

Ocular Manifestations in Behçet's Disease

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Abstract

Behçet's disease is a refractory inflammatory disease; its cause is unknown and it presents with repeated acute inflammation in various organs throughout the body. Its 4 major manifestations are oral aphthae, ocular manifestations, skin manifestations, and genital ulcers. Frequently appearing in the mongoloid population in the vicinity of the Silk Road, the disease is rare in Europeans and Americans. There are currently no laboratory findings useful in and specific to the diagnosis of Behçet's disease. Behçet's disease is diagnosed based on a combination of clinical manifestations. In Japan, the diagnostic criteria have major and minor manifestations and the disease is classified as a complete, incomplete, possible, or specific type based on the combination of those manifestations. This review discusses the clinical manifestations of Behçet's disease with a focus on ocular manifestations.

Key words Behçet's disease, HLA-B51, Uveitis, Vasculitis

Introduction

Behçet's disease was first described by Professor Hulusi Behçet, a Turkish dermatologist, in 1937,¹ but an ailment akin to Behçet's disease had previously been described by the noted Greek physician Hippocrates in the 5th century BC. The history of this disease is extremely old, but it was first systematically described by Professor Behçet in the 20th century.

Behçet's disease is a refractory inflammatory disease; its cause is unknown and it presents with repeated acute inflammation in various organs throughout the body. Its 4 major manifestations are oral aphthae, ocular manifestations, skin manifestations, and genital ulcers. Frequently appearing in the mongoloid population in the vicinity of the Silk Road, the disease is rare in Europeans and Americans (Fig. 1). In Japan, registered patients are described as numbering about 18,000 people,^{2,3} however, this number is assumed to be even higher if potential patients are also included. The causes of Behçet's disease are still unknown, but the mechanism of its

pathogenesis is becoming clearer.

Demographic Characteristics/ Epidemiology in Japan

Epidemiology

The male-to-female patient ratio in Japan is 0.98. Total patients in Japan: 18,300 people (1991), 19,800 people (1996). 135 people out of a population of 1 million.

Distribution

Prevalent along the Silk Road, 30–45 degrees north on the Eurasian landmass.
Prevalent in the north of Japan.
Widely prevalent in Turkey, Jordan, Syria, Israel, Lebanon, and Saudi Arabia. Also found in the Mediterranean, Spain, Portugal, Greece, and Italy. Not found in Caucasians of Northern European descent and Sub-Sahara Africans.
Not found in Southeast Asia or in Hawaiians or Brazilians of Japanese descent.
Not found in any of the races in North, Central, or South America.

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Table 1 Diagnostic criteria for Behçet's disease according to the Behçet's Disease Research Committee of Japan

