

Behçet's syndrome and the nervous system

Aksel Siva, Ayse Altintas and Sabahattin Saip

Purpose of review

Behçet's syndrome (BS) is a multi-system, vascular-inflammatory disease of unknown origin, involving the nervous system in a subgroup of patients. The syndrome is rare, but as patients with BS are young and frequently present with an acute or subacute brainstem syndrome or hemiparesis, as well as with other various neurological manifestations, the syndrome is often included in the differential diagnosis of multiple sclerosis, stroke of the young adult, and another wide range of neurological disorders. The present review summarizes the neurological involvement in BS, and emphasizes recent clinical concepts and ethiopathogenetic findings.

Recent findings

Over the last years the growing clinical and imaging evidence had suggested that neurological involvement in BS may be subclassified into two major forms: one, which is seen in the majority of patients, may be characterized as a vascular-inflammatory CNS disease, with focal or multifocal parenchymal involvement; the other, which has few symptoms and a better neurological prognosis, may be caused by isolated cerebral venous sinus thrombosis and intracranial hypertension. These two types rarely occur in the same individual, and their pathogenesis is likely to be different. A nonstructural vascular type headache is relatively common, whereas isolated behavioral syndromes and peripheral nervous system involvement are rare.

Summary

The involvement of the nervous system in BS is heterogeneous as clinical and imaging data reveal. Currently it is unknown which factors determine or have a role in the development of neurological involvement, but some progress has been achieved in understanding the neurological spectrum of the syndrome, which may lead to a better management of these patients.

Keywords

Behçet's syndrome, cerebral venous sinus thrombosis, imaging, immunology/immunopathogenesis, nervous system involvement, treatment, vasculitis

Curr Opin Neurol 17:347–357. © 2004 Lippincott Williams & Wilkins.

Department of Neurology, Clinical Neuroimmunology Division, Cerrahpaşa School of Medicine, University of Istanbul, Cerrahpaşa 34303, Istanbul, Turkey

Correspondence to Aksel Siva, MD, Hacı Emin Sok No. 20/7 Nişantaşı, 34365 Istanbul, Turkey
Tel: +90 212 532 6156781; fax: +90 212 2402106; e-mail: asiva@tnn.net

Current Opinion in Neurology 2004, 17:347–357

Abbreviations

BD	Behçet's disease
BS	Behçet's syndrome
CNS	central nervous system
CNS-NBS	central nervous system-neuro-Behçet syndrome
CSF	cerebrospinal fluid
CVST	cerebral venous sinus thrombosis
EDSS	expanded disability status scale
MRI	magnetic resonance imaging
MS	multiple sclerosis
NBS	neuro-Behçet syndrome
SPECT	single-photon emission computed tomography
Th	T helper

© 2004 Lippincott Williams & Wilkins
1350-7540

Introduction

Behçet's syndrome (BS) is a chronic relapsing vascular-inflammatory disease of unknown origin, which affects many organs and systems, causing mucocutaneous lesions, uveitis sometimes resulting in blindness, nervous system involvement, major vessel disease that may be fatal, musculoskeletal problems, gastrointestinal involvement and others. The diagnosis remains mostly clinical, and currently the most widely used diagnostic criterion is the International Study Group's classification, according to which a definitive diagnosis requires recurrent oral ulcerations plus two of the following: recurrent genital ulcerations, skin lesions, eye lesions and a positive pathergy test [1] (Table 1).

BS occurs in the third decade, with a slightly increased tendency to affect men more than women in the general population (world average of 1.4:1) and has a more severe course in men [2•]. The epidemiology of the disease shows a geographical variation, seen more commonly along the Silk Route that extends from the Mediterranean region to Japan. This is coupled by a similar variation in HLA-B51, which is strongly associated with the disease in high prevalence areas [3,4]. Interestingly, BS also shows a geographical variation in disease expression, with severe eye involvement and inflammatory bowel disease being more common in the Far East than in the Mediterranean basin, and the pathergy reaction being less frequent in western countries than the Mediterranean region and Japan. As a result of this genetic and clinical variation, it is preferred by many to call Behçet's a syndrome rather than a disease [5•]. The frequency of the clinical manifestations of BS is shown in Table 2.

Table 1. Criteria for diagnosis of Behçet's disease

Finding	Definition
Recurrent oral ulceration	Minor aphthous, major aphthous, or herpetiform ulcers observed by the physician or reliably described by the patient, which recurred at least three times over a 12-month period.
Recurrent genital ulceration	Aphthous ulceration or scarring observed by the physician or reliably described by the patient.
Eye lesions	Anterior or posterior uveitis or cells in the vitreous body on slit-lamp examination; or retinal vasculitis detected by an ophthalmologist.
Skin lesions	Erythema nodosum, pseudofolliculitis, papulopustular lesions or acneiform nodules not related to glucocorticoid treatment or adolescence.
Positive pathergy test	Test interpreted as positive by the physician at 24–48 h.

For a clinical definite diagnosis of BD the patient must have recurrent oral ulceration plus at least two of the other findings in the absence of any other clinical explanations.

From the International Study Group for Behçet's Disease [1], reproduced from Siva and Yazıcı [4], with permission.

Table 2. Frequency of clinical manifestations of Behçet's syndrome^a

Manifestation	Frequency
Oral ulcers	97–100%
Genital ulcers	~85%
Eye disease	~50%
Skin lesions	
Papulopustular lesions	~85%
Erythema nodosum	~50%
Pathergy reaction	~60% ^a
Arthritis	~50%
Thrombophlebitis	25%
Involvement of major arteries/veins	~4%
CNS disease	~5–10%
Epididymitis	~5%
Gastrointestinal lesions	1–30%

(more prevalent in Far East)

CNS, Central nervous system.

^aMediterranean countries and Japan.

Reproduced from Siva and Yazıcı [4], with permission.

