

In the name of God



S.U.M.S.

Department of Internal Medicine

Shiraz E-Medical Journal

Vol. 5, No. 2, April 2004

Behcet's Disease

Afshin Borhani Haghighi

Assistant Professor, Department of Internal Medicine, Shiraz University of Medical Science, Shiraz, Iran

Correspondence: Dr. Borhani Haghighi, Department of Internal Medicine, Nemazee Hospital, Shiraz, Iran, Phone: +98 (711)626-1089, E-mail: medicine@sums.ac.ir

Abstract:

Behcet's Disease, first introduced in 1937 from Turkey, is a multi-system involving disease. It is now reported from most countries all around the world. Here in this article, a full review of this disease is presented.

Key Words: Becet disease, Neurobehcet.

History:

In 1937 Huluci Behcet a Turkish dermatologist described three patients with oral and genital ulceration and hypopyon uveitis.¹ Three years later he reported four similar cases and named this constellation of symptoms as "triple symptom complex."²

However, the first evidences of acquisition to this stymptomatology returns to age of Hippocrates. He wrote in his third book of epidemiology : "There

were other forms of fever . . . Many developed aphthae, ulceration. Many ulcerations about the genital parts . . . Water ophthalmies of a chronic character, with pains: Fungus excretions of the eyelids externally , internally destroyed the sight of many persons . . . there were fungus growths on ulcers, and on those localized on the genital organs. Many anthraxes through the summer . . . other great affections: many large herpes."³

Before Behcet's description, association between iritis and mucocutaneous ulcers was diagnosed by Blüthe (1906)⁴, Planner and Remenovskiy (1929)⁵ and Shigeta (1924)⁶; but none of them presented constellation of symptoms as a discrete clinical entity and considered infectious cause for these presentations.

In Greece, the disease is named Adamantiades - Behcet's syndrome because Adamantiades presented a case of recurrent hypopyon iritis, phlebitis, oral and genital ulcerations and knee arthritis six years before Behcet's paper.⁷

Since Behcet's introduction many musculoskeletal, gastrointestinal, urogenital, cardiac, cutaneous and neurologic symptoms were added to "triple symptom complex" and Behcet's disease (not syndrome) is designated to a discrete clinical entity with autoimmune and vasculitic properties.

Epidemiology:

Geographic distribution:

Although cases of Behcet's disease were reported from all around the world, It is more prevalent in far east (Japan, Korea); middle East (Iran, Iraq, Israel, Saudi Arabia, Kuwait, Syria) and countries around Mediterranean sea (Turkey, Italy, Egypt, Greece, Morocco, Algeria, Tunis). Therefore, Behcet's disease occurs most commonly in the countries along the ancient "silk road".⁸ As an interesting point,

Ehrlich notified common "Altaic" roots of Japanese and Turkish languages.⁹ Table-1: demonstrates important demographic data and frequency of different manifestations of Behcet's disease in several countries.¹¹

The prevalence rate of Behcet's disease is 10 to 15 of 100,000 in Japan¹², 16 of 100,000 in Iran¹¹, 20 of 100,000 in Saudi Arabia¹³, 2 in 100,000 in Germany and 80 to 300 in 100,000 in Turkey (based on spot surveys in Turkey).¹⁰ Rate of progression, frequencies of different manifestations and HLA-B51 association also shows geographic variation. Patients from Japan and Mediterranean countries has more acute courses¹⁴. Central nervous system involvement is more prevalent in patients of northern Europe and United States of America and gastrointestinal manifestations are more common in Japanese cases.¹⁵ The link with HLA-B51 is more strong in patients from Mediterranean countries and Japan.¹⁶ One can conclude although Behcet's disease is unique clinical entity, its presentation is heterogenous in different areas of the world.