Behçet's disease clinical diagnostic criteria (2003 revision)	
(1) Major manifestations	
①	Recurrent aphthae of oral mucosa
②	Skin manifestations
	(a) Erythema nodosum
	(b) Subcutaneous thrombophlebitis
	(c) Folliculitis-like rash, acne-like rash
	Referential finding: enhanced skin irritability
③	Ocular manifestations
	(a) Iridocyclitis
	(b) Uveoretinitis (retinochoroiditis)
	(c) If the following findings are present, they conform to (a) (b)
	Posterior synechia, lens pigmentation, chorioretinal atrophy, optic atrophy, complicated cataract, secondary glaucoma, or phthisis bulbi considered to be the progress of (a) (b)
④	Genital ulcers
(2) Minor manifestations	
①	Arthritis without deformation or stiffness
②	Epididymitis
③	Digestive tract sores as typified by ileocecal ulcers
④	Vascular lesions
⑤	Moderate or more severe CNS lesions
(3) Criteria for diagnosis of the type of disease	
①	Complete type
	4 major manifestations appear in the course of the illness
②	Incomplete type
	(a) 3 major manifestations or 2 major and 2 minor manifestations appear in the course of the illness
	(b) Typical ocular manifestations and 1 major or 2 minor manifestations appear in the course of the illness
③	Possible type
	Some major manifestations appear but do not qualify as the incomplete type and typical minor manifestations repeat or worsen
④	Specific lesions
	(a) entero-Behçet's disease—The presence/absence of abdominal pain and occult blood test result will be listed.
	(b) vasculo-Behçet's disease—Impairment of large arteries, small arteries, or large & small arteries will be listed.
	(c) neuro-Behçet's disease—The presence/absence of headaches, palsy, cerebrospinal-type symptoms, psychiatric manifestations, etc. will be listed.
(4) Test once for HLA-B51 (B5) positivity	
	The type of HLA should be listed
(5) Laboratory findings for reference (not mandatory)	
①	Negative/positive in a positive skin pathergy test
	A relatively large injection needle of 22–18 G will be used
②	Negative/positive on a prick test with a streptococcus vaccine
	Hypersensitivity to streptococcus
	Many patients with Behçet's disease display strong hypersensitivity to oral streptococci like <i>Streptococcus sanguinis</i> , so in a prick test (fine 26 G needle) with <i>Streptococcus sanguis</i> antigen, this can be seen as a strong flare reaction 20–24 hrs later.
③	Inflammatory response
	Enhanced level of sedimentation, positive serum CRP, increased WBC count in peripheral blood, rise in complement titer
④	HLA-B51(5) positive
⑤	Pathological findings
	With acute-stage erythema nodosum, cells infiltrating because of septal panniculitis are due to the infiltration of polymorphonuclear and mononuclear leukocytes.
	Initially, polymorphonuclear leukocytes are prevalent but infiltration is mainly of mononuclear leukocytes, presenting an image of "lymphocytic vasculitis."
	This may also be accompanied by necrotizing vasculitis, which suggests the possibility of systemic vasculitis, so the presence/absence of this vasculitis will be examined.

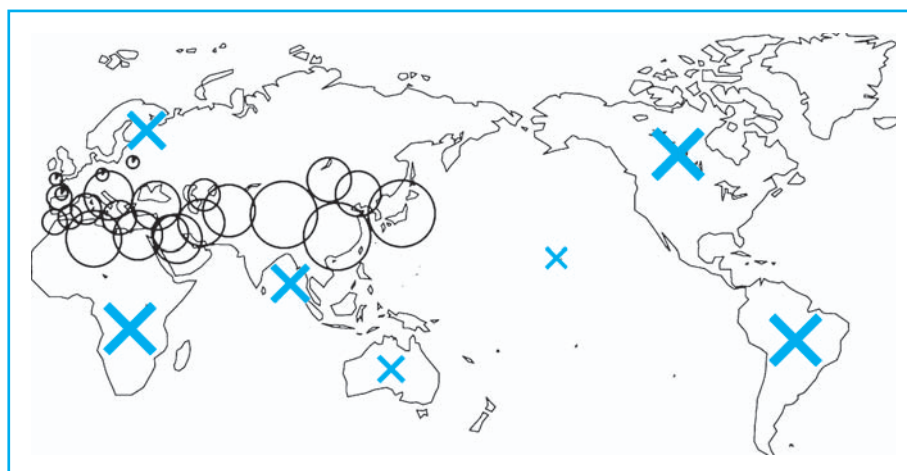


Fig. 1 Global distribution of Behçet's disease

Plotting the global distribution of Behçet's disease on the chart indicates that countries with a prevalence of this disease are concentrated in the region along the Silk Road from 30 to 45 degrees north. With its eastern end in Japan, the region covers East Asia, Central Asia, Eurasia, West Asia, and then the Mediterranean before reaching its western end in Morocco, Spain, and Portugal. The ○'s indicate countries with a prevalence of Behçet's disease and the ×'s indicate regions where it is only rarely seen. (Studies on exogenous and endogenous factors associated with various ocular diseases⁶)