Neurological involvement in Behçet's syndrome

Clinical and imaging data suggest that the clinical variation is also seen with the neurological involvement in BS, which may be subclassified into two major forms. One is attributable to small venous inflammatory disease with focal or multifocal central nervous system (CNS) parenchymal involvement, and is seen in the majority of patients. It is designated the central nervous system-neuro-Behçet syndrome (CNS-NBS or intra-axial neuro-Behçet syndrome). The other form is caused by cerebral venous sinus thrombosis (CVST or extra-axial NBS) with limited symptoms and a better neurological prognosis [6,7]. It is very uncommon for these two types of involvement to occur in the same individual [6,7]. An article by Akman-Demir *et al.* [6], in which the clinical features, evoked potentials, cerebrospinal fluid (CSF) and imaging studies and prognostic factors of patients with BS and neurological involvement were evaluated retrospectively, is the largest case series of its kind. Another study based on the clinical, diagnostic and prognostic features of 164 well-documented cases with NBS [7] introduced

Table 3. The neurological spectrum of Behçet's disease

Primary neurological
• The non-structural (migrainous) headache of BS
• Subclinical NBS
• Cerebral dural venous sinus thrombosis (extra-axial NBS)
• CNS involvement (parenchymal NBS/intra-axial NBS)
• Neuro-psycho-Behçet syndrome
• Peripheral nervous system involvement
Secondary neurological
• Complications related to treatments of BS (i.e. CNS neurotoxicity with cyclosporine; peripheral neuropathy secondary to thalidomide or colchisin)
• Complications of systemic disease (i.e. intracranial hypertension related to superior vena cava syndrome; cerebral emboli from cardiac complications of BD)
Coincidental (non-BS) neurological involvement

BD, Behçet's disease; BS, Behçet's syndrome; CNS, central nervous system; NBS, neuro-Behçet syndrome.

some new clinical concepts in understanding the patterns of neurological involvement in BS.

In addition to the most common primary neurological involvement patterns of CNS-NBS and CVST, rarely neuro-psycho-BS and peripheral nervous system involvement may also occur [4]. Neurological complications of treatments of BS (i.e. CNS neurotoxicity with cyclosporine and neuropathy with thalidomide use), or complications related to other systemic problems (i.e. cerebral emboli from cardiac complications of BS) are included among the secondary neuro-psychiatric consequences of the syndrome [4,7] (Table 3).

The reported frequency of neurological involvement among BS patients ranges from 2.2 to 49.0%, but larger series have shown a rate of approximately 5% [6,7]. However, these are frequency estimates from cross-sectional studies. In a recent study from our centre, when the frequency of neurological involvement was evaluated prospectively, the frequency was 13.0% among men and 5.6% among women after two decades of follow-up [2••]. The mean age of onset for BS and NBS was found to be 26.7 ± 8.0 and 32.0 ± 8.7 years, respectively [7], which is consistent with some other

recent series [6,8]. However, in our series, when the patients with neurological disease were stratified according to the two major types of neurological involvement, the age of onset for male patients with CVST was significantly earlier than that of CNS-NBS: 23.1 ± 8.8 versus 32.0 ± 7.5 years ($P=0.002$) [9].

An article by Kidd *et al.* [8] described the clinical, imaging, laboratory and neurophysiological features and prognostic factors of Behçet's disease (BD) patients with neurological involvement in a case series of 50 patients in a region where the disease is infrequently seen.

Neurological involvement in BS occurs more commonly in men, with a male to female ratio of up to 4:1 [7]. Such a significant male predominance has also been noted for other vascular complications of BS [2**]. Some demographic features and the frequency of clinical subtypes of NBS in large series are summarized in Table 4.

In some clinical series the onset of neurological disease was reported to be the first manifestation of the disease in some of the patients of the study cohort [6,8,11*,13]. However, the onset of NBS seldom precedes the onset of oral ulcers or other systemic manifestations of the disease, and in most cases who present initially with neurological symptoms and signs related to BS, a carefully taken past medical history will reveal recurrent oral aphthous ulcers and probably some other systemic findings that were already present at the time of the initial admission with the neurological problem [7].

Aetiopathogenesis

The proposed aetiological factors of BS still need to be clarified. Genetic, immunological and bacterial factors, viral agents and coagulation abnormalities have been studied [2**,5*,14,15].

BS is not a genetic disease with a Mendelian inheritance pattern, although a clustering of BS patients in families is well known. Although no heritable factor has yet been identified [2**,14], the observation of an earlier disease onset in the offspring of affected parents, as well as a high sibling recurrence risk ratio are the indications for a genetic background of the disease [16,17].

The association between BS and HLA-B51 has been confirmed in BS patients of many ethnic groups [18]. However, it is still unknown whether the HLA-B51 gene is responsible for BS, or if some other nearby genes that are in linkage disequilibrium with B51 are responsible [14]. Mizuki *et al.* [19] performed HLA class I typing using the polymerase chain reaction–sequence-specific primer method to map and localize the susceptible locus of BS in the HLA region in 84 Iranian patients with BS. In their previous studies [20,21], the authors narrowed down the BS-related gene to 46 kb between the MICA and HLA-B genes in Japanese BS patients. They reported that the MICA-A6-MIB-348-C1-4-1-217-HLA-B51 haplotype appeared to be predominant among the Iranian patients similar to the Japanese BS patients. In conclusion, they suggested that 46 kb between the MICA and HLA-B genes is the critical segment for BS susceptibility. In order to identify the BS-susceptible locus, it is necessary to increase the number of BS patients with different ethnic backgrounds.

Two other studies have recently been published about the HLA and clinical variables of BS. Kaya *et al.* [22] studied the association of HLA class I antigens with specific clinical findings of the disease (thrombophlebitis, genital ulceration, eye involvement and erythema nodosum) in 85 Turkish BS patients. Their results suggested that the increase in HLA-B51 may serve as a

Table 4. Demographic features and frequency of clinical subtypes of neuro-Behçet syndrome in large series (20 or more patients) published within the past 5 years

Author	Akman-Demir <i>et al.</i> , 1999 [6]	Kidd <i>et al.</i> , 1999 [8]	Siva <i>et al.</i> , 2001 [7]	Houman <i>et al.</i> , 2002 [10]	Al-Araji <i>et al.</i> , 2003 [11•]	Sbai <i>et al.</i> , 2003 [12••]
No. of patients	200	50	164	27	20	109 ^c
Male:female	3.4	1.6	3.82	2.85	2.3	2.5
Mean age of onset of BS	25.8 ± 7.8		26.7 ± 8.0	28.5	30.85	
Mean age of onset of NBS	31.5 ± 8.9		32.0 ± 8.7	34.26 ± 8.79	34.1	M: 32 ± 13 F: 31 ± 10
Clinical type						
Intra-axial NBS (%)	81	76	75.6	70.3	50	
Extra-axial NBS (%)	10	4	12.2	11.1 ^a	30	
Both (%)	–	–	–	–	20	
Other/indefinite diagnoses ^b (%)	9	20	12.2	3.7		

BS, Behçet's syndrome; NBS, neuro-Behçet syndrome.

^aIncluding only cases with cerebral venous sinus thrombosis.

^bIncludes cases with optic neuropathy, isolated eighth nerve involvement, intracranial hypertension but no dural sinus thrombosis or other abnormalities on neuroimaging, aseptic meningitis, isolated seizures, and other diagnoses/or cases not properly studied.

^cOnly central nervous system-neuro-Behçet syndrome cases.

marker for the increased risk of thrombophlebitis in BS disease patients. The authors also reported that HLA-B35 was found to be related to a decreased risk of thrombophlebitis. Choukri *et al.* [23] have also performed a similar study in Moroccan BS patients, and reported that the presence of B-51 or B-15 did not predispose to a particular clinical manifestation. These results need to be confirmed in a larger number of BS patients from different countries.

