The association between the parenchymal neurological involvement and posterior uveitis in Behçet's syndrome

B. Bitik[1], A. Tufan[2], K. Sahin[3], Y. Sucullu Karadag[4], S. Can Sandikci[3], R. Mercan[2], F. Ak[4], Y. Karaaslan[3,5], M.A. Ozturk[2], B. Goker[2], S. Haznedaroglu[2]

[1]Department of Internal Medicine/ Rheumatology, Ankara Education and Research Hospital, Ankara;
[2]Department of Internal Medicine/ Rheumatology, Gazi University Faculty of Medicine, Ankara;
[3]Department of Internal Medicine/ Rheumatology, Numune Education and Research Hospital, Ankara;
[4]Department of Neurology, Numune Education and Research Hospital, Ankara;
[5]Department of Internal Medicine/ Rheumatology, Hitit University School of Medicine, Ankara, Turkey.

Berivan Bitik, MD
Abdurrahman Tufan, MD
Kubilay Sahin, MD
Yesim Sucullu Karadag, MD
Sevinc Can Sandikci, MD
Ridvan Mercan, MD
Fikri Ak, MD
Yasar Karaaslan, MD
Mehmet Akif Ozturk, MD
Berna Goker, MD
Seminur Haznedaroglu, MD

Please address correspondence to:
Berivan Bitik, MD,
Ankara Education and Research Hospital,
Department of Internal Medicine,
Division of Rheumatology,
06500 Altındag, Ankara, Turkey.
E-mail: berivanbitik@hotmail.com

Received on December 18, 2015; accepted in revised form on June 14, 2016.

Clin Exp Rheumatol 2016; 34 (Suppl. 102): S82-S85.

© Copyright CLINICAL AND EXPERIMENTAL RHEUMATOLOGY 2016.

Key words: Behçet's syndrome, neuro-Behçet's syndrome, posterior uveitis

Competing interests: none declared.

ABSTRACT

Objective. *Behçet's syndrome (BS) is a systemic vasculitis, which may involve multiple organ systems simultaneously. Clinical findings in BS often fit into well-recognised patterns, such as the association between papulo-pustular skin lesions and arthritis. We have recently observed a distinct pattern, in which a subtype of neuro-Behçet's syndrome (NBS) is often preceded by specific ophthalmic manifestations of the disease process. The purpose of this study is to evaluate the association between the parenchymal subtype of NBS and posterior uveitis (PU).*

Methods. *We retrospectively reviewed the clinical records of 295 patients with BS, who met the international classification criteria for BS, diagnosed at two major rheumatology clinics from 2010 to 2014. Patient demographics, ophthalmic examinations, clinical and radiologic patterns of neurological involvement were recorded. Manifestations of BS were classified as PU, NBS, vascular involvement, and arthritis. The association between clinical findings was analysed for statistical significance.*

Results. *Of the 295 patients, 100 had PU and 44 had NBS. 30 patients had parenchymal NBS and 14 had vascular NBS. Patients with PU were significantly more likely to have neurological involvement compared to those without PU ($p<0.001$; odds ratio: 3.924; 95% CI: 1.786–8.621). Rate of posterior uveitis was higher in patients with parenchymal NBS when compared to patients with vascular NBS, vascular BS or arthritis (63.3%, 21.4%, 22% and 4.2% respectively, $p<0.001$).*

Conclusion. *Our findings suggest a clinically and statistically significant association between posterior uveitis and parenchymal type of neurologic involvement in BS. The development of posterior uveitis in a patient with previously diagnosed BS should be recognised as a "warning sign" for predisposition to neurologic involvement. These patients should be informed about the possible signs and symptoms of neurological involvement, which can cause very rapid and irreversible damage unless recognised and treated immediately.*

Introduction

Behçet's syndrome (BS) is a systemic vasculitis that may involve multiple organ systems simultaneously or consecutively. Diagnosis is primarily based on clinical features such as oral and genital aphthous ulcers, characteristic skin lesions, and a positive pathergy reaction. These clinical features were organised into diagnostic criteria by the International Study Group on Behçet's Disease which are widely used in current practice (1).