Table 2 Major manifestations

A) Recurrent aphthae of the oral mucosa:	98.2%
B) Skin manifestations:	87.1%
Erythema nodosum	
Subcutaneous thrombophlebitis	
Folliculitis-like rash	
C) Ocular manifestations:	69.1%
Iridocyclitis	
Uveoretinitis, etc.	
D) Genital ulcers:	73.2%

(Results of a National Epidemiological Survey of Patients with Behçet's Disease (First report)²)

Table 3 Minor manifestations

A) Arthritis without deformation or stiffness:	56.9%
B) Epididymitis:	6.0%
C) Digestive tract sores as typified by ileocecal ulcers:	15.5%
D) Vascular lesions:	8.9%
E) Moderate or more severe CNS lesions:	11.0%

(Results of a National Epidemiological Survey of Patients with Behçet's Disease (First report)²)

Epidemiology by type of disease (1991)²

The complete type accounts for 28.9%, the incomplete type for 55.3%, and possible cases account for 8.4%.

Epidemiology by manifestation (1991)²

According to a large-scale epidemiological study² that compared cases in 1972 and 1991, many patients having the incomplete type with ocular manifestations were men (sex ratio: 1.87); many patients having the incomplete type with genital ulcers were women (sex ratio: 0.42).

Incidence of major and minor manifestations (1991)²

Recurrent aphthae of the oral mucosa manifested in 98.2%, skin manifestations in 87.1% (erythema nodosum, subcutaneous thrombophlebitis, folliculitis-like rash, and ocular manifestations in 69.1%, and genital ulcers in 73.2%). (see Table 2)

Arthritis without deformation or stiffness manifested in 56.9%, epididymitis in 6.0%, digestive tract sores as typified by ileocecal ulcers in 15.5%, vascular lesions in 8.9%, and moderate or more severe CNS lesions in 11.0%. (see Table 3)



Fig. 2 Global distribution of HLA-B51

HLA-B51 is frequently seen in East Asia, e.g. Japan, Central Asia, Eurasia, West Asia, and the Mediterranean. However, it is infrequent in Sub-Sahara Africa and in Europe and the US where Caucasians live. In addition, HLA-B51 is rare in Southeast Asia. Thus, the global distribution of the genetic factors of HLA-B51 coincides impressively with the global distribution of Behçet's disease. (Studies on exogenous and endogenous factors associated with various ocular diseases⁶)

Pathology of Behçet's Disease

The pathogenesis of Behçet's disease clearly involves neutrophil dysfunction,⁴ lymphocyte abnormalities, cytokine abnormalities,⁵ immunological abnormalities, etc. Genetically, the disease is, based on an examination of HLA-B51 and related genes, a multifactorial illness in which the disease arises with some external environmental factors at work based on specific intrinsic genetic factors.⁶ The distribution of HLA-B51 is shown in Fig. 2. Traversing race, Behçet's disease is markedly correlated with the HLA-B51 antigen—a specific type of HLA, the human form of the major histocompatibility antigen—and is highly positive for HLA-B51; HLA-B51 is considered to play a major role in the pathogenesis of the disease. In addition, we have proffered the hypothesis that asparagine at position 63 and phenylalanine at position 67, amino acids specific to the HLA-B51 molecule, play a major role in the onset of this disease. In actuality, HLA-B51 carriers have a relative risk of suffering Behçet's disease of 17.1,⁷ which is extremely high. Additionally, the MICA (MHC class I chain-related gene A) gene is located in very close proximity to the HLA-B gene (slightly centro-

