical, imaging, and CSF data (e. g., clinical form of onset, initial and overall imaging diagnoses and course of disease) were subgrouped and compared by chi² or Fisher's exact test as indicated. Survival data were analyzed by Kaplan-Meier statistics, using duration of BD as time to hazard. In the next step, using duration of neurological involvement, survival analysis of selected disability levels (EDSS ≥3 as mild and ≥6 as moderate to severe) were performed to describe time-dependent endpoint disability attained. As the data are censored in time, the prognostic effect of variables on outcome were studied by multivariate, forward stepwise, Cox' proportional hazards analysis. Finally, to reveal possible associations, Pearson's correlation coefficients were calculated between prognostic factors significantly associated with outcome and other factors possibly related to these significant variables.

Results

Patient selection and the diagnostic scheme is presented in Fig. 1. We excluded 296 patients of 460 referrals over a period of 15 years. The diagnoses of exclusion were: isolated headache syndromes (n=291; 29.5 % migrainelike, 57.5 % tension type, 9 % mixed type, 4 % due to ocular inflammation), cardiogenic embolic stroke (n=2), astrocytoma (n=1), meningioma (n=1) and syringomyelia (n=1).

Demographic and clinical aspects

Demographic and clinical characteristics of the 164 patients are summarized in Table 1. Neurological involvement appeared together or after the onset of other systemic signs of BD. This was independent of the referral pattern and of whether the patients were first admitted to a neurology clinic prior to their diagnosis. A careful interview revealed a past history of at least recurrent oral ulcers with or without other systemic findings. The onset was polysymptomatic in 72.7 % of patients, most commonly with headache (61.6 %) and motor symptoms (53.7 %). Headache was the only symptom at onset

Tab. 1 Demographic features, clinical characteristics and final diagnoses of the studied population with Behçet's disease and neurological involvement (n=164)

Male/female ratio	3.82 (130/34)
Age at onset of BD	26.7±8.0
Age at onset of neurological involvement	32.0±8.7
BD duration before neurological involvement	5.3±4.5
Duration of neurological involvement at the last follow-up	2.97±3.2
Onset symptoms	
Headache	101 (61.6 %)
Motor symptoms	88 (53.7 %)
Cerebellar symptoms other than dysarthria	49 (29.9 %)
Brainstem symptoms other than dysarthria	48 (29.3 %)
Dysarthria[a]	37 (22.6 %)
Behavioral symptoms	20 (12.2 %)
Sensory symptoms	18 (11 %)
Alteration of consciousness	12 (7.3 %)
Cognitive symptoms	4 (2.4 %)
Other (seizures, peripheral neuropathy, optic neuritis, etc.)	16 (9.8 %)
Clinical form of onset	
Only HA	30 (18.3 %)
CNS symptoms, signs	127 (77.4 %)
Other symptoms, signs	7 (4.3 %)
Final diagnoses after CSF and imaging studies	
Venous sinus thrombosis	20 (12.2 %)
Neuro-Behçet syndrome	124 (75.6 %)
Optic neuritis	1 (0.6 %)
Psycho-Behçet syndrome	1 (0.6 %)
Indefinite diagnoses[b]	18 (11 %)

[a] "Dysarthria" was evaluated separately due to the difficulty of distinguishing dysarthria due to cerebellar or brainstem causes retrospectively

[b] See text

Tab. 2 Comparison of data recorded before and after 1994

	Before 1994 (n=104)	From 1994 (n=60)	P[a]
Age at onset of BD	25.9[b]	28.0	0.113
Age at onset of neurological involvement	31.1	33.7	0.062
BD duration before neurological involvement	5.1	5.7	0.437
Gender			0.664
male	82	49	
female	22	11	
Clinical form of onset[c]			0.360
only HA	23	8	
CNS symptoms, signs	75	49	
other symptoms and signs	6	3	
Disease course			0.025
single episode	41	30	
relapsing-remitting	27	21	
progressive	36	9	
Imaging diagnoses			0.496
normal	11	7	
venous sinus thrombosis	8	5	
parenchymal lesions	37	39	

[a] Statistical tests using χ^2 or t test (assuming equal variances based on F tests) as indicated
[b] Mean age in years
[c] Categories of clinical forms of onset are explained within text in the methods section

in 18.3 % of the patients (HA^+), although these patients either had papilledema at onset (n=26) or another symptom during the course of their follow-up (n=4).