Table-1: CNS manifestation in Behcet's Disease in different countries¹¹

	Age	M/F	OA	GA	Skin	Oph	Joint	CNS	GI
5	35.7	0.98	98.2	73.2	87.1	69.1	56.9	11	15.5
			100	88.5		21.4	30.6	9.2	35.7
4	29	0.64	97.5	57	61	16.4	29.5	<2.5	5.8
3	26.2	1.14	95.8	64	73.6	57.8	39.9	3.3	8.8
	29.3	3.4	100	87	57	65	37	>44	4
	29.4	3	97	83	75	48	48	10	10
	23.3	1.78	99.6	76.7	77.8	47.4	46.9	7.7	4.9
	25.8	2.18	100	88.5	88.5	40	71.4	14.2	37.1
	27.4	4.86	98	88	88	76	29	29	
	25.3	11	100	100	85	90	70	24.4	23
		2.45	100	85		72	60	16	16.1
		1.35	98	75		87	55		
5	25	2.4	98.1	73.5	85.8	91.6	76.8	16.7	34.1
	25	1.19	98	80	72	54	62	17	21

	24.7	0.6	100	91	66	25	46.9	25	9
	34.3	0.66	96	88	88	92	68	4	

No: Number of cases. Age: Mean age at the onset. MF: Male to female ratio OA: Oral aphthosis. GA: Genital aphthosis
Oph: Ophthalmologic Manifestations CNS: central nervous system involvement. GI: Gastrointestinal manifestations
Phl: Phlebitis. Epi: Epididymitis

Age and Sex distribution:

Behcet's disease is the illness of young persons. The mean age at onset is 20-35 years in different studies. Most authors consider the onset to be the age at which the patient fulfilled the diagnosis criteria of the disease. However the age at onset of the first symptom ranges from infancy to more than 78 years.¹⁷

The male to female ratio differs from 11:1 in Lebanon, 5.3:1 in Egypt , 3.8:1 in Israel , 3.4.:1 in Turkey, 1.2:1 in Iran , 1:0.9 in Germany , 1: 0.8 in Japan , 1:0.7 in Brazil and 1:0.2 in the United States.¹⁷ Behcet's disease is more severe and associated with worse prognosis in young men. ¹⁸

Etiology and Pathogenesis :

The cause of Behcet's disease is obscure now. Infectious agents, immune mechanisms and genetic factors are probable underlying causes.

Infectious cause: Although no microorganism have been isolated from lesions of patients with Behcet's disease , Herpes simplex virus (type-1)¹⁹ has been reported to be associated with this vasculitis. Anti- streptococcal antibodies against certain serotypes of Streptococcus Sanguis were found in Serum of some Behcet patients.²⁰ There are also reports about role of antibodies against Mycobacterium Tuberculosis heat shock protein-65 (HSP-65) and homologous peptides derived from patients with Behcet's disease in its pathogenesis.²¹

Immunologic causes: Both humoral and cell-mediated immunity is involved in pathogenesis of Behcet's disease . Increase in IgM and IgG level in serum of Behcet's patients are in favor of contribution of humoral immunity. Evidences of role of cell-mediated immunity include increase of CD₄⁺-T cell in the perivascular inflammatory exudates and increase in production of interleukin-2 (IL-2) , interferon-γ and tumor necrosis factor-β (TNF-β) by T cells.²²

Genetic Factors: The role of HLA-B₅ & B₅₁ has been studied extensively but recent researches showed that gene of Behcet's disease is located near the HLA-B₅₁ gene but not on this gene itself. ²³

Environmental factors: Organophosphates, organochlorides, heavy metal intoxication and allergens are environmental factors that may trigger initiation or exacerbation of Behcet's disease.²⁴ Kaklamani et al summarized the ethiopathogenesis of Behcet's disease :

“An Exogenous factor (virus or bacteria) is presented by macrophages and is recognized by CD₄⁺ - T cells in the context of class-II MHC antigens. Activated Th1 T cells produce cytokines (IL-2, IFN-γ, IFN-β) and induce B cell proliferation. IFN-γ activates macrophages to release TNF-α, IL-1 and IL-8; which induce the expression of adhesion molecules on endothelial cells. IL-8 also induce chemotaxis and activates neutrophils , both events being responsible for the passage of polymorphonuclear neutrophils and activated T lymphocytes through the endothelium to inflammatory area.”¹⁷

Clinical Manifestations:

Behcet's Disease is characterized by exacerbations and remissions. The duration of attacks ranges between few days to few weeks. Attacks are usually ended to complete remissions but sequella can also be left in behind .