Several abnormalities of immune responses have recently been reported in patients with BS. These include a predominant T-cell infiltration of inflamed tissue, increased numbers of CD4, CD8 and $\gamma\delta$ T lymphocytes, suppressor T-cell dysfunction, defective IL-2 activity of mitogen-activated T cells, increased phenotypically activated or memory circulating T cells, increased serum concentrations of soluble CD8 and CD25, and polyclonal B cell activation [14,24]. A recent study from the Netherlands [24] determined the phenotype and antigen-specificity of T cells expanded by mitogenic stimulation from intra-ocular fluid samples of BS uveitis and non-BS uveitis patients. In contrast to the non-BS uveitis patients, high numbers of $\gamma\delta$ T cells, predominantly CD3+CD4–CD8– were detected in the intra-ocular fluid-derived T-cell lines of BS uveitis patients. They also showed that these $\gamma\delta$ T cells expressed T-cell receptor V γ 9V δ 2, and were found to be specific to non-peptide antigen prenyl pyrophosphates. The authors concluded that the presence of prenyl pyrophosphate-reactive V γ 9V δ 2 T cells at the site of inflammation and their T helper (Th) cell type 1-like phenotype may suggest their contribution in BS patients with uveitis.

The Th1/Th2 lymphocytes are known to play an important role in the induction and regulation of autoimmunity. Th1 polarization of the immune response is found in experimental autoimmune uveoretinitis. Analysis of Th1/Th2 type cytokines in CD3+ lymphocytes of BS patients revealed a polarized Th1 immune response that paralleled disease progression [14]. Alpsy *et al.* [25] investigated the serum activity of patients with BS on the antigen and chemokine expression of human macrophages *in vitro*, and they found that the serum of patients with BS induces pro-inflammatory activation of human peripheral blood macrophages *in vitro*.

Saruhan-Direskeneli *et al.* [26••] studied the serum and CSF levels of cytokines and chemokines in NBS compared to multiple sclerosis (MS) and other neurological diseases. Their study group included 33 patients with NBS, 25 MS patients, 20 patients with infectious or inflammatory neurological diseases and 14 cases with non-inflammatory neurological diseases. They evaluated IL-10, IL-12, IL-17, CXCL8, CXCL10 and CCL2 and found that CSF CXCL10 levels were significantly higher

in NBS and inflammatory neurological diseases than in non-inflammatory neurological diseases and MS, whereas CXCL8 was increased only in the CSF of NBS patients. No difference was detected for IL-10 and IL-17. The authors suggested that their results point to a dominance of chemokine effects in NBS CSF, and that this pattern resembles non-specific inflammation compared with autoimmune disorders such as MS.

B cells express increased levels of activation markers such as CD13, CD33, CD80 and CD45RO. The low levels of antibody-producing CD5+CD19+B cells suggests that BS is distinct from classic autoantibody-mediated disorders [15].

Histopathological and immunohistochemical studies of BS lesions revealed mononuclear cell infiltration of T lymphocytes, B lymphocytes and neutrophils, consistent with vasculitis affecting both the arterial and venous system [4]. However, the pathogenic mechanism and the relationship between thrombogenic events and vascular complications are still unknown. Thrombophilia of BS manifests as thrombosis. Approximately one-third of all patients with BS have thrombophlebitis [2••]. There is ample evidence both for thrombophilia, without any one specific coagulation abnormality apart from a decrease in fibrinolysis [27], and endothelial dysfunction [28]. It is more likely that endothelial dysfunction is the proximal event [5•]. As in many vasculitides, antiendothelial antibodies have been reported in BS, with little insight into their target antigen. Recent work from Korea has shown that α -enolase is the target antigen in the majority of the instances when antiendothelial antibodies are positive in BS. Furthermore, early data showed that this antibody might also have some specificity for BS [29]. An increased frequency of factor V Leiden and prothrombin G→A20210 mutations have been proposed, as well as homocysteine, endothelin-1 and nitric oxide, to induce thrombosis in BS, but their individual contributions to pathogenesis are not clear [3,5•,14,28,30].

The neurological spectrum of Behçet's disease

Headache is the most common neurological symptom seen in BS. In a study based on a questionnaire sent to members of the Behçet's Society in the UK, the prevalence of recurrent headaches was found to be 82.5% in responders, with the majority reporting features consistent with a vascular type of headache [31]. In another recent prevalence study of headache in patients with BS without overt neurological involvement, investigators reported migraine without aura to be significantly more frequent in 27 BS patients than controls (44.4 versus 11.1%, respectively, $P=0.013$), and suggested that a vascular or neuronal subclinical

dysfunction could justify this association [32•]. However, in a similar work in 111 patients with BS [33•], we also found that independent of neurological involvement, headache was a common symptom in BS, but the prevalence of migraine without aura or any of the other primary headaches was not increased in BS, whereas a non-structural recurrent, bifrontal, vascular-type headache that starts after the onset of the systemic manifestations of BS, and is sometimes associated with their exacerbations, was the most frequent, seen in 29% of the study group.

A substantial number of patients with BS may report a severe headache of recent onset, not consistent with a co-existing primary headache or with the above described non-structural headache of BS. These patients require further evaluation, even if they do not have neurological signs, as such a symptom may indicate the onset of NBS, of either the intra-axial or extra-axial type. Work up is essential in such patients when the reported headache is severe and incapacitating, if it is the first or worst headache of their life, if their symptoms began after or within 6 months of the onset of other systemic symptoms, if there is a change in character of the headache after the onset of systemic disease, or needless to say, when they have objective findings in neurological examination or the fundoscopic examination discloses papilloedema. Approximately 10% of patients presenting with an isolated severe headache will turn out to have a neurological syndrome caused by BS [7].

Intra-axial neuro-Behçet syndrome (central nervous system-neuro-Behçet syndrome)

The most common presentation of CNS-NBS is the onset of a subacute brainstem syndrome that consists of different combinations of cranial nerve findings, dysarthria, unilateral or bilateral corticospinal tract signs, cerebellar findings (i.e. ataxia), and a mild confusion with or without disturbance in consciousness [4]. However, it should be kept in mind that CNS-NBS does not always present with brainstem signs and symptoms. Hemiparesis, cognitive-behavioural changes, emotional lability, self-limited or progressive myelopathy, as well as other CNS manifestations, such as extrapyramidal signs and seizures, may be seen, but are less common [4,6–8,34]. Stroke-like presentations have been reported [8,11•,35], but they are not common, and when present the onset is usually subacute and the weakness is not complete. Other rare presentations are isolated optic neuritis, eighth nerve involvement and aseptic meningitis [4].

