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Clinical Manifestations of Behçet's Disease: An Analysis of 2147 Patients

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To evaluate the prevalence of the clinical findings in Behçet's disease, we retrospectively analyzed the clinical data of 2147 Behçet patients from 9 to 87 years of age (mean age 38.3 years) followed up during the years 1976 through 1997. One thousand ninety three patients were male and 1054 patients were female. The male/female ratio was 1.03. The mean age at onset was 25.6 years. A family history of Behçet's disease was present in 7.3 % of the patients. Positive pathergy was found in 1220 (56.8%) patients. All of the patients had mucocutaneous lesions. Out of the 2147 patients the disease manifested itself as only mucocutaneous involvement in 1168 patients. The prevalence of systemic manifestations was found as follows: 28.9% ocular involvement, 16.0% musculoskeletal involvement, 16.8% vascular involvement, 2.8% gastrointestinal involvement, 2.2% neurological involvement. Pulmonary involvement was seen in 20 (1.0%) patients, cardiac involvement was seen in 3 patients and renal involvement was observed in 2 patients. Male patients had vascular involvement 5.02, neurologic involvement 2.21 and ocular involvement 1.98 times more frequently than female patients.

Key Words: Behçet's disease, epidemiology, Turkey

Behçet's Disease was first defined by Hulusi Behçet, a Turkish Professor of Dermatology, in 1937 as a triad of recurrent aphthous stomatitis, genital ulceration and relapsing uveitis (Behçet, 1937). During the ensuing 60 years multiple systemic associations of the disease including articular, vascular, gastrointestinal, cardiopulmonary, neurologic involvement have become increasingly apparent.

In our study, to evaluate the prevalence of the clinical findings in Behçet's disease, we retrospectively analyzed the clinical data of our large series of Behçet patients and compared our findings with the literature.

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MATERIALS AND METHODS

During the years 1976 through 1997, 3000 patients were followed up at the multidisciplinary Behçet's disease center at the Medical school of Ankara University. Until 1990's, the diagnostic criteria recommended by the Behçet's disease research Committee of Japan and afterwards International Study group criteria was used for the diagnosis of Behçet's disease. Prevalence and the time of onset of each clinical manifestation was assessed and routine laboratory tests and three step pathergy test were performed. The patients were evaluated initially and annually by an ophthalmologist and by specialists of related symptoms whenever clinically indicated along the course of the disease.

RESULTS

Out of the 3000 patients, 2147 patients met the criteria for Behçet's disease. Of the 2147 Behçet patients, 1093 patients were male and 1054 patients were female. The male/female ratio was 1.03. The patients were from 9 to 87 years of age (mean age 38.3 years). The mean age at onset was 25.6 years. The mean duration of follow up per person was 6.10 years. A family history of Behçet's disease was present in first degree relatives of 157 patients (7.3 %). Demographic features are summarized in Table 1.

Recurrent aphthous ulceration was the initial manifestation of the disease in 1858 patients (86.5%) followed by genital ulceration usually accompanied by oral aphthosis in 161 patients (7.4%), erythema nodosum in 60 patients (2.8%), papulopustular eruptions in 43 patients (2.0%), articular involvement in 12 patients (0.5%), ocular involvement in 11 patients (0.5%) and thrombophlebitis in 10 patients (0.47%) (Table 2). An average delay of 6.6 years was noted from the manifestation of the first sign to the time of diagnosis.

All of the patients had mucocutaneous lesions. Out of the 2147 patients the disease manifested itself as only mucocutaneous involvement in 1168 patients. The male/female ratio was 0.68.

Among mucocutaneous lesions, aphthous ulcerations were seen in all patients. Aphthous ulcers were found with decreasing frequency on tongue (94.3%), lips (92.6%), buccal mucosa (84.2%), gingiva (57.2%), palate (54.4%) and tonsils (37%). Aphthous ulcerations were minor in 2128 patients (99.1%), major in 1197 patients(55.8%), and herpetiform in 156 patients (7.3%). Genital ulcerations were found in 1892 patients (88.2%). They were found most frequently on scrotum (93.8%) and glans penis (29.7%) in males and labium majus (83.6%) and labium minus (39%) in females. Genital ulcerations were noted to be larger and deeper in females leading to perforations in some cases. Erythema nodosum was found in 1023 patients (47.6%) localized in order of frequency to the lower and upper extremities, buttocks, face and neck and papulopustular lesions were seen in 1162 patients (54.2%), most frequently localized to the extremities and buttocks.

