

*Current Concepts***BEHÇET'S DISEASE**

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**B**EHÇET'S disease is an inflammatory disorder of unknown cause, characterized by recurrent oral aphthous ulcers, genital ulcers, uveitis, and skin lesions.<sup>1,2</sup> All these common manifestations are self-limiting except for the ocular attacks. Repeated attacks of uveitis can cause blindness.<sup>1,3</sup> Behçet's disease is not a chronic, persistent inflammatory disease, but rather one consisting of recurrent attacks of acute inflammation. Involvement of the gastrointestinal tract, central nervous system, and large vessels is less frequent (Table 1), although it can be life-threatening.<sup>1,2,4-6</sup> Susceptibility to Behçet's disease is strongly associated with the presence of the HLA-B51 allele.<sup>7,8</sup> Environmental factors such as infectious agents have also been implicated in its pathogenesis.<sup>9,10</sup>

**EPIDEMIOLOGY**

Cases of Behçet's disease cluster along the ancient Silk Road, which extends from eastern Asia to the Mediterranean basin.<sup>1,2,7</sup> Turkey has the highest prevalence: 80 to 370 cases per 100,000 population.<sup>1,2</sup> The prevalence in Japan, Korea, China, Iran, and Saudi Arabia ranges from 13.5 to 20 cases per 100,000, whereas it is lower in Western countries: 0.64 per 100,000 in the United Kingdom and 0.12 to 0.33 per 100,000 in the United States.<sup>1,2,4,5</sup> In Berlin, Germany, the prevalence among citizens of Turkish origin is 21 per 100,000, which is lower than that in Turkey but far higher than that among German natives (0.42 to 0.55 per 100,000).<sup>5</sup> Behçet's disease is rare among Japanese immigrants in Hawaii and California.<sup>5</sup>

Behçet's disease is somewhat more common among females in Japan and Korea, whereas males are more frequently affected in Middle Eastern countries.<sup>2,4,5</sup> The onset is typically in the third or fourth decade of life.<sup>1</sup> The frequency within families is 2 to 5 per-

cent, except in Middle Eastern countries, where it is 10 to 15 percent.<sup>5</sup> Although the rate of concordance among twins is not known, one pair of monozygotic twins who were concordant<sup>11</sup> and two pairs who were discordant<sup>12</sup> for Behçet's disease have been described. Epidemiologic findings suggest that both genetic and environmental factors contribute to the development of the disease.

**CAUSATION**

The prevalence of the HLA-B51 allele is high among patients with Behçet's disease who live in areas along the Silk Road (up to 81 percent of Asian patients have the allele) but not among white patients who live in Western countries (13 percent).<sup>4,5,7-9,13</sup> In Japan, the incidence of HLA-B51 is significantly higher among patients with Behçet's disease than among those without the disease (55 percent vs. 10 to 15 percent).<sup>4</sup> The relative risk of the disease among carriers of HLA-B51, as compared with that among noncarriers, is 6.7 in Japan, whereas it is only 1.3 in the United States.<sup>4,13</sup> Thus, this allele is an important contributor to the risk of Behçet's disease in areas in which the disease is prevalent but not in Western countries. The allele also affects the severity of disease, since it is more common among patients with posterior uveitis or progressive central nervous system disease than among those with milder disease.<sup>2,4,5,8,14</sup> More than 55 percent of patients with central nervous system lesions are positive for HLA-B51.<sup>4</sup> In one study, the frequency of visual acuity below 0.01 was 51 percent among HLA-B51-positive patients and 31 percent among HLA-B51-negative patients.<sup>8</sup> In another study, 84 percent of the patients with central nervous system involvement were positive for the allele.<sup>14</sup> Other HLA-related genes have been studied extensively, but none have been shown to be as important as HLA-B51 in Behçet's disease.<sup>7</sup>

Microbial infection has been implicated in the development of Behçet's disease. Herpes simplex virus DNA and serum antibodies against the virus have been found in a higher proportion of patients with Behçet's disease than in controls.<sup>2,10</sup> Other viruses, including hepatitis C virus and parvovirus B19, may also have some role.<sup>2</sup> *Streptococcus sanguis* has been suggested as a causative agent, because the bacteria and antibodies against the bacteria are frequently found in the oral flora and serum, respectively, of patients with the disease.<sup>10</sup> However, none of these infectious agents have been proved to cause Behçet's disease. In fact, the results of a series of studies led to the hypothesis that ubiquitous antigens, including heat shock protein of microorganisms, may trigger cross-reactive autoimmune responses in patients with Behçet's disease.