When the group was stratified into two groups to assess the compatibility of the initial data recorded before (n=104) and after (n=60) 1994, no difference was found in male to female ratio, age at onset of BD, duration of BD before neurological involvement, clinical characteristics at onset, imaging diagnoses, or the dose of corticosteroids used for acute treatment ($P > 0.05$; Table 2). However, as expected, there were significantly fewer patients with progressive disease in the group with disease onset after 1994 (15 %) than in those with disease onset before 1994 (34.6 %; P=0.025).

At the time of the data analysis 83 patients had not gone through a formal neurological evaluation within the last 2 years and 105 within the past year, reflecting the censored nature of the data. Of those who were not seen within 2 years of study completion, 2 had died of unknown cause and 21 could not be reached by phone after multiple trials. Sixty patients were interviewed over the phone to assess their current status: 12 reported recurrent or a new neurological event in the meantime. These patients were seen on follow-up visits.

Imaging and CSF findings

CT was the initial imaging modality in 90 patients. CT was repeated in 12, and a follow-up MRI was performed in 38 of the 90 patients. An initial MRI with or without a preceding CT was carried out in 96 patients, of whom 32 underwent one or more subsequent MRI studies during the follow-up period. All imaging studies, including serial CTs and MRIs, were evaluated together to assign final diagnoses. Eleven patients in whom CT but not MRI showed lesions were included in the final diagnostic group. Normal CT findings were excluded due to low sensitivity of this imaging modality in detecting parenchymal lesions. Overall 107 patients were assigned a final imaging diagnosis: parenchymal lesions were observed in 71.1 %, VST in 12.1 %, and normal MRI in 16.8 %. None of the patients had both VST and parenchymal disease. The parenchymal MRI findings in our study population are discussed in detail elsewhere [24].

The correlation between type of clinical onset and final imaging diagnoses were studied in 104 patients. Three cases in the category of other Sx were excluded from the analysis. Of 17 patients with HA^+ at onset, 5 had parenchymal lesions, 7 VST, and 5 normal MRI. Parenchymal lesions were more frequent in the group (n=87) with CNS Sx at onset (79 %), while VST and normal MRI were less frequent (7 % and 14 %). The differences in imaging findings between the two major forms of onset were significant (c^2=20.4, $P < 0.001$).

Cerebrospinal fluid analyses were performed in 47 patients. The results were normal in 14 (29.8 %). In 10 patients (21 %) only CSF opening pressure was increased. In 23 patients (48.9 %) inflammatory findings were present with or without accompanying increased pressure. Since lumbar puncture was always considered following imaging studies and usually as a supportive rather then a sole diagnostic measure, the number of CSF samples are low. While 39 of the 47 CSF studies followed MRI or a positive CT finding, only 8 were carried out after a negative CT. Of 39 patients 30 had parenchymal lesions, 4 VST, and 5 normal MRI. Inflammatory findings in CSF were observed only with patients who had parenchymal lesions (n=18). Other patients with parenchymal lesions had normal CSF (n=12). All of the four patients who had VST had increased CSF pressure alone, while those with normal imaging either had normal CSF (n=2) or only increased pressure without any inflammation (n=3). Overall, CSF studies were supportive of imaging diagnoses in 62 % of the cases. CSF studies provided additional diagnostic information only in three patients with normal MRI and two with normal CT (MRI not performed; Fig. 1). CSF was also evaluated for oligoclonal bands in eight patients, and two were positive (one with VST and one with parenchymal lesions).