Major manifestations of Behcet's disease include oral aphthosis, genital ulcers, cutaneous lesions, ocular manifestation (specially uveitis). Minor manifestations include arthritis, vascular involvement and pulmonary, cardiac, gastrointestinal, urogenital and neurologic manifestations. Different presentations can occur simultaneously or successively.

Oral Aphthae: Oral ulcers are usually the first manifestation of Behcet's disease and are sine qua non for the diagnosis. Oral aphthae are painful, shallow or deep, oval or round ulcers with central whitish or yellowish necrotic base and red halo. Their size ranges from one to twenty millimeters. They may a few days up to 2 weeks and are single or multiple. The most common site of oral ulcers are lips, buccal mucosa, tongue, gingiva, palate, tonsils, uvula and pharynx (respectively). It must be emphasized that oral ulcers of Behcet's disease are usually indistinguishable from ordinary recurrent oral ulcers except in multiplicity and involvement of unusual locations (soft palate and oropharynx).^{15,17,25}

Genital ulcers: The genital ulcers resemble the oral ones but they are usually larger, deeper, more long lasting and more painful than oral ulcers and they rarely occur at the onset of disease. They usually cause scar formation.

In male patients genital ulcers typically develop on the scrotum and less frequently on the shaft and the glans of penis.

In female patients, labia is the most common site of involvement but vaginal and cervical ulcers can also occur. Genital ulcers may be associated with menstrual cycles. Vulvar and vaginal ulcers of Behcet's disease can be

painless, therefore all suspected women must be examined carefully to find ulcers.^{12, 15, 20}

Skin lesions: Cutaneous manifestations of Behcet's disease include:

1. Erythema nodosum-like lesions (most common)
2. Pseudofolliculitis and folliculitis
3. Acne-like lesions
4. Superficial thrombophlebitis
5. Cutaneous vasculitis
6. Papulopostular lesions
7. Hypersensitivity reactions

Erythema nodosum-like lesions are multiple painful violet nodules which usually appear in lower extremities and eventually heal with residual pigmentations.

Pseudofolliculitis and acneiform nodules appear on the face, neck, breast and back.

Superficial thrombophlebitis develops in extremities and can be migrating.^{15, 17, 26}

The pathergy reaction: The pathergy reaction is skin hyper-reactivity induced by intradermal needle prick. It is performed by pricking and scratching of forearm skin with 20 or 22 gauge sterile needle. If an erythematous papule of more than two millimeters diameter develops, the test is considered positive. The rate of positivity in different populations is between 8% to 70%. However, the pathergy test can also be positive in other disease such as spondyloarthropathy and in chronic myelogenous leukemia treated with Interferon- α and therefore is not specific. It is not restricted to the skin and attacks of uveitis following eye surgery, aneurysm

formation after arterial puncture or exacerbation of synovitis following an arthrocentesis can also be manifestations of pathergy reaction.^{15, 17}

Ocular manifestations: The ocular involvement is the most hazardous complication of Behcet's disease because it can rapidly evolve to blindness. It is more common and severe in men. Inflammation of the eyes is usually episodic and resolve after a few weeks but recurrent attacks eventually cause sequella of blindness. Various ocular manifestations of Behcet's disease include:

1. Uveitis (anterior, posterior, intermediate or panuveitis)
2. Retinal vasculitis
3. Retinal detachment
4. Retinal veno-occlusive disease
5. Optic neuritis
6. Vitreous hemorrhage
7. Glaucoma
8. Cataract
9. Episcleritis
10. Corneal ulcers
11. Subconjunctival hemorrhage
12. Conjunctivitis
13. Keratitis

Recurrent anterior uveitis with hypopyon formation or posterior uveitis associated with retinal involvement are the most common ocular manifestations of Behcet's disease . The prognosis of the eye disease depends on the severity of post-inflammatory residues like synechiae and retinal scars.^{15, 25, 26, 27, 28, 29, 30}

Musculoskeletal involvement: Joint involvement of Behcet's disease presents as nondeforming, nonerosive mono - or oligo - arthritis. The most common sites of involvement include knees, ankles, wrists and small hand joints. Synovial fluid examination during acute attacks reveals cloudy fluid with increased viscosity and number of leukocytes (between 300 to 36200, with PMN predominance) and normal protein and glucose levels.