**PATHOPHYSIOLOGY**

Vascular injuries, hyperfunction of neutrophils, and autoimmune responses are characteristic of Beh-

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**TABLE 1.** FREQUENCIES OF VARIOUS SYMPTOMS IN PATIENTS WITH BEHÇET'S DISEASE IN JAPAN, GERMANY, TURKEY, AND GREECE.\*

SYMPTOM	JAPAN, 1972 (N=2031)	JAPAN, 1991 (N=3316)	GERMANY, 1996 (N=130)	TURKEY, 1993 (N=496)	GREECE, 1997 (N=64)
	percentage of patients				
Diagnostic					
Oral ulcers	96	98	98	100	100
Genital ulcers	72	73	79	77	78
Eye lesions	67	69	48	47	75
Skin lesions	83†	87†	73	78	94
Positive pathergy test	75	44	53	NA	30
Other					
Arthritis	54	57	59	47	48
Epididymitis	6	6	32	NA	17
Gastrointestinal lesions	25	16	NA	5	3
Central nervous symptoms	13	11	NA	8	20
Vascular lesions	7†	9†	NA	38	8

\*Data on Japan are from Nakae et al.,<sup>4</sup> data on Germany are from Zouboulis et al.,<sup>5</sup> data on Turkey are from Dilsen et al.,<sup>6</sup> and data on Greece are from Kaklamani et al.<sup>2</sup> NA denotes not available.

†Superficial thrombophlebitis was included in skin lesions.

çet's disease. Biopsies confirm the presence of vasculitis near the lesions of Behçet's disease, including oral and genital ulcers, erythema nodosum, posterior uveitis, epididymitis, enteritis, and central nervous system lesions.<sup>15</sup> Large vessels are affected by a vasculitis of the vasa vasorum. The vascular injuries are superimposed on the hypercoagulability that is also characteristic of Behçet's disease and that may be due in part to activated endothelial cells and activated platelets.

Active lesions, including those induced during the pathergy test by skin pricks with a sterile needle, are infiltrated by neutrophils in the absence of infection. Neutrophils from patients with Behçet's disease have increased superoxide production, enhanced chemotaxis, and excessive production of lysosomal enzymes, indicating that the neutrophils are overactive, which leads to tissue injuries.<sup>9,15</sup> Levels of circulating tumor necrosis factor  $\alpha$ , interleukin- $1\beta$ , and interleukin-8 have been reported to be elevated; thus, these cytokines may be involved in the activation of neutrophils and the augmented cellular interactions between neutrophils and endothelial cells as a result of enhanced expression of adhesion molecules.<sup>15</sup>

Lymphocyte function is abnormal in patients with Behçet's disease.<sup>9,16-20</sup> Lymphocytes specific for selected self peptides derived from heat shock protein 60, which are highly homologous with bacterial heat shock protein 65, have been found in patients with Behçet's disease, especially those with ocular involvement.<sup>21-23</sup> In experiments in rats, the peptides induced uveitis.<sup>24,25</sup> The epitopes recognized by autoreactive anti-heat shock protein T cells overlap with the B-cell epitopes of autoantibodies against heat shock protein in patients with Behçet's disease.<sup>23</sup> These epitopes

are totally distinct from the rheumatoid arthritis-related epitopes of heat shock protein 60.<sup>22</sup> The importance of the peptides derived from heat shock protein 60 to the development of Behçet's disease is supported by findings that the expression of this protein is aberrant in the oral mucosa,<sup>10</sup> circulating leukocytes, and skin of patients with Behçet's disease, but not in normal subjects. As a result, in patients with active Behçet's disease there is clonal expansion of autoreactive T cells specific for the peptide derived from heat shock protein 60.<sup>22</sup> However, it remains to be determined whether the autoimmune mechanism is a primary or a secondary event in the development of Behçet's disease.

#### DIAGNOSIS

Because Behçet's disease does not have any pathognomonic symptoms or laboratory findings, the diagnosis is made on the basis of the criteria proposed by the International Study Group for Behçet's Disease in 1990 (Table 2).<sup>26</sup> According to the criteria, recurrent oral ulceration must be present as well as at least two of the following: recurrent genital ulceration, eye lesions, skin lesions, and a positive pathergy test. The differential diagnosis includes chronic oral aphthosis, herpes simplex virus infection, Sweet's syndrome, and HLA-B27-related syndromes such as ankylosing spondylitis. The bowel symptoms of Behçet's disease must be distinguished from those of Crohn's disease and ulcerative colitis. The neurologic symptoms must be distinguished from those of multiple sclerosis. Because Behçet's disease has diverse clinical features, it is sometimes difficult to diagnose complicated cases. In such instances, analysis