Ocular involvement manifesting itself notably in the form of recurrent anterior and posterior uveitis and retinal vasculitis was noted in 621 patients (28.9 %). Male/female ratio of patients with ocular involvement was 1.98. Mean age at onset was 24.75 in patients with ocular involvement.

Musculoskeletal involvement was seen in 343 (16 %) patients (M/F: 1.08). 186 patients had arthralgia. Arthritis was noted in 144 patients mostly affecting the knees, ankles, wrists and elbows . Arthritis was monoarticular in 67.36%, oligoarticular in 27.37% and polyarticular in 10.00% of the patients. Sacroilitis was noted in 14 patients and myalgia was found in 5 patients.

Vascular involvement was present in 361 patients (16.8 %). Male/female ratio was 5.02 in patients with vascular involvement. Superficial thrombophlebitis mostly localized to the lower extremities was observed in 229 patients (10.6 %). 154 patients had deep vein thrombosis of lower extremities, 2 patients had deep vein thrombosis of upper extremities, 29 patients had occlusion of superior vena cava, 6 patients had occlusion of inferior vena cava, 1 patient had jugular vein thrombosis, 1 patient had renal vein thrombosis, 1 patient had hepatic vein thrombosis, 2 patients had brachiocephalic vein

Table 1. Demographic features

Total number of Behçet patients	2147
Male	1093
Female	1054
Male/ female	1.03
Mean age	38.3 years
Mean age at onset	25.6 years
Mean duration of follow up	6.10 years
Family history of Behçet's disease	7.3%

Table 2. Prevalence of the initial manifestations

Oral aphthous ulceration	1858 patients	86.5%
Genital ulceration	161 patients	7.4%
Erythema nodosum	60 patients	2.8%
Papulopustular eruption	43 patients	2.0%
Articular involvement	12 patients	0.5%
Ocular involvement	11 patients	0.5%
Thrombophlebitis	10 patients	0.5%

Table 3. Frequency of systemic manifestations

Ocular involvement	28.9%
Articular involvement	15.9%
Vascular involvement	16.8%
Gastrointestinal manifestations	2.8%
Neurologic involvement	2.2%
Pulmonary involvement	1.0%

thrombosis and 1 patient had cerebral sinus thrombosis. Arterial lesions were less frequently observed in Behçet patients. 4 patients had aneurysm of abdominal aorta, 1 patient had aneurysm of right subclavia, 7 patients had aneurysm of femoral artery, 2 patients had aneurysm of iliac artery, 3 patients had aneurysm of popliteal artery, 1 patient had aneurysm of carotid artery and 4 patients had aneurysm of pulmonary artery. Arterial occlusion was seen in 3 patients. Iliac artery occlusion was seen in 1 patient and popliteal artery occlusion was seen in 2 patients.

Gastrointestinal manifestations like nausea, vomiting, diarrhea and constipation mostly related to therapy were noted occasionally in our patients, but gastrointestinal involvement of Behçet's disease was found in 62 patients (2.8%). 7 patients had esophageal involvement and 55 patients had ulcers most frequently localized to the terminal ileum, colonic and rectal mucosa. Ileal perforation was noted in 3 patients.

Neurological involvement was observed in 46 patients (2.2%) presenting with central motor paresis, brain stem and cerebellar symptoms. Systemic manifestations of our patients are shown in Table 3.

Other less frequently detected systemic manifestations were pulmonary involvement seen in 20 (1.0%) patients, cardiac involvement seen in 3 patients and renal involvement observed in 2 patients.

Positive pathergy was found in 1220 (56.8%) patients.