Final diagnoses of patients

Of the 164 patients 146 were definitely diagnosed as having one of the major diagnoses (Fig. 1): 12.2 % as VST and 75.6 % as NBS (Table 1). None of the patients had both of these diagnoses. While 20 of 21 cases with psychiatric symptoms had other clinical or imaging evidence consistent with NBS, one patient with overt behavioral symptoms and no other CNS symptom or sign except headache, and normal MRI and CSF studies was diagnosed as having PBS. Another patient with opthalmological evidence of optic neuritis but no other lesion in MRI was diagnosed as having isolated ON although no CSF study was performed. The remainder of the patients (n=18) without clinically evident or laboratory-supported definite diagnoses were grouped as "indefinite". As such, a case of possible aseptic meningitis with headache but with a normal CT, no MRI, and aseptic inflammatory findings in CSF could not be diagnosed definitely. Also included in this diagnostic category were 2 patients with clinically isolated cognitive impairment with neither MRI nor CT; 3 with isolated generalized epilepsy; 1 with peripheral neuropathy with normal CT but no MRI nor CSF studies; and 11 who had headaches and papilledema but with lack of adequate imaging and CSF studies.

Disease course

While some patients had an obvious relapsing or primary progressive course from the beginning of the neurological involvement, there was an increase in tendency to relapse or progress over the years ($P < 0.001$). After 10 years of follow-up (n=10) six patients had progressive and four relapsing-remitting diseases while none had a limited single episode. The HA^+ and CNS Sx categories were significantly different ($P < 0.0001$) in respect to disease course (Table 2). Of 30 patients in the HA^+ category 80 % had a disease course limited to a single episode, and only 6.7 % had progressive disease. In radiologically diagnosed VST cases disease course was limited to a single episode (n=11) or rarely a relapse of VST occurred (n=2). Normal imaging did not predict a specific course although there was a tendency for these cases to relapse rather then progress. Patients with parenchymal lesions were equally distributed among various disease course groups. These differences are also significant ($P < 0.05$) when stratified according to imaging diagnoses (Table 3).

Survival and disability

By the time of the analysis nine patients had died: three of neurological problems, three of sepsis, and three of unknown cause. All of the patients who died of neurological problems had progressive cerebellopyramidal syndrome. A survival curve based on Kaplan-Meier analysis is shown in Fig. 2. Duration of BD from onset to death was used as the time factor in survival analysis. Ten-year survival was 95.7±2.1 % and 15-year survival 88.5±4.5 %. Since only ten patients were followed up longer than 10 years, the standard error is higher and the estimate of survival is unreliable.

The mean EDSS at the end of censored follow-up times is 3.03±2.38. Survival analysis, taking EDSS of 3 and higher or of 6 and higher as hazard and duration of neurological involvement as time is shown in Fig. 3. By 10 years after the onset of neurological symptoms and

Tab. 3 Correlation of neurological disease course with disease duration, clinical form of onset, and final radiological diagnoses

	Single episode	Relapsing remitting	Progressive	Total	P
Duration of follow-up					
< 1 year	37	5	8	50 (30.5 %)	
1–3 years	18	25	13	56 (34.1 %)	
> 3 years	19	17	22	58 (35.4 %)	
Total	74 (45.1 %)	47 (28.7 %)	43 (26.3 %)	164	< 0.001
Clinical form of onset[a]					
Only HA	24	4	2	30 (19.1 %)	
CNS symptoms, signs	47	39	41	127 (80.9 %)	
Total	71 (45.2 %)	43 (27.4 %)	43 (27.4 %)	157	< 0.001
Imaging diagnoses[b]					
Normal	9	6	3	18 (16.8 %)	
Venous sinus thrombosis	11	2	0	13 (12.1 %)	
Parenchymal lesions	27	25	24	76 (71.1 %)	
Total	47 (43.9 %)	33 (30.8 %)	27 (25.2 %)	107	< 0.05

[a] Categories of clinical forms of onset are explained in the text. Seven cases with other signs or symptoms at onset ("other symptoms and signs") are excluded from the analysis and hence the table

[b] In addition to the initial diagnostic MRI, positive CT with no MRI, and serial MRI studies as indicated by patients symptoms are included in the final diagnostic group. Categories of imaging diagnoses are explained in text