**TABLE 2.** CRITERIA FOR THE DIAGNOSIS OF BEHÇET'S DISEASE.\*

FINDING	DEFINITION
Recurrent oral ulceration	Minor aphthous, major aphthous, or herpetiform ulcers observed by the physician or patient, which have recurred at least three times over a 12-month period
Recurrent genital ulceration	Aphthous ulceration or scarring observed by the physician or patient
Eye lesions	Anterior uveitis, posterior uveitis, or cells in the vitreous on slit-lamp examination; or retinal vasculitis detected by an ophthalmologist
Skin lesions	Erythema nodosum observed by the physician or patient, pseudofolliculitis, or papulopustular lesions; or acneiform nodules observed by the physician in a postadolescent patient who is not receiving corticosteroids
Positive pathergy test	Test interpreted as positive by the physician at 24 to 48 hours

\*The criteria were drawn up by the International Study Group for Behçet's Disease.<sup>26</sup> For the diagnosis to be made, a patient must have recurrent oral ulceration plus at least two of the other findings in the absence of other clinical explanations.

of HLA phenotypes and measurement of serum IgD levels may help to make a diagnosis, since patients with active Behçet's disease often have elevated levels of serum IgD.

The pathergy test is useful for evaluating skin irritability and is a diagnostic criterion.<sup>26</sup> The test consists of pricking a sterile needle into the patient's forearm. The results are judged to be positive when the puncture causes an aseptic erythematous nodule or pustule that is more than 2 mm in diameter at 24 to 48 hours.<sup>1</sup> At the reaction site there is initially an accumulation of neutrophils, followed by the accumulation of mononuclear cells. The pathergy test can also be positive in some other diseases such as Sweet's syndrome and pyoderma gangrenosum.

### CLINICAL MANIFESTATIONS

Oral ulceration is usually an initial symptom and is seen in all patients at some time in the clinical course (Table 1).<sup>1,2,27</sup> This symptom sometimes precedes other manifestations by a number of years.<sup>27</sup> Painful oral ulcers appear in the gingiva, tongue, and buccal and labial mucosal membranes. The typical lesion is round, with a sharp, erythematous border, and the surface is covered with a yellowish pseudomembrane (Fig. 1A). The lesions heal within about 10 days without scarring.

Genital ulcers usually occur on the scrotum and penis in men (Fig. 1B) and on the vulva in women.<sup>1,2</sup> They are painful and morphologically similar to the oral ulcers but they are usually larger and deeper and have an irregular margin. The lesions recur and usually leave scars.

Ocular lesions occur in the uvea and retina. Ocular involvement is the first manifestation of Behçet's

disease in about 10 percent of patients, but it usually appears after oral ulceration.<sup>2</sup> Patients with ocular lesions have various subjective symptoms, including blurred vision, eye pain, photophobia, lacrimation, floaters, and periglobal hyperemia (probably as a result of episcleritis).

Hypopyon, a visible layer of pus in the anterior ocular chamber, is characteristic of Behçet's disease (Fig. 1C), though it is also present in some patients with HLA-B27-related arthropathy.<sup>2</sup> Although the episodes of anterior uveitis subside spontaneously, repeated attacks lead to irreversible structural changes, such as deformity of the iris and secondary glaucoma.<sup>3</sup>

The most serious ocular problem in patients with Behçet's disease is the retinal disease. Recurrent, explosive attacks can involve the posterior segment as a result of vaso-occlusive lesions. Patients usually have a painless, bilateral decrease in visual acuity. Ophthalmologic evaluations reveal hemorrhagic and exudative retinal lesions and a cellular infiltration in the vitreous humor during the acute phase. Fluorescein angiography can be used to identify retinal vascular damage, even during remission. Sarcoidosis and viral retinitis sometimes have features indistinguishable from the retinal lesions of Behçet's disease.<sup>3</sup>

Erythema nodosum is common in female patients and usually occurs on the front of the legs (Fig. 1D). The lesions are painful and usually resolve spontaneously, leaving a deeply pigmented area, but they sometimes ulcerate. Pseudofolliculitis and acneiform nodules are common in male patients and are distributed on the back, face, and neck, especially along the hairline. The presence of acneiform nodules in adolescents or in patients who are receiving corticosteroids cannot be used in the diagnosis.<sup>26</sup> Unlike idiopathic or other types of autoimmune-associated thrombophlebitis, superficial migratory thrombophlebitis of the arms and legs is more common in male patients than in female patients.<sup>1,2</sup> Because of the irritability of the skin of patients with Behçet's disease, shaving often causes pseudofolliculitis and intravenous punctures can lead to local thrombophlebitis.