Moreover, BS is commonly associated with signs of systemic involvement such as arthritis, vascular and neurologic lesions. Neurological involvement in BS [neuro-Behçet's syndrome (NBS)] is a dreaded complication of disease and almost always results in significant disability, unless recognised and treated immediately. NBS has been classified into parenchymal and vascular (non-parenchymal) subtypes. These subtypes of NBS are suggested to have different pathogenetic mechanisms (2, 3). Some previous reports revealed a possible association between parenchymal NBS and eye involvement in BS (2, 4-6). The coexistence of these pathologies may be explained by a theory of common embryonic origin between the retina and the brain parenchyma. Herein, we aimed to evaluate the possible association between NBS and posterior uveitis.

Materials and methods

Patients and data collection

Medical records of BS patients, who

met the criteria of the International Study Group for Behçet's Disease followed in two major rheumatology clinics were retrospectively reviewed (1). Between 2010 and 2014, a total of 295 patients with a diagnosis of BS and aged >18 years old were included in the study protocol. Patient charts and radiological images were retrospectively reviewed to collect data on demographic information, clinical manifestations of BS, ophthalmic findings and details of neurological involvement. For purposes of data analysis, manifestations of BS were classified as posterior uveitis, NBS, vascular involvement, arthritis and gastrointestinal involvement (entero-Behçet's syndrome). Vascular BS was comprised of deep venous thrombosis, pulmonary vascular disease and Budd-Chiari syndrome (Table I). The definition of posterior uveitis was defined as retinitis, choroiditis, vitritis and retinal vasculitis. Patients with papillitis or optic neuritis were not included in the posteior uveitis group. Neurological involvement was classified as parenchymal and vascular. Parenchymal NBS was defined as meningoencephalitis with or without spinal lesions. The differentiation was made by Magnetic Resonance Imaging (MRI) and MR venography, which were performed in all NBS patients.

Statistical analyses

For statistical analyses SPSS for windows v. 14.0 (Chicago, IL) was used. Normality distribution of groups were assessed with Kolgomorov-Smirnov test. Categorical variables of disease groups were compared with Chi-square test (or Fisher's exact test, where appropriate). Continuous variables were compared using the student's *t*-test or Mann-Whitney U-tests. Odds ratios were calculated along with their corresponding 95% confidence intervals (CI). A *p*-value of 0.05 or less is considered as statistically significant in all analyses.

Results

Of the 295 patients included in our study, 100 had posterior uveitis (67 men and 33 women; mean age, 36.9±9.6 years) and 44 had NBS (27 men and 17 women; mean age, 31.7±6.6 years). Demographic features and disease manifestations of patients with BS are shown in Table I. Of the 44 patients with NBS, 30 had parenchymal NBS and 14 had vascular NBS (Table II). In all vascular NBS patients, the vascular pathology was venous sinus thrombosis, exclusively.

Patients with posterior uveitis were significantly more likely to have parenchymal neurological involvement compared to those without posterior uveitis ($p<0.001$; Odds Ratio: 3.924; 95% CI: 1.786–8.621) (Table III). In all, 19 of 30 patients with parenchymal NBS and 3 of 14 patients with vascular NBS had posterior uveitis before or during the course of neurological involvement. Rate of posterior uveitis was higher in patients with parenchymal NBS when compared to patients with vascular NBS, vascular BS or arthritis (63.3%, 21.4%, 22% and 4.2% respectively, $p<0.001$) (Table IV). Rate of posterior uveitis was not significantly different in patients with or without vascular NBS, vascular BS or arthritis. Due to the small number of patients, entero-Behçet's syndrome was not included in the statistical analysis.

Interval between the first posterior uveitis attack and NBS

Data on the period between the development of NBS and the first attack of posterior uveitis was available for 16 patients. All of them had posterior uveitis before the development of NBS; the median time from the first posterior uveitis attack to the development of NBS was 28.5 months (range, 6–120 months; Table II). Of these 16 patients, 10 had active posterior uveitis along with NBS onset and six had posterior uveitis sequels. The median time from the diagnosis of BS to the development of NBS was 4 years (range, 0–10 years). Six out of 44 patients had diagnosed with BS at initial presentation of NBS.

