Behçet's Disease

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BEHÇET HASTALIĞI
190 OLGUNUN ANALİZİ

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SUMMARY

We analysed retrospectively the hospital records of 190 patients with Behcet's disease admitted to Hacettepe University Hospital between 1971-1983. Our series comprised of 128 male and 82 female patients with a mean age of 32.8 years. The most frequent manifestations were oral ulcers (96.3%), genital lesions (82.1%), ocular (35.3%) and joint involvement (40.5%), Cutaneous lesions of which the most frequent one was erythema nodosum (26,3%) constituted another prominent feature. Cardiovascular manifestations were observed in (38,4%) of the patients; the main involvement was venous thrombophlebitis and obstruction, two patients had Budd-Chiari syndrome due to hepatic vein thrombophlebitis. Two arterial aneurysms (4.7%) were detected angiographically. Nine of patients were found to be hypertensive. Renal amyloidosis was recorded in two patients. Nervous system involvement was recorded in 7.3% of the patients and most of them had pseudotumor cerebri. ESR was found to be elevated in 68.1% of patients during relapses. HLA-B$_5$ antigen was found in 75.5% of the investigated patients. We could not evaluate the therapeutic regiments in our series because of the diversity of the regimen and inadequate follow-up of those uncontrolled trial.

Key Words: Behcet's disease, oro-genital ulcers and iridocyclitis with hypopyon, HLA-B$_5$ tissue group antigenes

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ÖZET

Bu çalışmada 1971-1983 yılları arasında Hacettepe Üniversitesi Tıp Fakültesi Hastanelerine başvuran 190 Behçet Hastalığı olgusunun hastane kayıtları gözden geçirildi Grup 128 erkek ve 62 kadından oluşuyordu. En sık görülen manifestasyonlar oral ülserler (% 96.3), genital lezyonlar (%82.1), göz (%35.3) ve eklem hastalığı (%40.5) idi. Deri belirtilerinin kendisini en sık eritema nodosum şeklinde gösterdiği belirlendi (% 26.3). Kardiyovasküler lezyonlar hastaların % 38.4'ünde saptandı ve venöz tromboflebit ve obstrüksiyon en sık görülen klinik özellik idi. İki hastada Budd-Chiari sendromunun geliştiği saptandı, İki hastada anjiyografik olarak gösterilen arteriyel anevrizma belirlendi. Dokuz hastanın hipertansif olduğu ve iki hastada da renal amiloidozis geliştiği saptandı. En sık görülen sinir sistemi belirtisi pseudotumor cerebri idi. Eritrosit sedimentasyon hızının alevlenmeler sırasında % 68.1 olguda yüksek olduğu bulundu. HLA-B$_5$ antijeninin varlığının % 75.5 hastada gösterildiği anlaşıldı. Çok çeşitli tedavi biçimleri uygulandığı ve yetersiz süre izlenmiş olduğu için tedavi ile ilgili yorum yapılmadı.

Anahtar Kelimden Behçet hastalığı, oro-genital ülserler ve hipopyonlu iridos HLA-Bj doku grubu antijeni

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INTRODUCTION

Since the **first** description of the disease in 1937 **by Professor Hulusi** Behcet **(1), a Turkish** dermatologist, **the spectrum of** Behcet**'s disease has** been expanded. **It is** now **recognized as a multisystem disorder which has been called** Behcet**'s syndrome** by some **authors.** The **prominent** features **of** the syndrome are **mucocutaneous,** ocular, intestinal, **articular,** vascular, urogenital and neurological **involvements.** While classically **intermittent** in its **manifestations,** the disease may stabilize and become **chronic** in **a** given **organ** system.

Although Behcet suggested that viral etiology would account for the **disease, further studies have** not confirmed **this** hypothesis and the etiology remains obscure **(2).**

The majority of the reported cases have originated in Japan or in Mediterranean countries including Turkey (3-7).

In this report we present a series of 190 patients with Behcet's disease who were followed at Hacettepe University Hospital between 1971-1983.

MATERIAL and METHODS

The hospital records of 190 patients with typical Behcet's disease were analysed retroscpectively. All of the patients were defined according to the criteria proposed by Mason and Barnes (8) previously. Most of them had been followed as outpatients while some had been hospitalized during their follow-up periods at Hacettepe University Hospital between 1971-1983.