Primary hemispheric, brainstem and spinal cord involvement according to the clinical presentation of the patient have been reported in CNS-NBS [8,10,11•], but the significance of the predominant

clinical pattern of CNS involvement is not clear as magnetic resonance imaging (MRI) studies show more widespread involvement in most of these patients [36]. Furthermore, many patients when followed will develop further symptoms and signs consistent with the multifocal involvement of the syndrome [6–8].

It is usually considered that CNS lesions are caused by vasculitis with a venous predominance [36–38]. However, the pathology in NBS with CNS involvement is not always uniform and covers a wide spectrum, which include vasculitis, low grade inflammation, demyelination and degenerative changes. Definite vasculitis is not observed in all cases [39]. Radiological studies do not support strictly arterial vasculitis as lesions seen in imaging studies are not compatible with arterial territories in general [36]. Furthermore, there is a perilesional large oedema during acute disease, with a tendency to disappear or leave disproportionately small residua in follow-up studies, which is consistent with venous infarctions. This information supports the probable inflammatory-venous (small vessel) aetiology of the CNS lesions seen in intra-axial NBS. Koçer *et al.* [36] suggested that the anatomic variability of venous anatomic arrangements at different levels of the CNS might explain the predilection of lesions towards different regions and the occurrence of clinical and imaging findings.

Many CNS-NBS patients with small vessel inflammation have a relapsing-remitting course initially, with some ultimately developing a secondary progressive course later, and a few will have progressive CNS dysfunction from the onset.

Arterial involvement resulting in CNS vascular disease is rare, but has been reported in BS. Observations in cases with bilateral internal carotid artery occlusion, vertebral artery occlusion and intracranial arteritis as well as aneurysms, with their corresponding neurological consequences [10,36,40,41,42••] suggested that arterial involvement may be a subgroup of CNS-NBS. Intracranial haemorrhages may occur but are extremely rare, with most occurring within ischaemic lesions [36,43].

As patients with BS are young and frequently present with an acute or subacute brainstem syndrome or hemiparesis, as well as with other various neurological manifestations, they are often included in the differential diagnosis of MS, stroke of the young adult, and another wide range of neurological disorders [4,44]. This is especially true in patients with BS, in which symptoms other than those related to the CNS are not very pronounced. The differential diagnosis between MS and NBS including MRI findings are summarized in Table 5. The co-morbidity of BS and MS is also a possibility, and

we have observed a few such cases in whom systemic BS and MS co-existed. An acute stroke-like onset is not common in NBS, and MRI lesions compatible with classic arterial territories are also not expected. The absence of systemic symptoms and signs will serve to differentiate the primary CNS vasculitic disorders from NBS.

Neuro-psycho-Behçet syndrome

Some patients with BS develop a neurobehavioural syndrome, which consists of euphoria, loss of insight, disinhibition, indifference to their disease, psychomotor agitation or retardation, with paranoid attitudes and obsessive concerns. The development of such psychiatric symptoms may be seen with or without other neurological symptoms of NBS, and in the absence of other neurological manifestations the MRI findings may not be significant (personal observation). This syndrome should not be confused with psychosis associated with the use of glucocorticosteroid or other therapy [4,7]. Such a neurobehavioural syndrome was also observed by others [45], and the incidence of psychiatric symptoms varied between 5 and 25.5% in recent series [7,10,11*].

Oktem-Tanor *et al.* [45] conducted a noteworthy prospective neuropsychological study in 12 patients with NBS, and found that memory impairment was the major finding. The most severely affected memory process was delayed recall, being impaired in all of the patients either in the verbal or visual modalities. An impairment in the process of acquisition and storage; attention deficit and deficits of executive functions of the frontal system were the other cognitive functions involved in a declining order [45].

Subclinical neuro-Behçet syndrome

Al-Araji *et al.* [11*], in their prospective study, found two patients who had unilateral corticospinal tract signs, but who were neurologically and radiologically asymptomatic. The incidental finding of neurological signs in

patients with BS without neurological symptoms was also observed by others, with a minority developing mild neurological attacks later [6].

Electroneuromyographic studies had shown a subclinical neuropathy in some patients who did not report symptoms suggestive of neuropathy, and silent muscle involvement was also reported in patients without overt muscle involvement who were studied with electron microscopy [4,46]. Brainstem auditory and somatosensory evoked potentials and transcranial magnetic stimulation were studied in patients with CNS-NBS in several studies, and showed a wide range of abnormalities, but the demonstration of subclinical involvement by the detection of abnormal responses in examined areas without corresponding clinical symptoms and signs in some of these patients is noteworthy in providing information about the extent of CNS involvement [47–50]. In another recent study [51] subclinical involvement was investigated by using P300 in BS patients without neurological manifestations. Autonomic nervous system involvement was also reported in asymptomatic patients with BS [52]. On the other hand, subclinical CNS involvement was also detected by single-photon emission computed tomography (SPECT) studies as described below.

The detection of neurological abnormalities by clinical or neurophysiological studies as well as neuroimaging in asymptomatic patients suggest that there might be a subgroup of patients with subclinical NBS. However, the clinical and prognostic value of all these findings in this group of patients is currently not clear.

Extra-axial neuro-Behçet syndrome (cerebral venous sinus thrombosis)

CVST is seen in 10–20% of BS patients in whom neurological involvement occurs. Higher rates have been reported in a limited number of clinical studies from different geographical regions and ethnic backgrounds, causing difficulty in interpreting these rates [11*,12**].

Table 5. The differential diagnosis of multiple sclerosis and intra-axial (central nervous system) neuro-Behçet syndrome

	Multiple sclerosis	CNS-NBS
Sex	Female > male	Male > female
Symptoms at onset		
Common	ON; sensory; spinal cord; brainstem/INO; motor; cerebellar	Headache; motor; cerebellar; brainstem/cranial neuropathies
Uncommon	Headache; brainstem/cranial neuropathies	ON; sensory; spinal cord; brainstem/INO
Magnetic resonance imaging		
Periventricular and subcortical lesions	(+++)	(±)
Brainstem lesions	Small, discrete, up/downward extension (-)	Large, diffuse, up/downward extension (+)
Spinal cord lesions	(++)	(+)
Cerebrospinal fluid		
Inflammatory changes	(±)	(++)
Oligoclonal bands (+)	> 90%	< 20%

CNS, Central nervous system; INO, internuclear ophthalmoplegia; NBS, neuro-Behçet syndrome; ON, optic neuritis.

The co-occurrence of intra-axial and extra-axial NBS in the same patient is uncommon [6,7], but has been reported [10,11,53].