Immunosuppressive therapy at the time of NBS diagnosis in patients with a history of posterior uveitis

Data on the immunosuppressive therapy in patients with a history of posterior uveitis while NBS developed was available for 24 patients. 9 patients were using azathioprine (100–150mg/day), 6 were using interferon alfa-2a (3–6 million international units three times a week) and 4 were using cyclosporine (200 mg/day) at the time of NBS diagnosis. One patient was on combined azathioprine and cyclosporine regimen. Four patients with a history of posterior uveitis discontinued the recommended immunosuppressive therapy on their own will, at least one year prior to NBS diagnosis. None of the patients were using colchicine. Twenty-two patients were using corticosteroids at the time of NBS diagnosis.

Organ involvement other than neurological involvement in patients with NBS

Other disease manifestations in patients with parenchymal NBS were posterior

Table I. Demographic features and disease manifestations of patients with Behçet's syndrome.

Characteristics	Total n=295, (%)
Age, mean, years	36.9 ± 9.6
Male/Female	155/140
Posterior uveitis, n (%)	100 (33.8%)
Neurological involvement, n (%)	44 (14.9%)
Neural parenchymal, n (%)	*30 (10.1%)*
Neural vascular, n (%)	*14 (4.7%)*
Vascular	49 (16.6%)
Deep venous thrombosis, n (%)	*28 (9.4%)*
Pulmonary vascular disease, n (%)	*17 (5.7%)*
Budd-chiari syndrome, n (%)	*4 (1.3%)*
Arthritis, n (%)	29 (9.8%)
Entero-Behçet's, n (%)	5 (1.6%)

uveitis and arthritis while those in patients with vascular NBS were posterior uveitis, deep venous thrombosis, Budd-Chiari syndrome, and arthritis (Table II).

Table II. Characteristics of patients with neurological involvement.

Characteristics	Parenchymal NBS n=30	Vascular NBS n=14	*p*-value
Gender (Male/Female)	20/10	7/7	NS
Age at diagnosis of BS, years*	28.0 ± 6.9	29.2 ± 5.5	NS
Age at diagnosis of NBS, years*	31.8 ± 7.5	31.4 ± 3.8	NS
Time from diagnosis of BS to development of NBS, years*	4.5 (0-10 years)	4 (0-6 years)	NS
Posterior uveitis, n (%)	19	3	0,01
Vascular disease	0	4	0,00
Arthritis	2	1	NS
Time from first attack of PU to development of NBS**	6 months (6-120)	12 months (12-48)	NS

Values are given as mean±SD or median (range). NS: non-significant; *Data available on 30 NBS patients, **Data available on 16 NBS patients. BS: Behçet's syndrome; NBS: neuro-Behçet's syndrome; PU: posterior uveitis.

Table III. The association between posterior uveitis and the type of neurological involvement in patients with BS.

		Type of neurological involvement Parenchymal (n, %)	Vascular (n, %)	*p*-value	Odds ratio (95% CI)
Posterior uveitis, n	Present	19 (63.3%)	3 (21.4%)	*p*=0.02	6.33 (1.44-27.7)
	Absent	11 (36.7%)	11 (78.6%)		

Table IV. The rate of posterior uveitis in patients with parenchymal NBS and other types of involvement in patients with BS.

		Type of involvement				
		Parenchymal NBS n (%)	Vascular NBS n (%)	Vascular BS n (%)	Arthritis n (%)	*p*-value
Posterir uveitis, n (%)	Present	19 (63.3)	3 (21.4)	9 (22)	1 (4.2)	<0.001
	Absent	11 (36.7)	11 (78.6)	32 (78)	23 (95.8)	

Discussion

In this study, we analysed the association between neurological involvement and posterior uveitis in patients with BS. The frequency of NBS was 14%. The prevalence of posterior uveitis in patients with NBS was 50%. A strong association was observed between posterior uveitis and parenchymal NBS.