RESULTS

I- Clinical Features

1. Age and Sex: The patients comprised of 128 males and 62 females (ratio 2.1/1), ranging in age from 17 to 56 years with a mean age of 32.8 years.

2. Localization of the First Manifestation: Oral ulcers were the first manifestation in 140 patients (74%). Joint involvement, ocular, cutaneous, genital, neurological or vascular lesions were recorded in others.

3. Family History: Fifteen patients (7.9%) had a family history of Behcet's disease. Three of them were the same family of whom two were identical twins; the remainder comprised of father and son in one family and brothers in five families.-

4. **Oral Lesions:** Painful, recurrent oral ulcers were recorded in 183 patients (96.3%). These were single or multiple apthous lesions varying in size, located on the lips, gums, buccal mucosa, tongue or tonsils. They persisted usually for 7-14 days and recurred after an interval of several days to several months.

5. Ocular Lesions: Ocular involvement was observed in 35.3% of 67 patients (Table - I). The most prominent features were anterior and posterior uveitis and were detected in 56 of them (83.6%). Two patients (3.1%) had papillitis and 3 patients (4.5%) had retinitis. The complications of ocular involvement were as follows: optic atrophy in 1 patient (1%), blindness in 11 patients (16%), cataract in 7 patients (10%), glaucoma in 6 patients (9%) and phytisis bulbi in 7 patients (10%).

6. **Genital Lesions:** Genital lesions occured in 156 patients (81.2%). They were located on the scrotum or penis in men and on the vulva or in the vagina in women. The ulcers were usually painful (particulary in men) persisting up to several weeks and recurring quite irregularly. Scars of the previous genital ulcers were detected in 22 patients (14.1%). A perianal ulcer was recorded in one patient (0.5%). Orchitis was found in 2 patients (1.0%) and epididymitis in another two (1.0%).

7. Joint Manifestations: Seventy-seven patients (40.5%) developed joint involvement which were presented as arthralgias in 41 patients (53.3%) and arthritis in 36 patients (46.7%). The knee was the most frequently attacked joint in 35 patients (18.4%). The distribution of joint involvement is shown in Table II. Despite persistent or recurrent joint involvement, no deformities or x-ray changes were noted.

8. Cutaneous Lesions: In 104 of our patients (54.7%) skin lesions were observed. The detected lesions and their frequencies are listed in Table III. They consisted of a variety of lesions including acnea, furancles, erythema nodosum, skin ulceration, cutaneous vasculitis and the others. The skin manifestations have remitted spontaneously within several weeks but have tended to reappear at a later period. We also observed non-specific skin reactivity to needle pricks in 21 patients.

Table - I

Ocular Lesions

	Number of Patient	Percent
Anterior and posterior uveitis	56/67	83.6
Optic papillitis	2/67	3.1
Retinitis	3/67	4.5
Complications		
Optic atrophy	1/67	1.5
Blindness	11/67	16.4
Cataract	7/67	10.4
Glaucoma	6/67	9.0
Phytisis bulbi	7/67	10.4

Table - II

The Distribution of Joint Involvement

	Number of Patient	%
Small joints of the hand	9/190	4.7
Wrist	18/190	9.5
Elbow	14/190	7.3
Shoulder	8/190	4.2
Ankle	26/190	13.7
Knee	45/190	23.7
Hip	5/190	2.6

9. Cardiovascular Manifestations: Cardiovascular manifestations were observed in 73 patients (38.4%), As shown in Table IV, the main manifestation was venous thrombophlebitis and obstruction. A venography was performed in 13 patients (6.8%) and the others were diagnosed according to overt clinical features. Interestingly, two patients had Budd-Chiari syndrome due to hepatic vein thrombophlebitis (9). Two arterial aneurysms (aortic and pulmonary arterial) were detected angiographically. The cardiac manifestations were pericardial effusion in one patient and a moderate (3/4) aortic insufficiency in another.