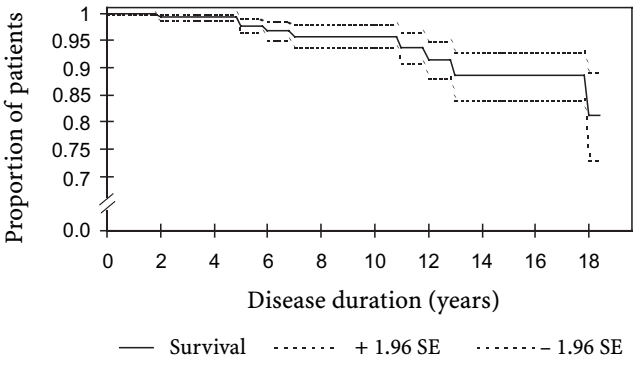

Fig. 2 Kaplan-Meier survival analysis in patients with Behçet's disease and neurological involvement. Behçet's disease duration is used as time to hazard

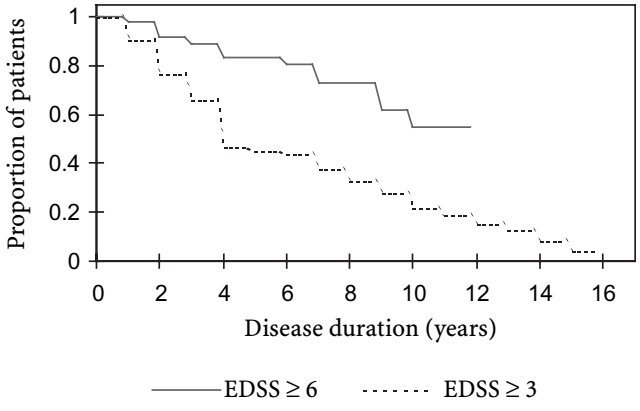

Fig. 3 Analysis of endpoint disability in patients with Behçet's disease and neurological involvement. EDSS of 3 or higher or of 6 higher in a modified Kurtzke scale are taken as the hazard point. All patients with VST, one with optic neuritis, and another with psycho-Behçet syndrome had EDSS of 3 or less; hence the figure represents disability of parenchymal neurological involvement

signs 78.2 % of the patients had developed at least mild (EDSS ≥3) and 45.1 % moderate to severe neurological disability (EDSS ≥6). All of the patients with VST had EDSS scores of either 1 or 2 (minimal disability).

Prognostic factors

The results of Cox' regression analysis are presented in Table 4. The first step represents univariate analysis of each factor's effect on outcome. The final step represents the multivariate analysis. Since some of the factors were associated with outcome in the univariate but not the multivariate analysis, we also studied the correlations among the predictive variables. Variables that have positive associations ($P < 0.05$) with endpoint disability (EDSS) were: duration of neurological disease, progressive disease course, dysarthria, cerebellar symptoms other than dysarthria, and motor symptoms at onset. Factors negatively correlated (i. e., favorable) were: disease course limited to a single episode and headache at onset. Progressive disease, the most significant factor found to be associated with outcome in the regression analysis, was positively correlated with duration of BD, age at onset of neurological involvement, dysarthria, cerebellar symptoms other than dysarthria, and motor symptoms at onset. Headache at onset was negatively correlated with progressive disease and positively with course limited to a single episode. Variables found to be positively associated with progressive course were negatively associated with a limited single episode or vice versa. Other positive correlations were observed among dysarthria, motor symptoms, and cerebellar symptoms other than dysarthria at onset, probably due to clustering of these symptoms together as a cerebellopyramidal syndrome.

Discussion

This study examined the diagnostic and prognostic aspects of neurological involvement in BD. In a 15 year follow-up period we achieved nearly complete ascertainment within a large clinical practice of BD cases with a 15.1 % rate of referral for neurological consultation due to any neurological symptom. Of all BD patients 4.8 %

Tab. 4 Cox regression analysis of prognostic factors using time to EDSS of 6 or higher as the outcome measure and Pearson's correlation of significant factors with EDSS[a]

	First step		Final step		Correlation with EDSS	
	P	*P*	RR	CI	*r*	*P*
Age at onset of BD	0.0306	0.051	1.07	1.00–1.15	0.088	0.260
Headache present at onset	0.5837	0.010	4.28	1.41–12.96	–0.233	0.003
Dysarthria present at onset	0.0001					
Cerebellar symptoms other than dysarthria present at onset	0.0000	0.002	5.81	1.87–18.05	0.407	0.006
Motor symptoms present at onset	0.0233					
Progressive disease course	0.0000	0.002	8.87	2.26–34.87	0.584	< 0.001

[a] Other factors included in the analysis but not listed in the table because of nonsignificance are male sex, BD duration before onset of neurological involvement, onset with alteration of consciousness, onset with cognitive symptoms, onset with behavioral symptoms, onset with brainstem symptoms other than dysarthria. Imaging or CSF results were not studied as individual factors

developed definite neurological involvement due to their systemic disease.