Monarthritis or polyarthritis develops in about half of patients (Table 1). The joints most frequently affected are the knees, followed by the wrists, ankles, and elbows.<sup>2,28</sup> Histologically, there is infiltration of neutrophils and mononuclear cells into the synovium and small-vessel lesions with thrombosis. Destructive changes rarely occur in the joints.<sup>2</sup>

Gastrointestinal involvement causes abdominal pain, diarrhea, melena, and sometimes perforation.<sup>1,2</sup> Oral ulceration is usually considered separately from the gastrointestinal involvement, because oral ulceration is such a major and troublesome symptom. The ileocecal region is the most commonly affected part of the gastrointestinal tract, but the transverse colon and ascending colon are sometimes involved, as is the esophagus. It is often difficult to distinguish be-



**Figure 1.** Characteristic Lesions of Behçet's Disease.

Panel A shows multiple aphthous ulcers on the buccal membrane, gingiva, and labial mucosal membrane (arrows). Panel B shows an active genital ulcer (short arrow) and scars (long arrows) on the scrotum. Panel C shows hypopyon (arrow) — a horizontal layer of inflammatory cells in the anterior ocular chamber — and deformity of the iris. The bright circle in Panel C is reflected light. Panel D shows new and old lesions of erythema nodosum on the front of the legs.

tween Behçet's disease and inflammatory bowel diseases, because of the similarity in extraintestinal symptoms, such as oral ulceration, erythema nodosum, uveitis, and arthritis. Histologically, the intestinal ulcers of patients with Behçet's disease are indistinguishable from those of patients with ulcerative colitis; the finding of the granuloma formation that is characteristic of Crohn's disease can be used to rule out Behçet's disease. The pathergy test is usually negative in patients with inflammatory bowel diseases. HLA typing may also be helpful in the differential diagnosis.

Chronic, progressive involvement of the central nervous system occurs in 10 to 20 percent of patients with Behçet's disease, particularly male patients in whom the disease began at an early age.<sup>1,2,29</sup> Classically, meningitis or meningoencephalitis, neurologic deficits such as motor disturbances and brain-stem symptoms, and psychiatric symptoms including personality changes develop more than five years after Behçet's disease is diagnosed. The symptoms have exacerbations and remissions and gradually cause irreversible disability. In the terminal stage, dementia becomes evident in about 30 percent of affected pa-

tients.<sup>2</sup> In addition, acute aseptic meningitis or meningoencephalitis sometimes develops in the early stage of the disease as part of the symptoms of acute inflammation. It usually responds well to corticosteroids and has a good prognosis.

Magnetic resonance imaging (MRI) and computed tomography are used to detect the neurologic lesions. Multiple high-intensity focal lesions in the brain stem, basal ganglia, and cerebral white matter are typical findings on T<sub>2</sub>-weighted MRI.<sup>1</sup> Electrophysiologic examinations such as measurement of brainstem auditory evoked potentials are also helpful in the diagnosis of neurologic complications.<sup>2</sup> Examination of cerebrospinal fluid reveals elevated protein levels, high IgG levels, and pleocytosis consisting of unusually high numbers of both polymorphonuclear cells and lymphocytes.<sup>2</sup> Oligoclonal bands and antibodies against myelin basic protein are not found in patients with Behçet's disease.

Small-vessel vasculitis is common and accounts for much of the pathologic process in Behçet's disease. Large venous or arterial lesions occur in about 7 to 38 percent of patients (Table 1).<sup>15</sup> Venous involvement, including superficial thrombophlebitis and deep venous thrombosis, is a characteristic manifestation. Occlusion of major veins and arteries and aneurysms often causes bleeding, infarction, organ failure, and restricted movement of the arms and legs. The rupture of such aneurysms may be fatal. Vascular lesions in the lung, including thrombosis, aneurysm, and arteriobronchial fistula, cause recurrent episodes of dyspnea, cough, chest pain, and hemoptysis.<sup>30</sup> Cardiac manifestations such as coronary and valvular diseases occur in some patients.<sup>2,15</sup> Serologically, Behçet's disease is distinct from vasculitis characterized by antibodies against neutrophil cytoplasm and antiphospholipid-antibody syndrome.<sup>15</sup> Computed tomography, MRI, angiography, and ventilation-perfusion scintigraphy are useful for detecting vascular lesions.<sup>2</sup>

### TREATMENT

The choice of the treatment depends on the patient's clinical manifestations (Table 3). Priority is given to the treatment of gastrointestinal symptoms, central nervous system involvement, and large-vessel lesions, which require high-dose corticosteroids, immunosuppressants, or both and, in some cases, surgical intervention. Treatment of ocular lesions requires more careful consideration than the treatment of mucocutaneous symptoms. Close communication among the various specialists is essential for successful treatment.

#### Mucocutaneous Lesions

Topical corticosteroids are useful for oral and genital ulcers.<sup>1,2</sup> Colchicine has beneficial effects on the mucocutaneous symptoms, presumably by inhibiting

neutrophil function.<sup>31</sup> Thalidomide is reported to be effective for oral and genital ulcers and pseudofolliculitis.<sup>32</sup> Systemic corticosteroids are prescribed for erythema nodosum that is refractory to treatment with colchicine.