Thrombosis of the venous sinuses may cause increased intracranial pressure, with severe headache, mental changes and motor ocular palsies, but in some patients the only manifestation may be headache. It is well known that the clinical manifestations resulting from CVST vary according to the site and rate of venous occlusion and its extent. Our experience suggests that CVST in BS may evolve relatively slowly in most patients, as in none of our patients have we observed a fulminating syndrome of violent headache, convulsions, paralysis and coma.

Haemorrhagic venous infarcts or other parenchymal CNS lesions on MRI in patients with CVST are rare [6,7,53]. This observation further suggests that CVST in BS may not be an acute process in most cases. However, acute onset cases have been reported, in whom seizures and focal neurological signs also occurred besides headache [53]. Papilloedema and sixth nerve paresis are the most common signs reported, and hemiparesis may develop in some [6,7,53].

Any of the dural sinuses may be affected, but the superior sagittal sinus is the most commonly thrombosed, with a substantial number of these patients also disclosing lateral sinus thrombosis [53,54]. Intracranial hypertension, without any demonstrable neuro-imaging pathology has been reported, with some of the patients developing neuroimaging findings consistent with CVST in further later attacks [54].

We have recently reported that CVST in BS is strongly associated with systemic major vessel disease, and tends to occur earlier in the disease course compared with the parenchymal–CNS type of neurological involvement [9], confirming some other works [10,53]. We believe that these observations also support the notion that two forms of CNS disease in BS might have different pathogenic mechanisms. It is also well established that neurological disease in the form of CVST has a better neurological prognosis than that of CNS–parenchymal involvement. However, considering the fact that patients with major vessel disease have a higher rate of morbidity and mortality, a diagnosis of CVST in a patient with BS may not be associated with a favourable outcome.

Peripheral nervous system involvement in Behçet syndrome

The limited number of BS patients who have been reported with peripheral nervous system involvement had clinical and electrophysiological findings consistent with mononeuritis multiplex, a peripheral neuropathy

prominent in the lower extremities and poly-radiculo-neuritis [55,56]. However, in a small series of patients with BS in a Caribbean population from the French West Indies, two of the seven cases were reported to have peripheral nervous system involvement, with one having a sensorimotor axonal neuropathy and the other an axonal sensory neuropathy with recurrent episodes of myositis [13]. Muscle involvement is also rare, a limited number of cases with focal or generalized myositis have been reported [46,57].

Neuro-imaging

Neuro-imaging studies in CNS-NBS have shown that lesions are generally located within the brainstem, occasionally with extension to the diencephalon, or less commonly within the periventricular and subcortical white matter. The most commonly affected region is the mesodiencephalic junction, followed by the pontobulbar region [6,36]. The hypothalamothalamic region, basal ganglia, cerebral hemispheres, cerebellum and the spinal cord are also involved, but less commonly. Most patients who do have mesodiencephalic junction lesions also show an upward extension involving the diencephalic structures or a downward extension involving the pontobulbar region. Hemispheric lesions are not seen commonly in intra-axial NBS, and are almost always associated with diencephalic and brainstem lesions. A frequent finding is the resolution or the decrease in the size of the lesions, when follow-up imaging studies are available [36]. Such studies may also disclose the appearance of new 'silent' lesions without corresponding clinical symptoms and signs. Recently, diffusion MRI and proton magnetic resonance spectroscopy findings were reported in a number of patients with acute CNS-NBS [58–60]. The authors concluded that their findings were suggestive of vasogenic oedema rather than infarction of the lesions seen during the acute phase of the disease. These observations further confirm the changing nature of CNS lesions in NBS.

Single-photon emission computed tomography studies in Behçet syndrome

Eight cases of BS with neurological symptoms were studied using perfusion SPECT, which disclosed areas of hypoperfusion localized in the deep basal ganglia or in the frontal and temporal cortex. MRI was normal in five of them. However, it is interesting that seven of the patients studied were paediatric cases, a population in which BS is rare [61]. In another similar study performed in 10 adults with neuropsychiatric manifestations related to BS [62], whose MRI were normal, SPECT demonstrated hypoperfusion areas in the brains of all patients, with the parietal and temporal lobes being the most commonly involved regions. These SPECT findings, consistent with multiple hypoperfusion areas that correlate with decreased metabolic demand, are not

specific for NBS, but they may be interpreted as being indicative of early functional changes in the brains in this patient population.

Prognosis

In a recent study from our centre [2••], the long-term mortality and morbidity of BS was studied over two decades. The 'disease burden' of BS was found usually to be confined to the early years of its course, and it was shown that in many patients the syndrome burnt out over the years. However, major vessel disease and CNS involvement were found to be exceptions and could appear for the first time relatively late in the course of the disease. Furthermore, most of the deaths seen in this cohort were caused by these two conditions. Neurological involvement in BS is also a remarkable cause of morbidity, and with the use of the modified expanded disability status scale (EDSS) of Kurtzke, 10 years after the onset of neurological symptoms and signs, 78.2% of our patients were found to develop at least mild (EDSS ≥ 3), and 45.1% moderate to severe neurological disability (EDSS ≥ 6). However, when patients were evaluated separately, all with CVST had EDSS scores of either 1 or 2 (minimal disability) [7].

Onset with cerebellar symptoms and a progressive course were unfavourable factors, whereas onset with headache, a diagnosis of CVST, and disease course limited to a single episode were neurologically favourable [6–8]. An elevated protein level and pleocytosis in the CSF were also reported to be associated with a poorer prognosis [6,8].

Treatment

Neurological involvement in BS is not uniform, and it is difficult to predict its course and prognosis, and response to treatment. Currently, there is no evidence for the efficacy of the various treatment modalities for any form of neurological treatment in BS, and it is only empirical impressions that are the basis for our current guidelines in management [63,64•].

Intra-axial neuro-Behçet syndrome: acute episodes

Corticosteroids are used to treat acute CNS involvement in BS, but their effects are short-lived and they do not prevent further attacks or progression. Acute episodes of intra-axial NBS are treated with either oral prednisolone (1 mg/kg for up to 4 weeks, or until improvement is observed) or with high-dose intravenous methylprednisolone (1 g/day) for 3–7 days [63]. Both forms of treatment should be followed with an oral tapering dose of corticosteroids over 2–3 months in order to prevent early relapses [63,64•]. There is no apparent difference between the two regimens, but our impression is that the high dose intravenous methylprednisolone regimen is associated with earlier improvement. Our current prac-

tice is to give intravenous methylprednisolone, 1 g/day for 7 days, followed by the oral regimen.