Excluding a large group of noncomplicated common disorders such as headache has the advantage of preventing our sample from being diluted by coincidental associations between diagnostic and prognostic variables. However, we are well aware that incidental cases of complicated headache related to BD may also be discarded by this approach, especially if the follow-up time is short. Hence 291 patients with headache who were excluded from this study are currently followed by the NBS outpatient clinic and the long-term outcome of these patients is the subject of an ongoing study. Given the high number of patients with chronic headache, we suspect an increase in headache incidence from the population baseline in BD. A population-based prospective survey is necessary to answer this question.

We used several strategies to overcome the problems of pooling retrospective and prospective data. We compared the earlier records with prospective ones for compatibility of demographic, clinical, and imaging data and acute treatment protocols used. We tried to reach patients without current follow-up information by telephone so that we would not miss a recurrent or new neurological event. We chose to use EDSS 6 as cutoff for prognostic factor analysis, which is an easy-to-assess clinical disability level that is reliably replicated even from retrospective data [44]. Finally, we used survival methods and time to EDSS 6 as an outcome measure rather than EDSS by itself as a linear measure to account properly for the censored follow-up times.

In this study imaging studies were performed on the basis of clinical suspicion, availability, and affordability, followed by CSF studies only as supportive measures. Therefore the results of imaging and CSF studies do not reflect complete investigation of all individuals with BD and a neurological symptom; hence these are not studied as independent prognostic factors. The presence of oligoclonal bands in the CSF is an interesting finding but remains to be studied in larger number of cases before accepted as a definite finding or as pointing to a different subgroup of patients. Although limited to one or two bands, a similar finding was observed in 16 % of patients in another study [2].

Given the above limitations, the demographic aspects of our study are generally consistent with those of previous studies [1, 2, 22, 37, 41]. The male to female ratio in BD increases from 1:1 to 3.5:1 in a geographical distribution from east to west along the Silk Road [32]. The figure reported for Turkey is 3.3:1, combining the data from independent hospital-based series that were reported by that time [32]. However, the male to female ratio in the total BD population recorded in our center between January 1983 and January 1998 was 1.8:1. The male to female ratio of 3.8:1 in this study and our preliminary work [40, 41] suggests that there is a male predisposition for the development of neurological complications in BD. A prominent male dominance has also been previously observed for vascular complications of BD [28]. In a smaller group of patients with neurological involvement Serdaroglu et al. [37] observed a lower ratio (1.7:1 and 1.8:1) than that in our later results [40, 41]. However, in a recent updated study from the same institution [2] the ratio was also found to be 3.4:1, confirming ours. The earlier discrepancy was probably due to a sampling bias. Even though we have excluded "noncomplicated" headache referrals, the most common initial symptom is a single episode of headache. Onset with headache alone with or without papilledema is predictive of a limited form of disease. As such, patients with VST have disease limited to a single episode with rarely a relapse. Patients having other CNS symptoms or signs at onset, however, more often develop a relapsing or progressive course.

Considering two major forms of clinical onset and imaging findings, one conclusion is that patients with CNS symptoms and signs have a higher chance of having CNS parenchymal disease in MRI (79 %) than those with only headache at onset (29 %). On the other hand, having headache alone carries a 41 % chance of having VST, hence a total of 70 % chance of having some imaging abnormality. In a 7-year follow-up study 33 % of patient with only headache at onset considered initially as benign developed other CNS symptoms or signs [1, 37]. The initial diagnoses were based mostly on CT, and since very few patients underwent MRI or CSF studies, it is possible that parenchymal involvement and VST were underrepresented. Our study showed CSF examination to complement imaging studies and to be able to differentiate between NBS and VST, especially when MRI is not available or initially normal. It can be concluded that any patient with BD and headache that has just started or has shown a major change in character should be accepted as a case with probable VST. Therefore thorough clinical and MRI examinations followed by CSF studies and possibly magnetic resonance venography are indicated.