meric at 46 kb) and is in strong linkage disequilibrium with the HLA-B gene. The MICA gene is an HLA-like molecule and has 30% amino acid homology with the HLA class I antigen. The MICA molecule is primarily expressed in intestinal epithelium, vascular endothelial cells, keratinocytes, etc. and coincides with local inflammation in Behçet's disease. We previously analyzed the MICA gene and clarified the fact that the MICA-A6 allele (MIC-A*009 allele) increases significantly in patients with Behçet's disease, suggesting its secondary involvement in the onset of the disease.⁸⁻¹⁰ Recent studies have also indicated that the A6 allele of the MICA molecule (and particularly MICA-A*009) displays a high level of affinity for HLA-B51,⁸⁻¹² and further analysis is required with regard to the involvement of the MICA molecule in the onset of this disease. Additionally, immunological abnormalities due to self- and/or bacterial/microbial heat shock proteins (HSPs) are also critical. T lymphocytes of patients with Behçet's disease who have ocular manifestations are specific and highly reactive to self HSP and exogenous HSP with cross-reactivity to self HSP and actively produce proinflammatory cytokines and neutrophil-directed cytokines.¹³ Based on reports that TNF α production is significantly



Fig. 3 Typical oral aphtha is apparent (→)
(Courtesy of [Assoc.] Professor Mitsuhiro Takeno, First Department of Surgery, Yokohama City University)



Fig. 4 Typical genital ulcer (→)
(Courtesy of [Assoc.] Professor Mitsuhiro Takeno, First Department of Surgery, Yokohama City University)

enhanced in the active stage of ocular manifestations^{14–16} and that the serum concentration of TNF α is higher regardless of whether oral aphthae and erythema nodosum are present, TNF α is also involved in the pathology of Behçet's disease. Though in the clinical trial stage, the efficacy of anti-TNF α chimeric antibody (infliximab), a form of anti-TNF α antibody therapy, as a therapeutic agent has also been confirmed.^{17,18}

Diagnostic Criteria for Behçet's Disease

Nevertheless, there are currently no laboratory findings useful in and specific to the diagnosis of Behçet's disease at this time. HLA-B51 antigen is positive in about 60% of patients, which is somewhat high, and this positivity can serve as a reference, but it is positive in about 15% of healthy individuals, so this result cannot be considered definitive.⁷ Thus, Behçet's disease is diagnosed based on a combination of clinical manifestations. Diagnostic criteria in Japan and the West differ. International diagnostic criteria²⁰ by an International Study Group cite recurrent oral aphthae as a mandatory manifestation; with this, if 2 of 4 items—genital ulcers, ocular manifestations, skin manifestations, or a positive pathergy test—are satisfied, then the condition can be diagnosed as Behçet's disease. Ocular manifestations have a high specificity in Behçet's disease; the complete type in Japan's diagnostic criteria agrees 100% with international diagnostic criteria but incomplete Behçet's with ocular manifestations is excluded. In addition, the positive pathergy test, one of the international diagnostic

criteria, is 43.8%, which is not frequent enough to be considered a major manifestation in Japan,² so cases that cannot be definitively diagnosed as Behçet's disease with Japan's diagnostic criteria can be diagnosed as Behçet's disease with international diagnostic criteria.

Thus, future reappraisal of international diagnostic criteria is probably required.

In Japan, criteria are divided into major and minor manifestations and the disease is classified as a complete, incomplete, possible, or specific type based on the combination of those manifestations (Table 1).

Clinical Features

This section cites a 1991 Ministry of Health and Welfare Committee report and notes the incidence of major and minor manifestations of Behçet's disease (Tables 2 and 3).

Recurrent aphthae (included in major manifestations)

Oral aphthae (Fig. 3) are the first manifestation to appear in Behçet's disease. Aphthae may be present singly or clustered in the buccal mucosa in the mouth, on the gingiva, on the tongue, inside the lips, on the palate, etc. They may also appear on the tonsils, pharynx, and esophagus. The aphtha is a small, round ulcer with a clearly defined border and is painful. Characteristic of aphthae is that they heal in 1–2 weeks without