#### Ocular Lesions

Despite therapeutic intervention, about 25 percent of the patients with ocular lesions eventually become blind.<sup>3</sup> An early age at onset and male sex are risk factors for serious ocular symptoms.<sup>1-3</sup> Therapeutic goals are to reduce both the severity and frequency of ocular attacks.

Topical mydriatic agents and corticosteroid drops are given for attacks of anterior uveitis.<sup>1</sup> Colchicine is prescribed to prevent both anterior and posterior uveitis because of its high degree of efficacy and relatively low toxicity. Topical injection of corticosteroids, with systemic administration in some cases, is used for acute attacks of posterior uveitis.<sup>1</sup> Although oral corticosteroid therapy alone has a palliative effect on ocular attacks, it does not improve the visual prognosis and can even lead to secondary retinal thrombosis and cataracts. Cytotoxic agents such as azathioprine, chlorambucil, and cyclophosphamide help prevent ocular attacks in approximately 50 to 70 percent of patients.<sup>1,2,33,35,37,42</sup> In a single study, the rate of complete and partial responses was 50 percent with corticosteroids, 66 percent with colchicine, and 71 percent with azathioprine.<sup>42</sup> Azathioprine and chlorambucil have also been reported to improve the long-term visual prognosis.<sup>3,33</sup>

Cyclosporine is beneficial in 70 to 80 percent of patients with ocular lesions that have been refractory to the conventional therapies of colchicine, corticosteroids, azathioprine, and cyclophosphamide.<sup>38</sup> The efficacy of cyclosporine gradually declines.<sup>2</sup>

Renal impairment, hypertension, and hyperglycemia are major adverse effects of treatment with cyclosporine. Serum levels of the drug (trough levels) should be measured periodically to adjust the dosage. Although cyclosporine is rarely neurotoxic in patients with other diseases, it causes central nervous system symptoms indistinguishable from those of the classic neurologic lesions in 20 to 30 percent of patients with Behçet's disease.<sup>39</sup> Most of the cyclosporine-induced symptoms subside after the discontinuation of the drug, and sometimes, additional therapy with corticosteroids helps to reduce the symptoms. Cyclosporine-induced symptoms may lead to irreversible central nervous system disability in some patients. Therefore, this drug is contraindicated in patients with neurologic symptoms and patients with subclinical neurologic lesions detected by MRI.

Recent trials of interferon alfa for Behçet's disease have shown encouraging results.<sup>2,36,40</sup> In one study, 95 percent of the patients with ocular involvement had a response to therapy with interferon alfa.<sup>40</sup> In-

TABLE 3. TREATMENT FOR BEHÇET'S DISEASE.\*

TREATMENT	DOSE	USED AS FIRST-LINE THERAPY	USED AS ALTERNATIVE THERAPY
Topical corticosteroids			
Triamcinolone acetonide ointment	3 times a day topically	Oral ulcers	
Betamethasone ointment	3 times a day topically	Genital ulcers	
Betamethasone drops	1–2 drops 3 times daily topically	Anterior uveitis, retinal vasculitis	
Dexamethasone	1.0–1.5 mg injected below Tenon's capsule for an ocular attack	Retinal vasculitis	
Systemic corticosteroids			
Prednisolone	5–20 mg/day orally		Erythema nodosum, anterior uveitis, retinal vasculitis, arthritis
	20–100 mg/day orally	Gastrointestinal lesions, acute meningoencephalitis, chronic progressive central nervous system lesions, arteritis	Retinal vasculitis, venous thrombosis
Methylprednisolone	1000 mg/day for 3 days IV	Acute meningoencephalitis, chronic progressive central nervous system lesions, arteritis	Gastrointestinal lesions, venous thrombosis
Tropicamide drops	1–2 drops once or twice daily topically	Anterior uveitis	
Tetracycline	250 mg in water solution once a day topically		Oral ulcers
Colchicine	0.5–1.5 mg/day orally	Oral ulcers,† genital ulcers,† pseudofolliculitis,† erythema nodosum, anterior uveitis, retinal vasculitis	Arthritis
Thalidomide	100–300 mg/day orally		Oral ulcers,† genital ulcers,† pseudofolliculitis†
Dapsone	100 mg/day orally		Oral ulcers, genital ulcers, pseudofolliculitis, erythema nodosum
Pentoxifylline	300 mg/day orally		Oral ulcers, genital ulcers, pseudofolliculitis, erythema nodosum
Azathioprine	100 mg/day orally		Retinal vasculitis,† arthritis,† chronic progressive central nervous system lesions, arteritis, venous thrombosis
Chlorambucil	5 mg/day orally		Retinal vasculitis,† acute meningoencephalitis, chronic progressive central nervous system lesions, arteritis, venous thrombosis
Cyclophosphamide	50–100 mg/day orally		Retinal vasculitis, acute meningoencephalitis, chronic progressive central nervous system lesions, arteritis, venous thrombosis
	700–1000 mg/mo IV		Retinal vasculitis, acute meningoencephalitis, chronic progressive central nervous system lesions, arteritis, venous thrombosis
Methotrexate	7.5–15 mg/wk orally		Retinal vasculitis, arthritis, chronic progressive central nervous system lesions
Cyclosporine‡	5 mg/kg of body weight/day orally	Retinal vasculitis†	
Interferon alfa	5 million U/day IM or SC		Retinal vasculitis, arthritis
Indomethacin	50–75 mg/day orally	Arthritis	
Sulfasalazine	1–3 g/day orally	Gastrointestinal lesions	Arthritis
Warfarin§	2–10 mg/day orally	Venous thrombosis	Arteritis
Heparin§	5000–20,000 U/day SC	Venous thrombosis	Arteritis
Aspirin¶	50–100 mg/day orally	Arteritis, venous thrombosis	Chronic progressive central nervous system lesions
Dipyridamole	300 mg/day orally	Arteritis, venous thrombosis	Chronic progressive central nervous system lesions
Surgery	—		Gastrointestinal lesions, arteritis, venous thrombosis