10. Gastrointestinal Manifestations: Gastrointestinal involvement was not observed frequently in our series (Table V). We detected active duodenal ulcer in 10 patients (5.2%). One patient had marked hepatosplenomegaly and despite detailed investigations (including splenoportography and liver needle biopsy) we could not find any evidence of a disorder that could give rise to this manifestation. We detected esophageal varices in 3 patients (1.6%), in whom superior and/or inferior vena cava were obstructed. In one patient (0.5%) a solitary colonic ulcer was observed. Two patients (1.0%) developed perianal fistula.

11. Renal Manifestations: Nine of our patients (4.7%) were found to be hypertensive. Eight patients (4.2%) showed proteinuria, 9 (4.7%) piuria and 11 (5.8%) hematuria. A percutaneous renal needle biopsy was performed in 5 patients (2.6%), detailed in Table VI. Interestingly renal amyloidosis was recorded in two patients (1.0%) (10).

12. Neurological Manifestations: Nervous system involvement was recorded in 14 patients (7.3%), detailed in Table VII. Most of them had pseudotumor cerebri due to intracranial venous occlusions shown by cerebral venography. One patient had neurological dysfunction similar to a cerebellopontine angle lesion and another had manifestations suggesting cerebellar dysfunction.

13. Pulmonary Manifestations: Pleural effusion was observed in 7 patients (3.7%) of whom 5 had superior vena caval obstruction. In the other two no underyling disorder consistent with pleural effusion could be detected. One of these patients had also a coin lesion (3x3 cm) in the left pulmonary area.

14. Miscellaneous Features: Bouts of fever paralelling the severity of system involvement were observed in most patients during relapses. The fever was accompanied by chills occasionally and reached up to 40°C rarely.

Three of our patients developed malignant tumors during the course of the Behcet's disease, namely carcinoma of the breast, chronic myelocytic leukemia and epidermoid carcinoma of the skin (11).

Table - III

Analysis of Skin Lesions

Lesions	Number of Patient	%
Erythema nodosum	50	26.3
Acnea	23	12.1
Furuncle	17	8.9
Cutaneous vasculitis	3	1.6
Cutaneous ulcer	9	4.7
Miscellaneous	12	6.3
Maculopapular lesions	5	2.6
Macular, erythematous lesions	4	2.1
Ulticaria	1	0.5
Erythema marginatum	1	0.5
Panniculitis	1	0.5

Table - IV

Cardiovascular Manifestations

	Number of Patients	%
Superficial thrombophlebitis	39	20-.5
Hepatic vein obstruction	2	1.0
Superior vena caval obstruction	15	7.9
Inferior vena caval obstruction	9	4.7
Varicous leg veins	5	2.6
Aortic aneurysm	1	0.5
Pulmonary artery aneurysm	1	0.5
Pericardial effusion	1	0.5
Aortic insufficiency	1	0.5

Table - V

Gastrointestinal Manifestations

	Number of Patients	%
Active duodenal ulcer	10	5.2
llepatosplenomegaly	1	0.5
Esophageal varices	3	1.6
Colonic ulceration	1	0.5
Perianal fistula	2	1.0

Table - VI

Renal Biopsies

Renal lesion	Number of Patients	%
Amyloidosis	2	1.0
Membranoproliferative glomerulonephritis	2	1.0
Mesangial glomerulonephritis	1	0.5

Table - VII

Neurological Manifestations

	Number of Patients	%
Pseudotumor cerebri	5	2.6
Hemiparesis	5	2.6
Peripheral neuropathy	2	1.0
Cerebellopontine angle lesion signs	1	0.5
Cerebellar signs	1	0.5

II-Laboratory Features

Erythrocyte sedimentation rate was found to be elevated in 62 out of 91 patients (68.1%), whereas prominent leucocytosis was found in only 24 patients (12.6%) during relapses. Four patients (2.1%) showed mild monocytosis (11-16%), WBC differential was otherwise unremarkable. Seven patients (3.7%) had anemia (with a hemoglobin range of 7.8-9.60 g/dl), of whom one patient showed typical features of iron deficiency. No other specific hematologic abnormality was found in the rest of the anemic patients.

Urinalysis was normal in all patients except 8 who showed proteinuria (4.2%), 9 (4.7%) who showed pyuria and 11 (5.8%) who showed hematuria. Additionally, the patients with biopsy proven glomerulonephritis and amyloidosis showed lower creatinine clearence values (range 5-63 mg/min). Renal function studies were unremarkable in the rest of the patients.