Back pain is characteristically uncommon in Behcet's disease and prevalence of sacroiliitis is not increased in comparison to normal population.

Association of oral and genital aphthosis with inflammatory involvement of cartilages of nose, trachea and ribs, named Magic syndrome may develop in Behcet's disease.^{15, 31, 32}

Vascular involvement: Involvement of major vessels in Behcet's disease (Vasculo-Behcet's or Anigio- Behcet's) is one of the most serious manifestation of disease.

Venous lesions: Two types of venous lesions are present in Behcet's disease: thrombophlebitis of small and medium-sized vessels and occlusion of large veins. Involvement of small and medium-sized vessels may presents either as superficial thrombophlebitis or deep venous thrombosis. Although veins of the upper extremities are not spared, thrombophlebitis is more frequent in the lower extremities. Thrombophlebitis of lower extremities may cause chronic stasis dermatitis with ulceration. Venous puncture may predispose to thrombus formation. Interestingly, pulmonary thromboembolism is rarely seen. Involvement of large veins is less common but more severe in males. Distinct vascular syndromes such as superior vena cava syndrome, Budd-Chiari syndrome (hepatic vein thrombosis) and dural sinus thrombosis with intracranial hypertension are manifestations of large venous involvement in Behcet's disease.^{15, 25, 26, 30}

Arterial lesions: Arterial involvement can present as occlusion and/or aneurysm formation. Both of them are due to vasculitis of vasa vasorum. Aneurysm formation is more common but more dangerous compared to occlusive lesions. The most common sites of aneurysm formation are pulmonary arteries (recurrent hemoptysis), renal arteries (renovascular hypertension), subclavian, femoral or popliteal arteries (ischemia of extremities) and carotid arteries (cerebral infarction).³³

Pulmonary involvement: Pulmonary artery aneurysms and pulmonary infarcts are seen in less than 5% of Behcet's cases. Recurrent hemoptysis is the main symptom. Associations of pulmonary arterial aneurysm with deep vein thrombosis may lead to incorrect impression of pulmonary embolism and life-threatening administration of anticoagulants. Pulmonary aneurysms which are seen as noncavitating shadows on chest X-ray, can be confirmed by intravenous digital subtraction angiography and preferably high resolution CT scans because arterial puncture, mandatory for angiography is aneurysm - forming itself. Pulmonary hypertension, cor - pulmonale and mediastinal or hilar lymphadenopathy may also be seen.^{15, 17, 25, 26}

Cardiac involvement: The major cardiac manifestations are pericarditis (most common), granulomatous endocarditis, myocarditis and coronary arteritis. Cardiac arrhythmias, valvular heart disease and endomyocardial fibrosis are occasionally reported.^{15, 17}

Gastrointestinal manifestations: Due to unknown causes gastrointestinal involvement in Behcet's disease has a typical geographical pattern: It is frequent in Japan but much less common in Mediterranean countries.

Gastrointestinal manifestations can be divided in to nonspecific symptoms such as nausea, anorexia, vomiting and mild abdominal pain and more

specific presentations such as dysphagia and odynophagia due to esophageal ulcers, epigastric pain due to gastric aphthosis, colicky abdominal pain and bloody diarrhea due to intestinal ulcers which may become complicated with perforation and rectal bleedings.³⁴ Splenomegaly is observed in 20% of male patients but hepatic involvement is not a feature of Behcet's disease.¹⁵

Genitourinary involvement: Although there are case reports of glomerulonephritis in Behcet's disease renal involvement is seen much less frequently than one might expect in a systemic vasculitis. The incidence of epididymitis ranges from 4 to 11%. Patients show classic symptoms of pain and swelling of epididymal area which occasionally recur. Urethritis and recurrent cystitis are also reported.^{15, 17, 35} Central and Peripheral Nervous system, and muscular involvement: Manifestations of central nervous system (CNS), peripheral nervous system (PNS) and muscles in Behcet's disease will be reviewed in details in another article in the next issues of this journal.