Intra-axial neuro-Behçet syndrome: long-term treatment

Colchicine, azathioprine, cyclosporine-A, cyclophosphamide, methotrexate, chlorambucil, and immunomodulatory agents such as IFN- α , pentoxifylline and thalidomide have been anecdotally shown to be of benefit in treating some of the systemic manifestations of BS, but none of these agents has been shown to be effective in NBS in a properly designed study. A common clinical practice is to add an immunosuppressive drug, such as azathioprine, methotrexate or monthly pulse cyclophosphamide to corticosteroids in progressive NBS cases; however, the efficacy of such a combination has also not been demonstrated to date. Cyclosporine was reported to cause neurotoxicity or to accelerate the development of CNS symptoms, and therefore its use in NBS is not recommended [65,66].

The successful treatment of ocular and other systemic manifestations of BS with monoclonal anti-TNF- α antibody treatment with infliximab and etanercept have recently been reported [67], but no information is available as to whether they have significant effects in patients with neurological involvement. Mycophenolate mofetil and tacrolimus are other immunosuppressive/immunomodulator agents that were used to treat ocular inflammation and significant systemic manifestations in patients with BS [68], but there is also no information regarding the potential effect of all these drugs in preventing CNS involvement or new neurological attacks. There is a single case report of the successful treatment of NBS with IFN- α [69], a drug commonly used to treat eye disease in BS.

Cerebral aneurysms are rare in BS, but when small unruptured aneurysms are detected, medical therapy with steroids with or without cytotoxic agents may be tried. As an alternative to surgery, endovascular treatment is another option in the management of BD-associated intracranial aneurysms. This form of treatment was recently suggested for ruptured, peripherally located, fusiform shaped, dissecting pseudoaneurysms and posterior circulation aneurysms [42••].

Cerebral venous sinus thrombosis

There is a tendency to treat deep venous thrombosis in BS with anticoagulants and antiplatelet agents in combination with intermediate doses of corticosteroids. However, there is no consensus on the treatment of CVST. Some authors use a combination of anticoagulation with corticosteroids [53], whereas others administer corticosteroids alone [54]. When anticoagulation therapy is considered in the treatment of CVST, the presence of

pulmonary or other aneurysms needs to be ruled out first, as CVST in BS is strongly associated with systemic major vessel disease. In our current practice, to treat CVST we use a combination of subcutaneous low-molecular weight heparin with corticosteroids [63]. The CVST in BS is rarely severe enough to require systemic or thrombolytic treatment. The recurrence of CVST is uncommon after the initial episode. Therefore we do not recommend any form of long-term treatment in extra-axial NBS.

Conclusion

The prevalence of BS in the United States and northern Europe is 1/10⁵, whereas this rate is between 10 and 100/10⁵ in Mediterranean countries, the Middle East, Japan and in Far-Eastern countries, and NBS is seen in 5–10% of these patients. The male to female ratio in BS is almost equal, but in NBS this ratio is folded by 3–4. The mean age of onset of BS is within the third decade, with neurological involvement seen with a mean of 5 years later. Cases with CVST, whose age of onset is much earlier, are an exception. The major primary neurological symptoms and syndromes seen in BS are headaches, CNS involvement (intra-axial NBS), cerebral venous sinus thrombosis (extra-axial NBS), and neuro-psycho-BS. The diagnosis of NBS requires a diagnosis of BS, the onset of neurological symptoms not otherwise explained by any other known systemic or neurological disease or treatment, a positive neurological examination, neuro-imaging findings suggestive of NBS, or CSF abnormalities consistent with NBS.

The clinical features of CNS-NBS are commonly consistent with cranial neuropathies and (asymmetrical) corticospinal tract signs with or without cerebellar findings (ataxia), confusion or neurobehavioural syndromes. The clinical course may remain as a single episode, improving with or without sequelae, or may take a relapsing remitting form with secondary progression in some, and as a primary progressive form in a few. MRI is the first line diagnostic imaging study showing mesodiencephalic oedematous (in acute phase) lesions with upward and downward extension, which may show resolution over time; subcortical white matter lesions, periventricular lesions and myelopathy are rare. Neurological morbidity and mortality is high, with 50% of NBS patients reaching moderate to severe disability after 10 years of the disease. Patients with CVST (extra-axial NBS) have headache and other symptoms of intracranial hypertension, which may be limited to a single episode; recurrences are rare, but have been reported. MRI with MRI venography is the best imaging modality. Neurological morbidity and mortality is low; however, systemic major vessel complications may be life-threatening.

Treatment options are limited in patients with NBS; glucocorticoids are used for acute exacerbations, but

currently there is no effective treatment for recurrent and progressive NBS.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
 - of outstanding interest
- 1 International Study Group for Behçet's disease. Criteria for diagnosis of Behçet's disease. *Lancet* 1990; 335:1078–1080.
 - 2 Kural-Seyahi E, Fresko I, Seyahi N, *et al.* The long-term mortality and morbidity of Behçet syndrome: a 2-decade outcome survey of 387 patients followed at a dedicated center. *Medicine (Baltimore)* 2003; 82:60.
 - A comprehensive study on the long-term mortality and morbidity of BS. It clearly describes how this disease is more severe among the young and the male, and in general tends to become less severe with the passage of time.
 - 3 Gül A. Behçet's disease: an update on the pathogenesis. *Clin Exp Rheumatol* 2001; 19 (Suppl. 24):6–12.
 - 4 Siva A, Yazıcı H. Behçet's disease. In: Levine S, Doruk E, editors. *Handbook of systemic autoimmune diseases, neurology volume – the neurologic involvement in systemic autoimmune disorders*. New York: Elsevier Science; 2004 (in press).
 - 5 Yazıcı H. Behçet's syndrome: an update. *Curr Rheumatol Rep* 2003; 5:195–199.
 - An expert's view on the current developments in BS.
 - 6 Akman-Demir G, Serdaroglu P, Tasçi B, and the Neuro-Behçet Study Group. Clinical patterns of neurological involvement in Behçet's disease: evaluation of 200 patients. *Brain* 1999; 122:2171–2181.
 - 7 Siva A, Kantarci OH, Saip S, *et al.* Behçet's disease: diagnostic and prognostic aspects of neurological involvement. *J Neurol* 2001; 248:95–103.
 - 8 Kidd D, Steuer A, Denman AM, Rudge P. Neurological complications in Behçet's syndrome. *Brain* 1999; 122:2183–2194.
 - 9 Tunc R, Saip S, Siva A, Yazıcı H. Cerebral venous thrombosis is associated with major vessel disease in Behçet's syndrome. *Ann Rheum Dis* 2004; in press.
 - 10 Houman MH, Hamzaoui-B'Chir S, Ben Ghorbel I, *et al.* Neurologic manifestations of Behçet's disease: analysis of a series of 27 patients [in French]. *Rev Med Interne* 2002; 23:592–606.
 - 11 Al-Araji A, Sharquie K, Al-Rawi Z. Prevalence and patterns of neurological involvement in Behçet's disease: a prospective study from Iraq. *J Neurol Neurosurg Psychiatry* 2003; 74:608–613.
 - A prospective study to determine the prevalence and clinical patterns of neurological presentation in a cohort of 140 patients with BS.
 - 12 Sbai A, Wechsler B, Duhaut P, *et al.* Neuro-Behçet's disease (isolated cerebral thrombophlebitis excluded). Clinical pattern, prognostic factors, treatment and long term follow-up. *Adv Exp Med Biol* 2003; 528:371–376.
 - A well conducted and detailed clinical study of 109 patients with NBS who had CNS–parenchymal involvement.
 - 13 Lannuzel A, Lamaury I, Charpentier D, Caparros-Lefebvre D. Neurological manifestations of Behçet's disease in a Caribbean population: clinical and imaging findings. *J Neurol.* 2002; 249:410–418.
 - 14 Sakane T, Suzuki N. Behçet's disease. In: Theofilopoulos AN, Bona CA, editors. *The molecular pathology of autoimmune diseases*, 2nd ed. NY, USA: Taylor and Francis; 2002. pp. 828–840.
 - 15 Direskeneli H. Behçet's disease: infectious aetiology, new autoantigens, and HLA-B51. *Ann Rheum Dis* 2001; 60:996–1002.
 - 16 Kone Paut I, Geisler I, Wechsler B, *et al.* Familial aggregation in Behçet's disease: high frequency in parents of pediatric probands. *J Pediatr* 1999; 135:89–93.
 - 17 Fresko I, Soy M, Hamuryudan V, *et al.* Genetic anticipation in Behçet's syndrome. *Ann Rheum Dis* 1998; 57:45–48.
 - 18 Mizuki N, Inoko H, Ohno S. Molecular genetics (HLA) of Behçet's disease. *Yonsei Med J* 1997; 38:333–349.
 - 19 Mizuki N, Yabuki K, Ota M, *et al.* Analysis of microsatellite polymorphism around the HLA-B locus in Iranian patients with Behçet's disease. *Tissue Antigens* 2002; 60:396–399.