The reason why BS presented with different symptoms in each patient is unknown. Clinical findings of BS fit into well-recognised patterns such as association between papulopustular skin lesions and arthritis (7, 8). A recent study showed that cerebral venous sinus thrombosis frequently co-occurs with peripheral venous vascular events such as deep venous thrombosis and pulmonary vascular disease (9). It has been previously suggested that more than one pathological pathway is involved in what is called BS today (10). The different pathological pathways in vascular and non-vascular BS may also be suggested as well (11, 12). Thus, based on these hypotheses, it is also suggested that pathways involved in the pathogenesis of parenchymal NBS may differ from those involved in vascular NBS (2, 3). Although it is known that posterior uvea is a part of the central nervous system, not all patients with posterior uveitis develop neurological involvement.

Male to female ratio was 1.5:1 among patients with NBS. Although a prominent male dominance in NBS was reported in several studies (2, 13, 14), this ratio seems to be lower in studies recently published (6, 15). This ratio may change depending on the population region or size. In this study, posterior uveitis was diagnosed before the development of neurological involvement in all patients with NBS. This may be because more intensive immunosuppressive treatment given for NBS generally suppresses the disease activity; hence, the development of subsequent posterior uveitis is less likely in these patients. In our study, the median period between the first posterior uveitis attack and the development of NBS was 28.5 months. A recent case study reported that NBS developed 2 years after the diagnosis of posterior uveitis (5). Moreover, this period was suggested to be a "risk window" for the development of NBS. Although the population size in our study and in the above mentioned study was small, it can be suggested that patients with BS having posterior uveitis would be at risk of developing NBS in approximately two years time. The duration of immunosuppressive therapy in patients with posterior uveitis is controversial; however, in clinical practice, most clinicians recommend maintenance of immunosuppressive therapy for at least two years (11). Our findings support this suggested period of therapy for posterior uveitis.

In this study, it is observed that NBS developed despite immunosuppressive therapy. Four of 24 patients (16.6%) were taking cyclosporine when they presented with NBS. Cyclosporine was reported to be associated with NBS in large cohorts (16-18). However, in our study it is not possible to specify such an association due to small patient numbers.

Eye involvement was seen in 66% of 200 NBS patients in the largest cohort in the literature (2). A recent study showed ocular manifestation in 64% of 115 patients with parenchymal NBS (19). Distinction of eye involvement as an anterior or posterior uveitis was

not the primary goal of the above studies. Therefore, the actual ratio may be higher than expected.

In our series, the prevalence of pulmonary involvement or NBS was higher than previously published cohorts (9, 20). This difference in distribution, might be attributable to the "tertiary" setting of clinical care, since our institutions typically receive the complex/complicated cases from primary/secondary care units.

However, our study has some limitations: it is a retrospective chart review, and data on the immunosuppressive therapy at the time of NBS diagnosis in patients with posterior uveitis, was available for only 24 patients. 4 out of 24 patients were taking cyclosporine, and we cannot comment on whether NBS has evolved due to the use of cyclosporine or not. Additionally, data on steroid dosage could not be fully assessed. Anterior uveitis was not registered because of two reasons: (1) it is usually not documented by physicians and (2) patient-reported data may not be reliable, because they may interfere with some other eye diseases.

In conclusion, our findings suggest a clear association between posterior uveitis and neurological involvement. Patients with BS having posterior uveitis should be warned about the possible signs and symptoms of neurological involvement, which can progress quite rapidly.