\*Data are from Kastner,<sup>1</sup> Kalamani et al.,<sup>2</sup> Nussenblatt,<sup>3</sup> Miyachi et al.,<sup>31</sup> Hamuryudan et al.,<sup>32,33</sup> Yasui et al.,<sup>34</sup> O'Duffy et al.,<sup>35,36</sup> Kazokoglu et al.,<sup>37</sup> Masuda et al.,<sup>38</sup> Kotake et al.,<sup>39</sup> Zouboulis and Orfanos,<sup>40</sup> and Lee et al.<sup>41</sup> IV denotes intravenously, IM intramuscularly, and SC subcutaneously.

†The efficacy of this drug for this use has been reported in controlled clinical trials.

‡Cyclosporine is contraindicated in patients with acute meningoencephalitis or chronic progressive central nervous system lesions.

§This drug should be used with caution in patients with pulmonary vascular lesions.

¶Low-dose aspirin is used as an antiplatelet agent.

terferon alfa-2a is most effective for ocular symptoms: in one study, it resulted in complete remission of the ocular symptoms in 67 percent of the patients within four months.<sup>40</sup>

Intravenous infusions of immune globulin, plasmapheresis, and granulocytapheresis have also been tried in small numbers of patients, but the data are quite limited.

#### Arthritis

Nonsteroidal antiinflammatory drugs and colchicine are effective for most cases of arthritis in patients with Behçet's disease.<sup>1,2</sup> Sulfasalazine can also be used,<sup>1,2</sup> but other types of disease-modifying antirheumatic drugs are rarely used. Low-dose corticosteroids and azathioprine are used in patients whose arthritis is resistant to treatment with nonsteroidal antiinflammatory drugs, colchicine, or sulfasalazine.<sup>2</sup> Interferon alfa is also highly effective.<sup>2,40</sup>

#### Gastrointestinal Lesions

The treatments used for inflammatory bowel disease are also useful for the gastrointestinal lesions of Behçet's disease. Sulfasalazine and corticosteroids are the principal drugs.<sup>1,2</sup> The dose of corticosteroids depends on the severity of the lesions. Bowel rest is obligatory in patients with an acute abdomen and bleeding. Surgery is considered for patients with bowel perforation and persistent bleeding.<sup>41</sup> Invasive surgical procedures often result in excessive infiltration of inflammatory cells into the treated tissues, with subsequent anastomotic leakage. To prevent this complication, intermediate doses of corticosteroids are given to the patients for several days after surgery. Even if the operation is successful, repeated operation because of recurrence is required in about half of the patients.<sup>41</sup>

#### Central Nervous System Lesions

High doses of corticosteroids are administered during the acute phase of neurologic involvement, with subsequent tapering of the dose.<sup>2</sup> Pulsed corticosteroid therapy is an alternative.<sup>2</sup> Corticosteroids can be supplemented with cytotoxic agents such as cyclophosphamide, chlorambucil, and methotrexate.<sup>2,35</sup> Aseptic acute meningitis or meningoencephalitis in the early phase of the disease responds well to treatment with corticosteroids. In contrast, chronic progressive central nervous system disease is resistant to all the currently available therapies. In one study, 20 percent of patients with chronic neurologic involvement died within seven years.<sup>43</sup>

#### Large-Vessel Involvement

Arteritis is treated with a combination of corticosteroids and cytotoxic agents.<sup>1,2,15</sup> Anticoagulants and antiplatelet agents are used for deep venous thrombosis, together with short-term administration of in-

termediate doses of corticosteroids.<sup>1,15</sup> Anticoagulant drugs should be given carefully in patients with pulmonary-vessel disease because of the risk of potentially fatal hemoptysis. Half of patients die within three years after the onset of hemoptysis.<sup>30</sup> Surgical treatment may be considered for refractory large-vessel disease.