Hepatitis B surface antigen were sought in 11 patients and were found to be negative. Serum albumin levels were decreased in 8 patients (with a reversed albumin/globulin ratio). Liver function studies were performed in 83 patients and no abnormality was detected. However, a patient with inferior vena caval and hepatic venous obstruction developed progressive hepatic failure and eventually coma.

Tissue typing was performed in 45 patients with Behcet's disease and HLA-B$_5$ antigen was found in 35 of them (75.5%) (12, 13).

Autoantibodies were investigated in 71 patients and antinuclear antibodies were detected in 2 patients (2.8%), smooth muscle antibodies in 8 patients (11.3%), antireticular antibodies in 3 patients (4.2%) and parietal cell antibodies in one patient (1.4%). Latex fixation test was performed in 11 patients and in only one of them it was found to be positive.

DISCUSSION

Today, nearly 50 years after the first recognition, many aspects of the disease are not known widely. Most of the previous reports have been limited to epidemiologic studies, definition of the diverse clinical features and experiences with some empiric forms of therapies. Many authors have proposed diagnostic criteria for Behcet's disease, which are based on clinical grounds alone and many of them are much too complicated to be practical (15). According to some of these criteria the disease has frequently been discriminated as "complete" or "incomplete" forms (3, 15). However, as far as our current knowledge about the expanding spectrum of Behcet's disease is concerned, such a differentiation does not seem to be meaningful.

The familial occurence of Behcet's disease has rarely been reported (4, 5). In our series, 15 patients had a family history of Behcet's disease. It seems likely that some genetic factors are important in the development of the disease. However, it has not been possible as yet to define a specific mode of inheritance. On the other hand, in various reports from different countries a high prevalence of HLA-B$_5$ histocompatibility antigen in patients with Behcet's disease has been stressed (3, 12, 13, 16-18). Our experiences were consistent with these reports and we found a frequency of 75.5% in our series. These observations also suggest a probable genetic predilection for the development of Behcet's disease.

Oral ulcers were the first manifestation in 74% of our patients. However, the majority of them called upon medical advice only for more severe clinical manifestations that could restrict their daily activities.

The incidence of the principal clinical manifestations has been different in various reports (3, 4, 5, 8). These differences can be attributed to the different medical speciality of the authors, the duration of the disease before reporting and the ethnic origin of the cases reported. We found painful, recurrent oral ulcers in 96.3% of our patients. The incidence and the main features of oral ulcers were in accordance with the previous reports (3-5). The frequency of genital ulcers was 82.1% and in 22 patients (14.1%) they were found to be scar forming. Ocular lesions were less frequent than the previous reports (3, 6,19). Among the ocular complications, especially blindness had a very low frequency (16%) as compared to the other reports (4,19).

We noticed joint involvement in 40.5% of our patients and large joints, especially knee and ankle were the most frequently affected joints. This figure was consistent with the previous series (4, 5, 6, 19). Although it has been reported rarely, we could not find any deformities and the involvement of the sacroiliac joint (8, 19).

Skin lesions are observed in the great majority of the patients with Behcet's disease. We found various

cutaneous lesions in 54.7% of our cases. The non-specific hyperreactivity of the skin to a needle prick (the pathergy test) has been reported as an established feature of the Behget's disease (3, 19, 20). It has also been suggested as a very sensitive discriminator for the disease in combination with the presence of the HLA-B, antigen (20). Moreover, in a recent study on Turkish and British patients with Behget's disease the pathergy test has been found to be positive in only Turkish patients and this finding has not been clearly explained yet (21, 22). Interestingly, we detected skin hyperreactivity to a needle prick in only 21 patients. However this figure should not be regarded as a real incedence because of the retrospective character of our study.

Nervous system involvement in Behget's disease is usually associated with a poor prognosis and it is responsible for the mortality in a great number of cases (3). Both motor and sensory neurologic symptoms may appear, although the former are much more prominent. Neurologic involvement is. said to occur in 1/4 of all patients worldwide with Behget's disease, and it manifests itself as meningoencephalitis, benign intracranial hypertension or as signs or symptoms related to brainstem, cranial nerve, pyramidal, extrapyramidal, cerebellar spinal cord or peripheral nerve involvement (19, 23). In our series, neurological involvement were detected as pseudotumor cerebri (2.6%), hemiparesis (2.6%), peripheral neuropathy (1.0%), pontocerebellar angle lesion (0.52%) and cerebellar dysfunction (0.52%).