Fig. 5 Erythema nodosum (portion circled with a ○)
(Courtesy of [Assoc.] Professor Mitsuhiro Takeno, First Department of Surgery, Yokohama City University)

scarring but repeatedly reappear. During recurrence, the location of the aphtha often differs. However, aphthae are not specific to Behçet's disease and are no different from chronic recurrent aphthae in ordinary individuals, so caution is required since, in the initial stages, they are simply regarded as stomatitis and are left untreated. Oral aphthae are the most frequent initial manifestation of Behçet's disease.² They often appear 10–15 years prior to definitive diagnosis and have a final incidence of almost 100%.²

Genital ulcers (included in major manifestations)

Genital ulcers (Fig. 4) are a characteristic finding of Behçet's disease. The ulcers are painful with a clear boundary and also cause considerable pain. They occur on the penis, scrotum, labia minora, vaginal walls, in the anal region, etc. They heal in 1–2 weeks, but unlike oral aphthae and erythema nodosum, scarring may remain even after the site has healed. The occurrence of ulcers at such sites is rare for other illnesses, so this is a specific finding that strongly suggests Behçet's disease.

Skin manifestations (major manifestations)

With regard to skin manifestations, major manifestations are erythema nodosum (Fig. 5), subcutaneous thrombophlebitis, and folliculitis-like rash, and a positive pathergy test is a referential finding.

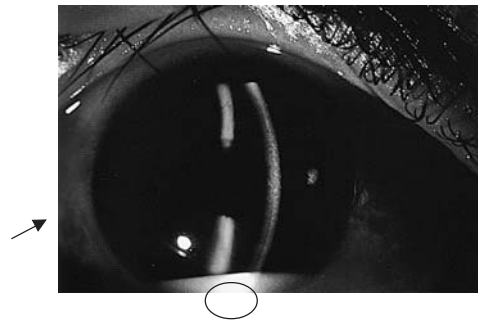


Fig. 6 Recurrent hypopyon iridocyclitis
Ciliary hyperemia (→) and a hypopyon (circled portion) are apparent.

Erythema nodosum is painful erythema of 1–several cm that favors the extensor aspects of the lower extremities and is characterized by a somewhat raised area. It heals in about 1–2 weeks without scarring but repeatedly recurs.

A folliculitis-like rash involves circular follicular sterile pustules of several mm and often appears on the face, trunk, and at sites subjected to mechanical irritation. However, such skin manifestations are not findings specific to Behçet's disease and are not readily differentiated from those due to other illnesses.

When pricked with a needle, the area forms a sterile pustule after 24–48 hours; this is called a positive pathergy test. Occurrence in Japan is low at 43.8%,^{2,24} but a foreign source (Israel) did find the test to have a high sensitivity and specificity.²¹

Skin irritability is observed along with purulence and development of a rash.

Ocular manifestations

The age at onset of ocular manifestations is often in the 30s, and these manifestations tend to be severe in men.

One year after onset, 40% of patients have visual acuity of less than 0.1; after 8 years, 80% of patients have visual acuity of less than 0.1. After 10 years, 40% of cases become blind.^{2,22,23}

Iridocyclitis type: recurrent hypopyon iridocyclitis

Acute non-granulomatous inflammation occurs in the anterior eye (iris, ciliary bodies, etc.) and often forms a hypopyon (Fig. 6). The hypopyon may be seen by the patient himself while looking in a mirror when an attack occurs or it may be



Fig. 7 Fundal attack
Bleeding and exudate are apparent.

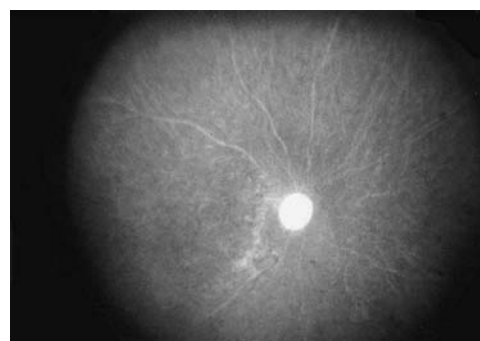


Fig. 8 End-stage fundus photography
Vessels appear as white lines due to vascular occlusion; optic and chorioretinal atrophy are apparent.