- 20 Ota M, Mizuki N, Katsuyama Y, *et al.* The critical region for Behçet disease in the human major histocompatibility complex is reduced to a 46-kb segment centromeric of HLA-B, by association analysis using refined microsatellite mapping. *Am J Hum Genet* 1999; 64:1406–1410.
- 21 Mizuki N, Ota M, Katsuyama Y, *et al.* Association analysis between the MIC-A and HLA-B alleles in Japanese patients with Behçet's disease. *Arthritis Rheum* 1999; 42:1961–1966.
- 22 Kaya TI, Tursen U, Gurler A, Durt H. Association of class I HLA antigens with the clinical manifestations of Turkish patients with Behçet's disease. *Clin Exp Dermatol* 2002; 27:498–501.
- 23 Choukri F, Chakib A, Himmich H, *et al.* HLA-B phenotype modifies the course of Behçet's disease in Moroccan patients. *Tissue Antigens* 2003; 61:92–96.
- 24 Verjans GMGM, Van Hagen PM, Van Der Kooij A, *et al.* V γ 9V δ 2 T cells recovered from eyes of patients with Behçet's disease recognize non-peptide prenyl pyrophosphate antigens. *J Neuroimmunol* 2002; 130:46–54.
- 25 Alpsoy E, Kodoljaj V, Goerdts S, *et al.* Serum of patients with Behçet's disease induces classical (pro-inflammatory) activation of human macrophages *in vitro*. *Dermatology* 2003; 206:225–232.
- 26 Saruhan-Direskeneli G, Yentür SP, Akman-Demir G, *et al.* Cytokines and chemokines in neuro-Behçet's disease compared to multiple sclerosis and other neurological diseases. *J Neuroimmunol* 2003; 145:127–134.
- A detailed and well-organized study about the role of cytokines and chemokines in BS.
- 27 Espinosa G, Font J, Tassies D, *et al.* Vascular involvement in Behçet's disease: relationship with thrombophilic factors, coagulation activation and thrombomodulin. *Am J Med* 2002; 112:37–43.
- 28 Chambers JC, Haskard DO, Kooner JS. Vascular endothelial function and oxidative stress mechanisms in patients with Behçet's syndrome. *J Am Coll Cardiol* 2001; 37:517–520.
- 29 Lee KH, Chung HS, Kim HS, *et al.* Human alpha-enolase from endothelial cells as a target antigen of anti-endothelial cell antibody in Behçet's disease. *Arthritis Rheum* 2003; 48:2025–2035.
- 30 Er H, Evereklioglu C, Cumurcu T, *et al.* Homocysteine level is increased and correlated with endothelin-1 and nitric oxide in Behçet's disease. *Br J Ophthalmol* 2002; 86:653–657.
- 31 Kidd D. The prevalence of headache in Behçet's syndrome. *Adv Exp Med Biol* 2003; 528:377–379.
- 32 Monastero R, Mannino M, Lopez G, *et al.* Prevalence of headache in patients with Behçet's disease without overt neurological involvement. *Cephalalgia* 2003; 23:105–108.
- This study evaluates the frequency of different headache syndromes in 27 patients with BS without neurological involvement and in an equal number of controls, and suggests that migraine without aura was significantly more frequent in BS.
- 33 Saip S, Siva A, Altintas A, *et al.* Characteristics of headache in Behçet's disease. *Cephalalgia* 2003; 23:683–P4L59.
- A study looking into the prevalence and demographic and clinical characteristics of headaches in 111 patients with BS, who were randomly recruited in the setting of a multi-disciplinary BS clinic.
- 34 Aykutlu E, Baykan B, Serdaroglu P, *et al.* Epileptic seizures in Behçet disease. *Epilepsia* 2002; 43:832–835.
- 35 Farah S, Al-Shubaili A, Montaser A, *et al.* Behçet's syndrome: a report of 41 patients with emphasis on neurological manifestations. *J Neurol Neurosurg Psychiatry* 1998; 64:382–384.
- 36 Koçer N, Islak C, Siva A, *et al.* CNS involvement in neuro-Behçet's syndrome: an MR study. *Am J Neuroradiol* 1999; 20:1015–1024.
- 37 McMenemy WH, Lawrence BJ. Encephalomyelopathy in Behçet's disease: report of necropsy findings in two cases. *Lancet* 1957; 24:353–358.
- 38 Kawakita H, Nishimura M, Satoh Y, Shibata N. Neurological aspects of Behçet's disease: a case report and clinico-pathological review of the literature in Japan. *J Neurol Sci* 1967; 5:417–438.
- 39 Hadfield MG, Aydin F, Lippman HR, Sanders KM. Neuro-Behçet's disease. *Clin Neuropathol* 1997; 16:55–60.
- 40 Krespi Y, Akman-Demir G, Poyraz M, *et al.* Cerebral vasculitis and ischaemic stroke in Behçet's disease: report of one case and review of the literature. *Eur J Neurol* 2001; 8:719–722.
- 41 Sağdıy A, Sirin H, Oksel F, *et al.* An unusual case of Behçet's disease presenting with bilateral internal carotid artery occlusion. *J Neurol Neurosurg Psychiatry* 2002; 73:343.
- 42 Kizilkilic O, Albayram S, Adaletli I, *et al.* Endovascular treatment of Behçet's disease-associated intracranial aneurysms: report of two cases and review of the literature. *Neuroradiology* 2003; 45:328–334. Epub 11 April 2003.