The association of Behget's disease and amyloidosis is rather rare. There are only a few cases reported previously (24, 26, 27). We reported additional two cases elsewhere in the literature (10). There is no known pathogenetic relationship between amyloidosis and Behget's disease. As it was suggested by Beroniade (25), chronic suppuration of mouth and genital ulcers or eye lesions might be predisposing factors for secondary amyloidosis.

Although it is quite rare, the occurance of the renal involvement has been reported previously (28-31). In our series, membranoproliferative glomerulonephritis was recognized in 2 patients and mesangial glomerulonephritis in another one. The precise mechanism of the renal lesions in Behget's disease has as yet not been clearly understood. However, the finding of circulating immune complexes and deposition of complement in glomerular and arteriolar tissues in some studies supports an immune complex mediated nephropathy (32, 33).

Pulmonary manifestations of Behget's disease are rare. Tuberculosis-like shadows resistant to antituberculous therapy, fluctuating opacities, pulmonary hypertension and hemoptysis have been reported (3). These changes have been ascribed to pulmonary vasculitis (31, 34). However, the precise mechanism is presently not clear. We observed pleural effusions in 7 patients. In 5 of them the underlying disturbance was superior vena caval obstruction while no other disease that results in pleural effusion could be detected in the other two. One of these patients also showed a coin lesion in the left pulmonary area.

Serious involvement of the digestive tract may occur in Behget's disease, although it is not so frequent. However, some gastrointestinal symptoms have been reported in more than 50% of the patients (3). Major gastrointestinal involvement, namely entero-Behget's disease, have been rarely detected in our country. We could only observe active duodenal ulcer, esophageal varices, colonic ulceration and perianal fistula in our series. A11 of these manifestations seem to be related to vasculitis changes in the gastrointestinal mucosa and/or vena caval obstruction.

Direct involvement of liver in Behget's disease is also uncommon (3, 35). We observed marked hepatosplenomegaly in one patient and despite detialed investigations we could not detect any underlying disorder other than Behget's disease. It is necessary to accumulate more experiences with liver and spleen involvement in Behget's disease before reaching a definit conclusion.

Bizarre presentation of arterial and venous thrombosis or arterial aneurysm formation have been reported as interesting clinical features of Behget's disease and up to 20% of those with prominent vascular involvement die because of these complications (3, 19, 36, 37).

Venous lesions are more common than arterial lesions. Recurrent superficial thrombophlebitis occurs in one third of the patients (36). We detected a high prevalence of superficial thrombophlebitis mostly recurrent and migratory and in our opinion this manifestation should be regarded as suggestive of Behget's disease.

Obstruction in the inferior or superior vena cava is a common finding causing superior vena cava syndrome and Budd-Chiari syndrome in some patients (3, 33, 37, 38). Our observation in 24 patients (13.1%) with vena caval obstruction pointed out that Behget's disease is an important cause in patients with superior or inferior vena caval obstruction and should be kept in mind as an underlying disorder in these patients (38).

Reports of lesions localized to the aorta and cerebral, carotid, subclavian, brachial, ulnar, renal and popliteal arteries have been published. Although spontaneous arterial aneurysm formation is relatively common both in the aorta and its major branches, pulmonary artery aneurysm has a rather rare occurence (3, 36). To our knowledge aortic insufficen-

cy associated with Behcet's disease has not been reported previously. In our unique patient with aortic insufficiency we could not demonstrate any underlying disorder other than Behcet's disease.

Pericarditis is a rare manifestation of the disease (36). We could detect pericardial effusion in only one patient during acute illness. However, in our opinion, to uncover the real incidence of pericardial involvement, it should be sought by echocardiography in all patients during relapses.

It is still early to confirm statistically the value of any specific therapy. Until recently, all treatment regimens were empiric and palliative (3). So, it has not been possible to evaluate the relationship between the diverse therapeutic regimens and various manifestations of the disease in our series.

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