Constitutional symptoms and other symptoms: Fever, weight loss and generalized lymphadenopathy have been occasionally reported in Behcet's disease.¹⁷

Diagnostic Criteria:

The diagnosis of Behcet's disease is difficult in some cases, specially in oligosymptomatic patients, therefore, planning of a diagnostic criteria is mandatory. In 1990, the International Study Group proposed a diagnostic

criteria based on the computer analysis of clinical features from cases collected worldwide. These criteria are mentioned in table1-1.

Table1-1: International Study Group Criteria for Behcet's Disease ⁽³⁶⁾

<p>Recurrent Oral Ulcerations</p>	<p>Minor aphthous, major aphthous or herpetiform ulceration observed by physician or patient, which recurred at least 3 times in one 12 month period .</p>
<p>Plus 2 of :</p>	
<p>Recurrent Genital Ulceration</p>	<p>Aphthous ulceration or scarring observed by physician or patient</p>
<p>Eye lesion</p>	<p>Anterior uveitis, posterior uveitis, or cells in vitreous on slit lamp examination or retinal vasculitis observed by ophthalmologist</p>
<p>Skin lesion</p>	<p>Erythema nodosum observed by physician or patient, pseudofolliculitis or papulopustular lesions, or acneform nodules observed by physician in postadolescent patients not on corticostreoid treatment</p>

Positive pathergy test	Read by physician 24-48 hours.
------------------------	--------------------------------

(findings applicable only in absence of other clinical explanation)

Table-2: Classification tree or Iran criteria for Behcet's disease.³⁷

Laboratory Data:

There is no diagnostic test for Behcet's disease. The erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), C9 and/or C3, C4 complements may be elevated during the active phases of disease.

Immunoglobulins (IgM and IgG) may be elevated and immune complex are also found in serum of some patients.^{15, 30}

Platelet rosette formation around neutrophils can be seen in acute attacks of disease and disappears after recovery. This phenomenon is relatively specific but nonsensitive.^{39, 40}

Course and Prognosis :

Behcet's disease usually has a relapsing–remitting course and the overall prognosis is good. Poor prognostic factors are:

1. male gender
2. CNS involvement
3. Vascular complications.^{17, 18, 41, 42}

Morbidity is due to blindness, long–lasting arthritis, thrombophlebitis and disabling CNS complications.²⁸ Mortality is higher than expected in general population of the same age.⁴³

Treatment

As all diseases which had no definite etiopathogenesis, Behcet's disease has many drugs for treatment. We review medications suggested for

involvement of different organs or systems.

Oral and genital ulcers: corticosteroid creams, tetracycline solutions and Azelastine spray (an H1 -blocker) can be used for topical treatment of oral and genital ulcers.¹⁷ For severe and recurrent ulcers systemic, Dapsone¹⁷ Colchicine¹⁷, Azathioprine⁴⁴, Methotrexate²⁶, interferon- α ⁴⁵, rebamipide⁴⁶ and thalidomide⁴⁷ are recommended.

Skin: Skin involvement specially erythema nodosum is treated with Colchicine, Dapsone or corticosteroids.¹⁷

Arthritis: Joint manifestations respond in non-steroidal anti-inflammatory drugs or prednisolone.¹⁷ Sulfasalazine may be useful to non-responders.⁴⁶ Interferon α -2b⁴⁹, Levamisole⁵⁰ and azathioprine⁴⁴ are alternative options.