DISCUSSION

Behçet's disease is a multisystem vasculitis with a high prevalence in Japan and eastern Mediterranean countries and relatively low in the United States and northern Europe. It usually affects young adults between 20 and 40 years of age and a slight male predominance has been reported (Wong *et al.* 1984; Arbesfeld and Kurban, 1988; Michelson and Friedlaender, 1990; Pande *et al.* 1995; Mangelsdorf *et al.* 1996). In our patients the mean age at onset was 25.6 years and the male/ female ratio was 1.03. Behçet's disease is characterized by remittance and exacerbations and the symptoms are separated from one another by years which results in delay of diagnosis (O'Duffy, 1990). We noted an average delay of 6.6 years from the onset of first symptoms to the time of diagnosis.

The etiopathogenesis of Behçet's disease is still not clarified but a genetic predisposition has been postulated (Goolamali *et al.* 1976; Chamberlain, 1978; Steward, 1986). We noted a family history of the disease in 7.3% of our patients.

The percentage of Behçet patients with a positive pathergy test varies with a higher prevalence (40～88%) in the Mediterranean countries and in Japan. In several studies conducted in Turkey positive pathergy was found in 66～92 % of the patients (Tzn *et al.* 1980; Dilşen *et al.* 1993a). Positive pathergy test is, together with the mucocutaneous and systemic manifestations, more frequently noted in active stage of the disease and has a high diagnostic value (Michelson and Friedlaender, 1990). In our study positive pathergy was found in 56.8% of the patients. This high frequency of pathergy test positivity points to the importance of its inclusion as a major criteria in the diagnostic criteria of Behçet's disease.

Recurrent oral aphthous ulcerations occur in all patients diagnosed as Behçet's disease and the International study group criteria doesn't permit diagnosis in the absence of oral ulcerations (International study group for Behçet's disease, 1990). Recurrent oral aphthous ulcerations are reported as the first manifestation of the disease in 75% of the patients (Wong *et al.* 1984). In our study recurrent aphthous ulceration was the initial manifestation of the disease in 86.5% of the patients. In previous reports the prevalence of genital ulcerations and cutaneous lesions were 60～90 % and 42～90% respectively and genital ulcers were reported to be more painful and disturbing to men than women

(Arbesfeld and Kurban, 1988; James, 1990; Gharibdoost *et al.* 1993; Pande *et al.* 1995). When compared with these series the prevalence of the mucocutaneous lesions fell within the range of these studies but in our patients genital ulcerations on the contrary tended to be larger and deeper in female patients sometimes even leading to perforations.

It was previously reported that male patients have a worse overall prognosis than females with increased ocular, neurologic and vascular involvement (Yazici *et al.* 1984; Dilşen *et al.* 1993b; Prokaeva *et al.* 1993). In our series we noted in male patients vascular involvement 5.02, neurologic involvement 2.21 and ocular involvement 1.98 more frequently than female patients.

The prevalence of systemic manifestations of Behçet's disease has been reported as follows: 27～79% ocular involvement, 28～100% arthritis, 3～30% neurologic disease and 7～60% vascular involvement (James, 1990; Benamour *et al.* 1991; Dilşen *et al.* 1993b; Gharibdoost *et al.* 1993; Pande *et al.* 1995; Mangelsdorf *et al.* 1996). Ocular and central nervous system involvements are the main prognostic determinants in Behçet's disease. Severe ocular involvement occur with increased frequency in Japanese patients and 50～80% of the patients suffer partial loss of vision along the course of the disease(Shimizu *et al.* 1979; Wong *et al.* 1984). In our patients, ocular involvement (28.9%) and central nervous system involvement (2.2%) were observed less frequently than most of the large series reported in the literature. It was previously suggested that patients treated with long term colchicine and other drugs in combination developed fewer vital organ involvements (Dilşen *et al.* 1993b). Therefore we believe that the low frequency of ocular and central nervous system involvement in our patients may be the result of the beneficial effect of colchicine therapy we initiate at the time of diagnosis, early along the course of the disease.

Behçet's disease has a variable clinical course, but in the absence of central nervous system, arterial and gastrointestinal involvement leading to bowel perforation the overall prognosis appears to be good.

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