noted by family. A hypopyon also occurs with HLA-B27-associated uveitis and uveitis in diabetes, ulcerative colitis, Crohn's disease, and herpes virus infection but it is naturally frequent in Behçet's disease. A hypopyon resulting from Behçet's disease is facile and moves in accordance with gravity, but when the patient lays on his side, it moves horizontally and a niveau is formed at an angle. In contrast, a hypopyon resulting from HLA-B27-associated uveitis has a large amount of fibrin, is sticky, and does not move, so this serves as a reference for differentiation of the two. At times, an angle hypopyon can be seen with a gonioscope. Posterior synechia is found in 32%²²⁻²⁴ and is more frequent than with other types of uveitis. With complete posterior synechia, moreover, iris bombe occurs in 71%. When ciliary body function declines, rubeosis iridis and phthisis bulbi may occur. Keratic precipitates are infrequent, but even if they are detected, they do not become mutton-fat keratic precipitates. Peripheral anterior synechia is also seen, but it does not lead to "tenting."

In Behçet's disease, the iridocyclitis type accounts for about 20% of ocular manifestations overall. Patients often complain of blurred vision but may have partial whitening of the visual field and be unable to see. Initially, symptoms often clear up within several weeks but may become prolonged with repeated attacks.

**Uveoretinitis type:
vasculitis with bleeding and exudate**

Repeated inflammation occurs in the choroid and retina, and permanently blurred vision remains. About 5 years later the peak of inflammation occurs, after which the inflammation winds

down. Retinal vasculitis with bleeding and exudate is found in funduscopy of the uveoretinitis type (Fig. 7). Such fundal attacks can occur anywhere in the retina. Exudate runs along retinal vessels and displays the same distribution as bleeding. In addition to Behçet's disease, such findings are also seen in viral retinochoroiditis, tuberculous retinochoroiditis, etc. There are instances where visual acuity of 1.0 may drop to less than 0.1 with just one attack. However, even if visual acuity drops to the hand motion level, visual acuity returns in a considerable number of cases once an antiinflammatory is given for several weeks to several months. There are frequently instances in which 80 to 90% of the previous visual acuity returns. However, visual acuity often gradually declines with repeated attacks and often ultimately results in blindness.^{2,22,23} The Ministry of Health, Labour and Welfare's Behçet's Disease Research Committee previously stated that individuals in which ocular manifestations appeared would have visual acuity of less than 0.1 in about 8 years; this condition would result in blindness for close to 40% of individuals in about 10 years. However, visual prognosis is gradually improving with the recent moderation of Behçet's disease and development of new therapies. When the condition is complicated with uveoretinitis, posterior sub-Tenon's injection of a steroid is added. And when frequent attacks are seen, systemic agents are also incorporated. Colchicine and cyclosporine are systemic agents, but orally administered medication is selected depending on the patient's age, level of disease activity, the wishes of the patient,

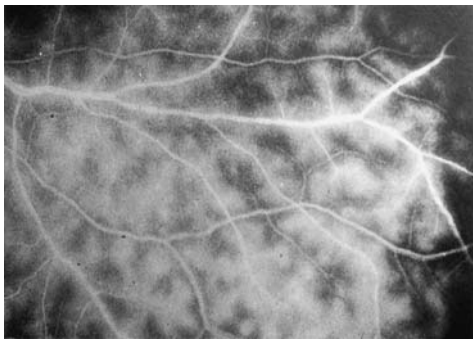


Fig. 9 Fluorescein angiography
Vascular leakage in a fern pattern is apparent

and the type of disease. If there is a possibility of pregnancy, colchicine, which is teratogenic, is contraindicated. The introduction of cyclosporine is examined when the condition is highly active, but the agent must be carefully administered with an initial dose of 2–3 mg/kg/day and the trough level should be observed periodically. With neuro-Behçet's, however, cyclosporine is contraindicated. In addition, concomitant use of colchicine and cyclosporine is contraindicated because it may induce myopathy.