We found no case with definite aseptic meningitis. The only patient whom we suspected of having aseptic meningitis did not have MRI data to eliminate parenchymal disease from differential diagnosis. Since the high frequency of aseptic meningitis reported previously in Turkish patients [37] is based on CT as the primary imaging modality, it can be suspected that otherwise parenchymal disease was misclassified as such due to lack of sensitive imaging data. A recent update from the same institution [2] reports aseptic meningitis 1 of 200 cases studied, and it is not clear whether this single patient had MRI data to support such a diagnosis. Similarly, the recent study of 50 patients by Kidd et al. [22] reports four to have meningitis symptoms while two of these had parenchymal lesions and two normal MRI. There is no discussion of meningeal enhancement, and

the CSF findings are within the same range as brainstem parenchymal involvement. In support of this, we have always observed inflammatory findings in CSF together with parenchymal disease in MRI. Taken together, we conclude that pure aseptic meningitis is very rare within the clinical spectrum of neurological involvement in BD.

The previously reported 10-year survival rate of 8 % for BD in the same population [44] is within the limits that we found in this study for patients with neurological involvement. Although this may suggest that neurological involvement does not affect survival, longer follow-up is necessary before a definite statement can be made.

Approximately one-half of patients are moderate to severely disabled by 10 years, i. e., require at least one-sided support to walk 100 m. Considering that this is even slightly higher than that reported for multiple sclerosis in the same population [21] using the same scale, neurological involvement in BD is a remarkable cause of morbidity, confined only to NBS and not to VST cases.

Based on the regression analysis and considering all the individual correlations among variables, onset with only headache, diagnosis of VST, and disease course limited to a single episode are the favorable prognostic factors. On the other hand, onset with cerebellar symptoms with or without pyramidal symptoms, diagnoses of parenchymal disease, and progressive course are unfavorable. A clinically unexplained observation is that the brainstem symptoms or signs are not associated with a poor prognosis while cerebellar symptoms are, and dysarthria is associated with poor prognosis only univariately. Gender, age at onset, and duration of BD are not associated with neurological outcome.

These results from the analysis of prognostic factors may help in establishing guidelines for the choice of patients for treatment trials. However, they do not reflect the exact natural history of neurological involvement in BD, because one-half of the patients were treated by at least one or more immunosuppressive or immunomodulatory agent for their primary disease which may have disease-modifying effects [47].

Taken together, there are obvious differences in clinical and prognostic aspects between VST and NBS. The observation that in a given patient none of the MRI studies show both VST and parenchymal disease, either simultaneously or in follow-up examinations, supports the presence of distinct ongoing pathological processes. A vascular involvement pattern in MRI is totally different in these two forms, with VST representing a large venous lesion, while parenchymal lesions would better be described as due to inflammation of small intra-axial veins [24]. All of these considerations suggest different pathogenesis of these subtypes of neurological involvement, which requires investigation by further morphological studies.

Acknowledgements We thank particularly Dr. Brian G. Weinshenker for his review and comments on the paper. Some of the information on clinical and radiological data reported here were presented separately at the 7th Meeting of the European Neurological Society, Rhodes, Greece, 14–18 June 1997 and received one of the "best oral presentation" awards [40]. The information pertinent to prognosis and survival was also presented in part at the 8th Meeting and 10th Anniversary of the European Neurological Society, 6–10 June 1998, Nice, France [41]. The study in part was originally presented as Dr. Kantarci's thesis (Istanbul University, in Turkish) in April 1998, for obtaining his degree as a clinical neurologist. No outside funds were received for the study.