#### CONCLUSIONS

In spite of recent advances in treatment, the functional prognosis of patients with Behçet's disease remains unsatisfactory. The final goal is to elucidate the pathogenesis of the disease and develop treatments aimed at the underlying pathologic process.

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#### REFERENCES

1. Kastner DL. Intermittent and periodic arthritic syndromes. In: Koopman WJ, ed. *Arthritis and allied conditions: a textbook of rheumatology*. 13th ed. Vol. 1. Baltimore: Williams & Wilkins, 1997:1279-306.
2. Kaklamani VG, Variopoulou G, Kaklamani PG. Behçet's disease. *Semin Arthritis Rheum* 1998;27:197-217.
3. Nussenblatt RB. Uveitis in Behçet's disease. *Int Rev Immunol* 1997;14:67-79.
4. Nakae K, Masaki F, Hashimoto T, Inaba G, Mochizuki M, Sakane T. Recent epidemiological features of Behçet's disease in Japan. In: Wechsler B, Godeau P, eds. *Behçet's disease*. Amsterdam: Excerpta Medica, 1993:145-51.
5. Zouboulis CC, Kötter I, Djawari D, et al. Epidemiological features of Adamantiades-Behçet's disease in Germany and in Europe. *Yonsei Med J* 1997;38:411-22.
6. Dilsen N, Konice M, Aral O, Öcal L, Inanc M, Gill A. Risk factors for vital organ involvement in Behçet's disease. In: Wechsler B, Godeau P, eds. *Behçet's disease*. Amsterdam: Excerpta Medica, 1993:165-9.
7. Mizuki N, Inoko H, Ohno S. Pathogenic gene responsible for the predisposition to Behçet's disease. *Int Rev Immunol* 1997;14:33-48.
8. Ohno S, Ohguchi M, Hirose S, Matsuda H, Wakisaka A, Aizawa M. Close association of HLA-Bw51 with Behçet's disease. *Arch Ophthalmol* 1982;100:1455-8.
9. Sakane T. New perspective on Behçet's disease. *Int Rev Immunol* 1997;14:89-96.
10. Lehner T. The role of heat shock protein, microbial and autoimmune agents in the aetiology of Behçet's disease. *Int Rev Immunol* 1997;14:21-32.
11. Hamuryudan V, Yurdakul S, Özbakir F, Yazici H, Hekim H. Monozygotic twins concordant for Behçet's syndrome. *Arthritis Rheum* 1991;34:1071-2.
12. Gül A, Inanç M, Öcal L, Aral O, Çarın M, Koniçe M. HLA-B51 negative monozygotic twins discordant for Behçet's disease. *Br J Rheumatol* 1997;36:922-3.
13. Zouboulis CC, Büttner P, Djawari D, et al. HLA-class I antigens in German patients with Adamantiades-Behçet's disease and correlation with clinical manifestations. In: Wechsler B, Godeau P, eds. *Behçet's disease*. Amsterdam: Excerpta Medica, 1993:175-80.
14. Inaba G. Clinical features of neuro-Behçet's syndrome. In: Lehner T, Barnes CG, eds. *Recent advances in Behçet's disease*. London: Royal Society of Medicine Services, 1986:235-46.
15. Ehrlich GE. Vasculitis in Behçet's disease. *Int Rev Immunol* 1997;14:81-8.
16. Yamashita N, Kaneoka H, Kaneko S, et al. Role of gammadelta T lymphocytes in the development of Behçet's disease. *Clin Exp Immunol* 1997;107:241-7.
17. Mochizuki M, Suzuki N, Takeno M, et al. Fine antigen specificity of human gamma delta T cell lines (V gamma 9+) established by repetitive stimulation with a serotype (KTH-1) of a gram-positive bacterium, *Streptococcus sanguis*. *Eur J Immunol* 1994;24:1536-43.
18. Sakane T, Suzuki N, Ueda Y, et al. Analysis of interleukin-2 activity in patients with Behçet's disease: ability of T cells to produce and respond to interleukin-2. *Arthritis Rheum* 1986;29:371-8.
19. Suzuki N, Sakane T, Ueda Y, Tsunematsu T. Abnormal B cell function in patients with Behçet's disease. *Arthritis Rheum* 1986;29:212-9.