Ocular prognosis and end-stage fundus findings

End-stage fundus findings for Behçet's disease are chorioretinal and optic atrophy (Fig. 8).

The portions of the retina and choroid are where fundal attacks have occurred because of Behçet's disease atrophy. In addition, bloodflow is impaired by the inflammation of vessels and occlusive vasculitis occurs; as this progresses, bloodflow is disrupted; retinal vessels whiten and appear as white lines. Cells of the retina and choroid in whitened vascular areas are damaged and regions suffering chorioretinal atrophy cause a decrease in visual performance, so portions of the visual field that cannot be seen gradually increase with attacks and the visual field also narrows. However, ocular attacks occur randomly in the fundus, so this is fundamentally different from the narrowing of the visual field that occurs in glaucoma as optic nerves are damaged. Thus, narrowing of the visual field gradually progresses with ocular attacks.

Fluorescein angiography

Fluorescein angiography is performed to diagnose Behçet's disease and determine the progress of the disease. Pathology involves retinal vasculitis

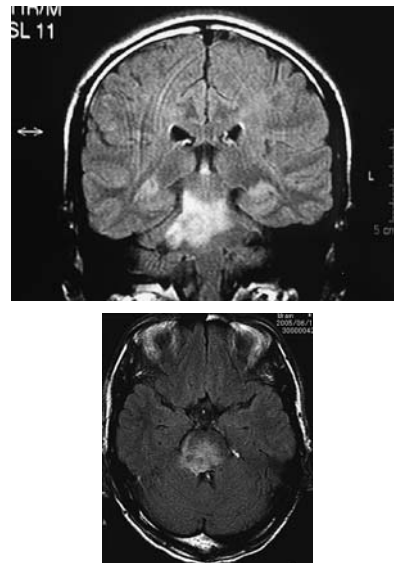


Fig. 10 Neuro-Behçet's
Hyperintensity presents in T2 MRIs

(and particularly thrombophlebitis); an indicative finding is fluorescein leakage in a fern pattern, i.e. exuding of the fluorescent agent (Fig. 9). In addition, occlusive vasculitis, avascular areas with that vasculitis, neovascularization, etc. are seen.

Other generalized manifestations

There are 5 types of minor manifestations. Arthritis appears in close to 60% of cases, meaning that its frequency is close to that of a major manifestation. It is characterized by a lack of deformation or stiffness in major joints and a lack of morning stiffness, which differentiates it from rheumatoid arthritis. Other manifestations include epididymitis, ulcers of the ileocecum (entero-Behçet's), vascular lesions, and neurological manifestations. These all have a frequency of about 10% (Table 3). Since they can be life-threatening, entero-, vasculo-, and neuro-Behçet's disease require vigilance and are classified into specific types of the disease. Neurological manifestations appear last in Behçet's disease and often in men; they occur after about 5–10 years have passed since the onset of this disease. With characteristic CNS manifestations, lesions of the base of the brain, i.e. the brainstem, mid-brain, and pons, occur in 80–90%. Brainstem and cerebellar manifestations such as motor paralysis of the hands and feet, hemiplegia and headaches, staggering, gait disturbance, dysar-

thria and diplopia and psychiatric manifestations such as personality changes are seen. Thus, if patients complain of headaches, staggering, or dysarthria, detailed examinations should be quickly performed. An MRI is useful for testing (Fig. 10). In terms of vascular manifestations, inflammatory or thrombotic occlusions occur in large and medium-sized vessels and sometimes

form an aortic aneurysm; this is a deadly complication. Use of cyclosporine therapy has recently become widespread, often leading to problems with the induction or promotion of neurological manifestations of Behçet's disease and differentiation from CNS manifestations that are adverse effects of cyclosporine itself.

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