References

1. Criteria for diagnosis of Behçet's disease. International Study Group for Behçet's Disease. *Lancet* 1990; 335: 1078-80.
2. AKMAN-DEMIR G, SERDAROGLU P, TASCI B: Clinical patterns of neurological involvement in Behçet's disease: evaluation of 200 patients. The Neuro-Behçet Study Group. *Brain* 1999; 122: 2171-82.
3. SIVA A, KANTARCI OH, SAIP S *et al*.: Behçet's disease: diagnostic and prognostic aspects of neurological involvement. *J Neurol* 2001; 248: 95-103.
4. IDEGUCHI H, SUDA A, TAKENO M *et al*.: Neurological manifestations of Behçet's disease in Japan: a study of 54 patients. *J Neurol* 2010; 257: 1012-20.
5. BITIK B, UCAR M, TEZCAN ME *et al*.: Transverse myelitis in Behçet's disease: a series of four cases and review of the literature. *Clin Exp Rheumatol* 2013; 31 (Suppl. 77): 20-4.
6. DAOUDI S, LOUNIS M, AIT-KACI-AHMED M: [Parenchymal neuro-Behçet's disease. Clinical and paraclinical characteristics, a report of 40 cases]. *Presse Med* 2014; 43: 119-25.
7. TUNC R, KEYMAN E, MELIKOGLU M, FRESKO I, YAZICI H: Target organ associations in Turkish patients with Behçet's disease: a cross sectional study by exploratory factor analysis. *J Rheumatol* 2002; 29: 2393-6.
8. DIRI E, MAT C, HAMURYUDAN V, YURDAKUL S, HIZLI N, YAZICI H: Papulopustular skin lesions are seen more frequently in patients with Behçet's syndrome who have arthritis: a controlled and masked study. *Ann Rheum Dis* 2001; 60: 1074-6.
9. TASCILAR K, MELIKOGLU M, UGURLU S, SUT N, CAGLAR E, YAZICI H: Vascular involvement in Behçet's syndrome: a retrospective analysis of associations and the time course. *Rheumatology* (Oxford) 2014; 53: 2018-22.
10. YAZICI H, UGURLU S, SEYAHI E: Behçet's syndrome: is it one condition? *Clin Rev Allergy Immunol* 2012; 43: 275-80.
11. YAZICI Y, YAZICI H, (Eds.): Behçet's Syndrome. Springer Science and Business Med LLC, 2010.
12. MELIKOGLU M, KURAL-SEYAHI E, TASCILAR K, YAZICI H: The unique features of vasculitis in Behçet's syndrome. *Clin Rev Allergy Immunol* 2008; 35: 40-6.
13. AL-FAHAD SA, AL-ARAJI AH: Neuro-Behçet's disease in Iraq: a study of 40 patients. *J Neurol Sci* 1999; 170: 105-11.
14. TALARICO R, d'ASCANIO A, FIGUS M *et al*.: Behçet's disease: features of neurological involvement in a dedicated centre in Italy. *Clin Exp Rheumatol* 2012; 30 (Suppl. 72): S69-72.
15. HOUMAN MH, BELLAKHAL S, BEN SALEM T *et al*.: Characteristics of neurological manifestations of Behçet's disease: a retrospective monocentric study in Tunisia. *Clin Neurol Neurosurg* 2013; 115: 2015-8.
16. KOTAKE S, HIGASHI K, YOSHIKAWA K, SASAMOTO Y, OKAMOTO T, MATSUDA H: Central nervous system symptoms in patients with Behçet disease receiving cyclosporine therapy. *Ophthalmology* 1999; 106: 586-9.
17. AKMAN-DEMIR G, AYRANCI O, KURTUNCU M, VANLI EN, MUTLU M, TUGAL-TUTKUN I: Cyclosporine for Behçet's uveitis: is it associated with an increased risk of neurological involvement? *Clin Exp Rheumatol* 2008; 26 (Suppl. 50): S84-90.
18. KOTTER I, GUNAYDIN I, BATRA M *et al*.: CNS involvement occurs more frequently in patients with Behçet's disease under cyclosporin A (CSA) than under other medications – results of a retrospective analysis of 117 cases. *Clin Rheumatol* 2006; 25: 482-6.
19. NOEL N, BERNARD R, WECHSLER B *et al*.: Long-term outcome of neuro-Behçet's disease. *Arthritis Rheumatol* 2014; 66: 1306-14.
20. SERDAROGLU P, YAZICI H, OZDEMIR C, YURDAKUL S, BAHAR S, AKTIN E: Neurologic involvement in Behçet's syndrome. A prospective study. *Arch Neurol* 1989; 46: 265-9.