20. Sakane T, Kotani H, Takada S, Tsunematsu T. Functional aberration of T cell subsets in patients with Behçet's disease. *Arthritis Rheum* 1982; 25:1343-51.
21. Pervin K, Childerstone A, Shinnick T, et al. T cell epitope expression of mycobacterial and homologous human 65-kilodalton heat shock protein peptides in short term cell lines from patients with Behçet's disease. *J Immunol* 1993;151:2273-82.
22. Kaneko S, Suzuki N, Yamashita N, et al. Characterization of T cells specific for an epitope of human 60-kD heat shock protein (hsp) in patients with Behçet's disease (BD) in Japan. *Clin Exp Immunol* 1997;108:204-12.
23. Direskeneli H, Hasan A, Shinnick T, et al. Recognition of B-cell epitopes of the 65 kDa HSP in Behçet's disease. *Scand J Immunol* 1996; 43:464-71.
24. Stanford MR, Kasp E, Whiston R, et al. Heat shock protein peptides reactive in patients with Behçet's disease are uveitogenic in Lewis rats. *Clin Exp Immunol* 1994;97:226-31.
25. Hu W, Hasan A, Wilson A, et al. Experimental mucosal induction of uveitis with the 60-kDa heat shock protein-derived peptide 336-351. *Eur J Immunol* 1998;28:2444-55.
26. International Study Group for Behçet's Disease. Criteria for diagnosis of Behçet's disease. *Lancet* 1990;335:1078-80.
27. Bang D, Hur W, Lee ES, Lee S. Prognosis and clinical relevance of recurrent oral ulceration in Behçet's disease. *J Dermatol* 1995;22:926-9.
28. Benamour S, Zeroual B, Alaoui FZ. Joint manifestations in Behçet's disease: a review of 340 cases. *Rev Rhum Engl Ed* 1998;65:299-307.
29. Serdaroglu P. Behçet's disease and the nervous system. *J Neurol* 1998; 245:197-205.
30. Hamuryudan V, Yurdakul S, Moral F, et al. Pulmonary arterial aneurysms in Behçet's syndrome: a report of 24 cases. *Br J Rheumatol* 1994; 33:48-51.
31. Miyachi Y, Taniguchi S, Ozaki M, Horio T. Colchicine in the treatment of the cutaneous manifestations of Behçet's disease. *Br J Dermatol* 1981;104:67-9.
32. Hamuryudan V, Mat C, Saip S, et al. Thalidomide in the treatment of the mucocutaneous lesions of the Behçet syndrome: a randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 1998;128:443-50.
33. Hamuryudan V, Özyazgan Y, Hizli N, et al. Azathioprine in Behçet's syndrome: effects on long-term prognosis. *Arthritis Rheum* 1997;40:769-74.
34. Yasui K, Ohta K, Kobayashi M, Aizawa T, Komiyama A. Successful treatment of Behçet disease with pentoxifylline. *Ann Intern Med* 1996; 124:891-3.
35. O'Duffy JD, Robertson DM, Goldstein NP. Chlorambucil in the treatment of uveitis and meningoencephalitis of Behçet's disease. *Am J Med* 1984;76:75-84.
36. O'Duffy JD, Calamia K, Cohen S, et al. Interferon-alpha treatment of Behçet's disease. *J Rheumatol* 1998;25:1938-44.
37. Kazokoglu H, Saatci O, Cuhadaroglu H, Eldem B. Long-term effects of cyclophosphamide and colchicine treatment in Behçet's disease. *Ann Ophthalmol* 1991;23:148-51.
38. Masuda K, Nakajima A, Urayama A, Nakae K, Kogure M, Inaba G. Double-masked trial of cyclosporin versus colchicine and long-term open study of cyclosporin in Behçet's disease. *Lancet* 1989;1:1093-6.
39. 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.
40. Zouboulis CC, Orfanos CE. Treatment of Adamantiades-Behçet disease with systemic interferon alfa. *Arch Dermatol* 1998;134:1010-6.
41. Lee KS, Kim SJ, Lee BC, Yoon DS, Lee WJ, Chi HS. Surgical treatment of intestinal Behçet's disease. *Yonsei Med J* 1997;38:455-60.
42. Kotter I, Durk H, Saal J, Fierlbeck G, Pleyer U, Ziehut M. Therapy of Behçet's disease. *Ger J Ophthalmol* 1996;5:92-7.
43. Akman-Demir G, Baykan-Kurt B, Serdaroglu P, et al. Seven-year follow-up of neurologic involvement in Behçet syndrome. *Arch Neurol* 1996; 53:691-4.

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