Ocular involvement: Topical and systemic corticosteroids are given in Behcet patients with ocular involvement. In some clinical trials Azathioprine was not only effective in control of uveitis and other manifestations of Behcet's disease but also its use was associated with better prognosis if it was started early.¹⁵ Cyclosporine through inhibition of CD4+ T cells and tacrolimus (FK-506) through reduction of calcineurin activity of T cells also suppress the activity of ocular inflammations.^{51,52} Sulfasalazine can be used as adjuvant therapy with corticosteroids.⁵³ Pentoxifylline is also tried with some success.⁵⁴

Vascular involvement: There is a controversy about use of anticoagulants in the treatment of deep vein thrombosis in Behcet's disease. Some authors advise only immunosuppressive treatment⁵⁵ but others stressed on the role of anticoagulants.⁵⁴ Cyclophosphamide (daily oral doses or monthly intravenous pulses) is recommended for arterial involvement. Aneurysms should be treated surgically but recurrence is common after resection.¹⁷

Gastrointestinal involvement: In gastrointestinal ulcers which are prone

to perforation, thalidomide has been used with good outcome.⁵⁶ Vasculitic complications are treated with corticosteroids and sulfasalazine.¹⁷

Pulmonary involvement: In severe pulmonary involvement corticosteroids, Azathioprine and Cyclosporine-A are indicated.¹⁷

In all aspects of Behcet's disease, evaluation of efficacy of different medications is difficult because of relapsing- remitting nature of disease.

References:

- 1- Behcet H. Uber rezidiverende aphthose durch ein virus verursachte Geschwure am Mund, am Auge und an den Genitalien. Dermatol Wochenschr. 105: 1152-1157; 1937.
- 2- Behcet H. Some observation on clinical picture of the so-called triple symptom complex. Dermatologica. 81: 73-83, 1940.
- 3- Hippocrates. The genuine works of . Translated from Greek. A preliminary discourse and annotations, Francis Adams. Vol1. Epidemics III. 403, 1849.
- 4- Bluthe L. Zur Kenntnis des recidiverenden hypopyon. Inaugural Thesis. Hiedelberg, 1908.
- 5- Planner H, Remenovskiy F. Beitrage Zur Kenntnis der ulceration am ausseren weiblichen Genitale. Arch Dermat U Syph. 140: 162-188, 1922.
- 6- Shigeta T. Recurrent iritis with hypopyon and its pathological findings. Acta Soc ophthalmol Jpn. 28: 516, 1924.
- 7- Adamantiades B. Sur un cas d'iritis a hypopyon recidivante. Ann Ocul . 168: 271-274, 1931.
- 8- James DG. Silk route disease. Postgrad Med J. 62: 151-153, 1986.
- 9- Ehrlich GE. Behcet's disease and the emergence of thalidomide. Ann Int Med. 128: 494-495 , 1998.
- 10- Yazici H, Yurdakul S, Hamuryudan V. Behcet's syndrome. In:

Rheumatology (edited by Kilppel JH , Dieppe PA). second edition. Mosby. 1997.

11- Davatchi F, Shahram F, Akbarian M, Gharibdoost F, Nadji A, Chams, Chams H, Jamshidi AR. Behcet's disease - analysis of 3443 cases. APLAR journal of Rheumatology. 1: 2-5 , 1997.

12- Shimuzu T, Ehrlich GE, Inaba G, Hayashi K. Behcet disease (Behcet syndrome). Semin Arthritis Rheum. 8: 223-260, 1979.

13- Al-Dalaan A, Al - Balla S, Al - Sukait M, Bahabri S, Mousa M, Bigari T. The prevalence of Behcet's disease in Al Qassim region of Saudi Arabia. In: VII th international conference on Behcet's disease. (Abstract C09). Revue du Rhumatisme. English Edition. 63: 539, 1996.

14- Erkan F. Caudar T. Pulmonary Vasculitis in Behcet's disease. Ann Rheum Respir Dis. 146: 232-239, 1992.

15- Yazici H, Pazarli H, Barnes CG . A controlled trial of azathioprine in Behcet's syndrome. N Engl J Med . 322: 281-285, 1990.

16- Ohno s, Ohguchi M, Hirose S, Matsuda H, Wakisaka A, Aizawa H. Close association of HLA-BW51 in Behcet's disease. Arch ophthalmol. 100: 1455-1458, 1982.

17- Kaklamani VG, Vaiopoulos G, Kaklamanis PG, Behcet's disease. Semin Arthritis Rheum. 27: 197-217, 1998.