References

1. Akman-Demir G, Baykan-Kurt B, Serdaroglu P, et al (1996) Seven-year follow-up of neurologic involvement in Behçet syndrome. Arch Neurol 53:691–694
2. Akman-Demir, Serdaroglu P, Tasçi B and the Neuro-Behçet Study Group (1999) Clinical patterns of neurological involvement in Behçet's disease: evaluation of 200 patients. Brain 122:2171–2181
3. Al Kawi ZM, Bohlega S, Banna M (1991) MRI findings in neuro-Behçet's disease. Neurology 41:405–408
4. Amrom D, Buisseret T (1991) Clinical-radiological correlation in the evolution of a neuro-Behçet's syndrome: case report. Eur Neurol 31:419–422
5. Banna M, El-Ramahi K (1991) Neurological involvement in Behçet disease: imaging findings in 16 patients. AJNR Am J Neuroradiol 12:791–796
6. Baslo P, Kara I, Erek E, et al (1979) Clinical, electrophsiological, immunological and electron microscopic investigation of Behçet's disease. In: Dilsen N, Koniçe M, Ovul C (eds) Behçet's disease. Excerpta Medica International Congress Series 467:178–182
7. Behçet H (1937) Über residivierende, aphtöse, durch ein Virus verursachte Geschwüre am Mund, am Auge und an den Genitalien. Dermatol Wochenschr 105:1152–1157
8. Behçet's Disease Research Committee of Japan (1974) Behçet's disease: guide to diagnosis of Behçet's disease. Jpn J Ophthalmol 18:291–294
9. Ben Ezra D, Cohen E (1986) Treatment and visual prognosis in Behçet's disease. Br J Ophthalmol 70:589–592
10. Bogdanova D, Milanov I, Georgiev D (1998) Parkinsonian syndrome as a neurological manifestation of Behcet' s disease. Can J Neurol Sci 25:82–85
11. Cengiz K, Özkan A (1991) Psychiatric aspects of complete Behçet's syndrome: review of fifteen cases. O'Duffy JD, Kökmen E (eds) Behçet's disease: basic and clinical aspects. Dekker, New York, pp 115–118
12. Clausen J, Bierring F (1983) Involvement of postcapillary venules in Behçet's disease. Acta Dermatovener (Stockh) 63:191–197
13. Devlin T, Gray L, Allen NB, et al (1995) Neuro-Behçet's disease: factors hampering proper diagnosis. Neurology 45:1754–1757
14. Dilsen N, Koniçe M, Aral O (1986) Our diagnostic criteria of Behçet's disease – an overview. In: Lehner T, Barnes CG (eds) Recent advances in Behçet's disease. International Congress Series no 103. Royal Society of Medicine Services, London, pp 177–180