- The authors review cases with arterial involvement in BS affecting the nervous system in the literature, and based on their experience with two cases they offer an alternative to surgery, endovascular treatment in the management of BD-associated intracranial aneurysms.
- 43 Kikuchi S, Niino M, Shinpo K, *et al.* Intracranial hemorrhage in neuro-Behçet's syndrome. *Intern Med* 2002; 41:692–695.
- 44 Ashjazadeh N, Borhani, Haghighi A, *et al.* Neuro-Behçet's disease: a masquerader of multiple sclerosis. A prospective study of neurologic manifestations of Behçet's disease in 96 Iranian patients. *Exp Mol Pathol* 2003; 74:17–22.
- 45 Oktem-Tanor O, Baykan-Kurt B, Gurvit IH, *et al.* Neuropsychological follow-up of 12 patients with neuro-Behçet disease. *J Neurol* 1999; 246:113–119.
- 46 Serdaroglu P. Neuromuscular manifestations in the course of Behçet's disease. *Acta Myologica* 1998; 2:41–45.
- 47 Nakamura Y, Takahashi M, Kitaguchi M, *et al.* Brainstem auditory and somatosensory evoked potentials in neuro-Behçet's syndrome. *Jpn J Psychiatry Neurol* 1989; 43:191–200.
- 48 Parisi L, Terracciano ME, Valente GO, *et al.* Pre-symptomatic neurological involvement in Behçet's disease: the diagnostic role of magnetic transcranial stimulation. *Electroenceph Clin Neurophysiol* 1996; 101:42–47.
- 49 Rizzo PA, Valle E, Mollicca MA, *et al.* Multimodal evoked potentials in neuro-Behçet: a longitudinal study of two cases. *Acta Neurol Scand* 1989; 79:18–22.
- 50 Stigsby B, Bohlega S, McLean DR, Al-Kawi MZ. Transcranial magnetic stimulation in Behçet's disease: a cross-sectional and longitudinal study with 44 patients comparing clinical, neuroradiological, somatosensory and brainstem auditory evoked potential findings. *Clin Neurophysiol* 2000; 111:1320–1329.
- 51 Kececi H, Akyol M. P300 in Behçet's patients without neurological manifestations. *Can J Neurol Sci* 2001; 2:66–69.
- 52 Karatas GK, Onder M, Meray J. Autonomic nervous system involvement in Behçet's disease. *Rheumatol Int* 2002; 22:155–159. Epub 2 July 2002.
- 53 Wechsler B, Vidailhet M, Bousser MG, *et al.* Cerebral venous sinus thrombosis in Behçet's disease: long term follow-up of 25 cases. *Neurology* 1992; 42:614–618.
- 54 Akman-Demir G, Bahar S, Baykan-Kurt B, *et al.* Intracranial hypertension in Behçet's disease. *Eur J Neurol* 1996; 3:66–70.
- 55 Namer IJ, Karabudak R, Zileli T, *et al.* Peripheral nervous system involvement in Behçet's disease. *Eur Neurol* 1987; 26:235–240.
- 56 Takeuchi A, Kodama M, Takatsu M, *et al.* Mononeuritis multiplex in incomplete Behçet's disease: a case report and the review of the literature. *Clin Rheumatol* 1989; 8:375–380.
- 57 Sarui H, Maruyama T, Ito I, *et al.* Necrotising myositis in Behçet's disease: characteristic features on magnetic resonance imaging and a review of the literature. *Ann Rheum Dis* 2002; 61:751–752.
- 58 Kang DW, Chu K, Cho JY, *et al.* Diffusion-weighted magnetic resonance imaging in neuro-Behçet's disease. *J Neurol Neurosurg Psychiatry* 2001; 70:412–413.
- 59 Hiwatashi A, Garber T, Moritani T, *et al.* Diffusion-weighted MR imaging of neuro-Behçet's disease: a case report. *Neuroradiology* 2003; 45:468–471.
- 60 Sener RN. Neuro-Behçet's disease: diffusion MR imaging and proton MR spectroscopy. *Am J Neuroradiol* 2003; 24:1612–1614.
- 61 Nobili F, Cutolo M, Sulli A, *et al.* Brain functional involvement by perfusion SPECT in systemic sclerosis and Behçet's disease. *Ann NY Acad Sci* 2002; 966:409–414.
- 62 Huang WS, Chiu PY, Kao A, *et al.* Decreased cerebral blood flow in neuro-Behçet's syndrome patients with neuropsychiatric manifestations and normal magnetic resonance imaging – a preliminary report. *J Neuroimaging* 2002; 12:355–359.
- 63 Siva A, Fresko I. Behçet's disease. *Curr Treatment Options Neurol* 2000; 2:435–447.
- 64 Kantarci O, Siva A. Behçet's disease: diagnosis and management. In: Nosenworthy J, editor. *Neurological therapeutics: principles and practice*, Chapter 95. London: Martin Dunitz Publishers; 2003. pp. 1084–1093.
- An extensive review on BS and its neurological involvement with available current treatment options.
- 65 Swartz RB, Bravo SM, Klufas RA, *et al.* Cylosporin neurotoxicity and its relation to hypertensive neuropathy: CT and MR findings in 16 cases. *Am J Roentgenol* 1995; 165:627–631.

- 66 Kotake S, Higashi K, Yoshikawa K, *et al.* Central nervous system symptoms in patients with Behçet disease receiving cyclosporine therapy. *Ophthalmology* 1999; 106:586–589.
- 67 Sfikakis PP. Behçet's disease: a new target for anti-tumour necrosis factor treatment. *Ann Rheum Dis* 2002; 61 (Suppl. 2):ii51–ii53.
- 68 Russel AI, Lawson WA, Haskard DO. Potential new therapeutic options in Behçet's syndrome. *BioDrugs* 2001; 15:25–35.
- 69 Nichols JC, Ince A, Akduman L, Mann ES. Interferon-alpha 2a treatment of neuro-Behçet disease. *J Neuroophthalmol* 2001; 21:109–111.