18- Hamuryudan V, Yurdakul S, Moral F etal. Pulmonary arterial aneurysm in Behcet's syndrome: A report of 24 cases. Br J Rheum. 33: 48-51 , 1994.

19- Lee E-S, Lee S, Bang D, Sohn s. Herpes simplex virus detection by polymerase chain reaction in intestinal ulcer of patients with Behcet's disease. In: seventh International conference on Behcet's disease. [Abstract A18]. Revue du Rhumatisme, English Edition. 63: 531, 1996.

20- Isogai E, Ohno S, Kotake S, Isogai H, Tsurumizu T, Fujii N etal. Chemiluminescence of neutrophils from patients with Behcet's disease and its correlation with an increased proportion of uncommon subtypes of

- Streptococcus sanguis in the oral flora. Arch Oral Biol . 35: 43-48, 1990.
- 21- Pervin K, Childerstone A, Shinnick T, Mizushima Y, Vanderzee R, Hasan A et al. T cells epitope expression of mycobacterial and homologous human 65-kilodalton heat shock protein peptides in short term cell lines from patients with Behcet's disease. J Immunol. 151: 2273-2282, 1993
- 22- Emmi L, Brugnolo F, Salvati G, Marchione T. Immunopathological aspects of Behcet's disease [Editorial]. Clin Exp Rheumatol. 13: 687-691, 1995.
- 23- Mizuki N, Ohno SH. Immunogenetic studies of Behcet's disease. In: seventh international conference on Behcet's disease. Revue du Rhumatisme. English Edition. 63: 520-527, 1996.
- 24- Barnes CG. Behcet's syndrome . Topical reviews No 18, 1991.
- 25- Moutsopoulos HM. Behcet's syndrome. In; Harrison's principle of Internal medicine. 15th edition. Mc Graw Hill. 2001.
- 26- Chate JV, Jorizzo J. Behcet's disease. In: Kelley's textbook of Rheumatology. 6th edition. W. B. Saunders. 1205-1211, 2001.
- 27- Banares A, Jover JA, Fernandez - Gutierrez B et al. Pattern of uveitis as a guide in making rheumatologic and immunologic diagnosis. Arthritis Rheum. 40: 358-370, 1997.
- 28- Michelson JB, Friedlaedner MH. Behcet's disease. International Ophthalmology Clinics. 30: 271-277, 1990.
- 29- Nussenblatt RB, Palestine AG, Behcet's disease and other retinal vasculitides. In: uveitis, fundamentals and clinical practice. Year book medical publishers, Inc. 212-233, 1989.
- 30- Mc Carty DJ, Koopman WJ. Behcet's syndrome . In: Arthritis and allied conditions. 12th edition. Lea and Febiger Co. 1130-1134, 1993.
- 31- Yurdakul S, Yazici H, Tuzun Y, Pazarli H , Yalcin B, Ahtac M et al. The arthritis of Behcet's disease: a prospective study. Ann Rheum Dis. 42: 505-515, 1983.

- 32- James DG. Silk route disease (Behcet's disease). *West J Med.* 433-437, 1988.
- 33- Thi Huong DL, Wechsler B, Papo TH, Piette J-CH, Bletry O, Vitroux JM et al. Arterial lesions in Behcet's disease: a study in 25 patients. *J Rheumatol* 22: 2103- 2113, 1995.
- 34- Yurdakul S, Tuzuner N, Yurdakul I, Hamuryudan V, Yazici H, Gastrointestinal involvement in Behcet's syndrome a controlled study. *Ann Rheum Dis.* 55: 208-210, 1996.
- 35- Serica K, Suzer O, Gurler A. Urological evaluation of Behcet's patients and the effect of colchicine on fertility. *Eur Urol.* 27: 39-42, 1995.
- 36- International Study Group for Behcet's Disease. Criteria for diagnosis of Behcet's disease. *Lancet.* 335: 1078-1080, 1990.
- 37- Davatchi F, Shahram F, Akbarian M, Gharibdoost F, Chams C, Chams H, Mansoori P, Nadji A. Classification tree for the diagnosis of Behcet's disease. In: Wechsler B, Godeau P (eds): *Behcet's disease. Excerpta Medica.* Amsterdam: 1993: 245-248.
- 38- Stratigos AJ, Laskanis G, Stratigos JD. Behcet's disease. *Semin Neurol.* 12: 346-357, 1992.
- 39- Kielsberg CR, Swanson. Platelet satellitism. *Blood.* 43: 831-836 , 1974.
- 40- Robert WL. Intermittent and periodic arthritic syndromes. In: *Arthritis and allied conditions.* 11th edition. Lea and febiger. 1989.
- 41- Akman-Demir G, Baykan-Kurt B, Serdaroglu P, Gurvit H, Yurdakul S, Yazici H, Bahar S , Aktin E. Seven year follow-up of neurologic involvement in Behcet's syndrome. *Arch Neurol.* 53: 691-694, 1996.
- 42- Yazici H, Tuzuner Y, Parali H et al. Influence of age of onset and patients sex on the prevalence and severity of manifestations of Behcet's syndrome. *Ann Rheum Dis.* 43: 783-789, 1984.
- 43- Yazici H, Basaran g, Hamuryudan V, Hizli N, Yurdakul S, Mat C et al. The