15. Hamuryudan V, Yurdakul S, Moral F, et al (1994) Pulmonary arterial aneurysms in Behçet's syndrome: a report of 24 cases. Br J Rheumatol 33:48–51
16. Harper MC, Kökmen E (1991) Magnetic resonance in Behçet's disease. O'Duffy JD, Kökmen E (eds) Behçet's disease: basic and clinical aspects. Dekker, New York, pp 335–341
17. International Study Group for Behçet's Disease (1990) Criteria for diagnosis of Behçet's disease. Lancet 335:1078–1080
18. International Study Group for Behçet's disease (1992) Evaluation of diagnostic (classification) criteria in Behçet's disease – towards internationally agreed criteria. Br J Rheumatol 31:299–308
19. James DG, Thompson A (1982) Recognition of the diverse cardiovascular manifestations in Behçet's disease. Am Heart J 103:457–458
20. Kansu T, Kirkali P, Kansu E, Zileli T (1989) Optic neuropathy in Behçet's disease. J Clin Neuroophthalmol 9:277–280
21. Kantarci O, Siva A, Eraksoy M, et al (1998) Survival and predictors of disability in Turkish MS patients. Neurology 51:765–772
22. Kidd D, Steuer A, Denman AM, Rudge P (1999) Neurological complications in Behçet' s syndrome. Brain 122:2171–2181
23. Koç Y, Güllü I, Akpek G, et al (1992) Vascular involvement in Behçet's disease. J Rheumatol 19:402–410
24. Koçer N, Islak C, Siva A, Saip S, Akman C, Kantarci O, Hamuryudan V (1999) CNS involvement in Neuro-Behçet's syndrome: an MR study. AJNR Am J Neuroradiol 20:1015–1024
25. Kurtzke JF (1983) Rating neurological impairment in MS: an expended disability status scale (EDSS). Neurology 33:1444–1452
26. Mason RM, Barnes CG (1969) Behçet's syndrome with arthritis. Ann Rheum Dis 28:95–103
27. Morrissey SP, Miller DH, Harmszewski R, et al (1993) Magnetic resonance imaging of the central nervous system in Behçet's disease. Eur Neurol 33:287–293
28. Müftüoglu AÜ, Yurdakul S, Yazici H, et al (1986) Vascular involvement in Behçet's disease – a review of 129 cases. Lehner T, Barnes CG (eds) Recent advances in Behçet's disease. Royal Society of Medicine Service, London pp 181–186
29. Nüssel F, Wegmüller H, Laseyras F, et al (1991) Neuro-Behçet: acute and sequential aspects by MRI and MRS. Eur Neurol 31:399–402
30. O'Duffy JD (1974) Suggested criteria for diagnosis of Behçet's disease. J Rheumatol 1 [Suppl 1]::18
31. O'Duffy JD (1990) Vasculitis in Behçet's disease. Rheum Dis Clin North Am 16:423–431
32. Ohno S (1986) Behçet's Disease in the world. Lehner T, Barnes CG (eds) Recent advances in Behçet's disease. Royal Society of Medicine Service, London pp 181–186
33. Pamir MN, Kansu T, Erbengi A, Zileli T (1981) Papilledema in Behçet's syndrome. Arch Neurol 38:343–345
34. Park JH, Han MC, Bettmann MA (1984) Arterial manifestations of Behçet's disease. AJR Am J Roentgenol 143:821–825
35. Perniciaro C, Molina J (1991) Cerebrovascular aneurysms in patients with Behçet's disease. In: O'Duffy JD, Kökmen E (eds) Behçet's disease: basic and clinical aspects. Dekker, New York, pp 119–123
36. Serdaroglu P (1998) Behçet's disease and the nervous system. J Neurol 245:197–205
37. Serdaroglu P, Yazici H, Özdemir C, et al (1989) Neurological involvement in Behçet's syndrome: a prospective study. Arch Neurol 46:265–269
38. Siva A, Özdogan H, Yazici H, et al (1986) Headache, neuro-psychiatric and computerized tomography findings in Behçet's syndrome. In: Lehner T, Barnes CG (eds) Recent advances in Behçet's disease. Royal Society of Medicine Service, London pp 247–254
39. Siva A, Necdet V, Yurdakul S, et al (1991) Neuroradiological findings in Neuro-Behçet syndrome. In: O'Duffy JD, Kökmen E (eds) Behçet's disease: basic and clinical aspects. Dekker, New York, pp 323–329
40. Siva A, Saip S, Kantarci O, et al (1997) Neuro-Behçet syndrome (NBS): clinical and imaging correlates. J Neurology 224 [Suppl 3]:S45
41. Siva A, Kantarci O, Saip S, Hamuryudan V, Altintas A, Yazici H (1998) Neuro-Behçet syndrome (NBS): prognostic factors and survival. J Neurol 245:362:97
42. Wechsler B, Dormont D, Lubetzki C, et al (1991) Magnetic resonance in Behçet's disease. O'Duffy JD, Kökmen E (eds) Behçet's disease: basic and clinical aspects. Dekker, New York, pp 331–334
43. Wechsler B, Vidailhet M, Bousser MG, et al (1992) Cerebral venous sinus thrombosis in Behçet's disease: long term follow-up of 25 cases. Neurology 42:614–618
44. Weinshenker BG (1995) The natural history of multiple sclerosis. Neurol Clin 1:119–146
45. Yazici H, Tüzün Y, Pazarli H, et al (1984) Influence of age at onset and patients' sex on the prevalence and severity of manifestations of Behçet's syndrome. Ann Rheum Dis 43:783–789
46. Yazici H, Basaran G, Hamuryudan V, et al (1996) The ten-year mortality in Behçet's syndrome. Br J Rheumatol 35:139–141
47. Yazici H, Yurdakul S, Hamuryudan V (1999) Behçet's syndrome. Curr Opin Rheumatol 11:53–57