- ten-year mortality in Behcet's syndrome a report of 24 cases. *Br J Rheumatol* 35: 139-141, 1996.
- 44- Hamuryudan V, Ozyazgan Y, Hizli N, Mat C, Yurdakul s, Tuzun Y etal. Azathioprine in Behcet's syndrome: effects on long term prognosis. *Arthritis Rheum* . 40: 769-774, 1990
- 45- O'Duffy JD, Calamia K, Cohen S etal. Alpha interferon treatment of Behcet's disease. *J Rheumatol* 25: 1938-1944, 1998.
- 46- Matsuda T, Tanaka C, Yukinari T, Yamada H, Ichikawa Y, Sakane T etal. The beneficial effect of Rebamipide on recurrent oral apthous. In: VIIIth International Conference on Behcet's disease [abstract K19] *Revue du Rhumatisme (English edition)*. 63: 561, 1996.
- 47- Gardner-Meduin JMM, Smith NJ, Powell RJ. Clinical experience with thalidomide in the management of severe oral and genital ulceration in conditions such as Behcet's disease: use of neurophysiological studies to detect thalidomide neuropathy. *Ann Rheum Dis*. 53: 825-832 , 1994.
- 48- Hamuryudan V, Ozdogan H, Yazici H. Other forms of vasculitis and pseudovasculitis. In: *Vasculitis Bailiers Clin Rheumatol*. 11: 335-355, 1997.
- 49- Hamuryudan V, Moral F, Yurdakul S, Mat C, Tuzun Y, Ozyazgan Y etal. Systemic interferon a-2b treatment in Behcet's syndrome. *J Rheumatol*. 21: 1098-1100, 1994.
- 50- Lavery HA, Pinkerton JHM. Successful treatment of Behcet's syndrome with levamisole. *Br J Dermatol* . 113: 372-373, 1985.
- 51- Shahram F, Davatchi F, Chams H, Akbarian M. Cyclosporine in severe ocular lesions of Behcet's disease. In: *Behcet's disease editor Hamza M. Tunis. Pub Adhoua*. 1997, 421-423.
- 52- Suzuki N. Kaneko S, Ichino M, mihara S, Wakisaka S, Sakane T. In vivo mechanisms for the inhibition of T-lymphocyte activation by long term therapy with tacrolimus (FK-506): experience in patients with Behcet's disease. *Arthritis Rheum*. 40: 1157-1167, 1997.

- 53- Samangoeei Sh, Mehryar M, Hakim SM, Safamanesh S. Clinical trial of sulfasalazine for treatment of uveitis in Behcet's disease. In: VIIth International conference on Behcet's disease [abstract K15]. Revue du Rhumatisme. English edition: 3: 561, 1996.
- 54- Ball EV. Behcet's disease. In: Cecil textbook of medicine. 21st edition. WB saunders company. 2001.
- 55- O'Duffy JD. Vasculitis in Behcet's disease. Rheumat Dis Clin North Am. 16: 423-431, 1990.