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ENS TEACHING REVIEW

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The spectrum of nervous system involvement in Behçet's syndrome and its differential diagnosis

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Abstract Behçet's Syndrome (BS) is a multi-system, vascular-inflammatory disease of unknown origin, involving the nervous system in a subgroup of patients. The growing clinical and imaging evidence suggests that primary neurological involvement in BS may be subclassified into two major forms: the first one, which is seen in the majority of patients, may be characterized as a vascular-inflammatory central nervous system (CNS) disease, with focal or multifocal parenchymal involvement mostly presenting with a subacute brainstem syndrome and hemiparesis; 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. Isolated behavioral syndromes and peripheral nervous system involvement are rare, whereas a nonstructural vascular type headache is relatively common and independent from neurological involvement. Neurologic complications secondary to systemic involvement of BS such as cerebral emboli from cardiac complications of BS and increased intracranial pressure due to superior vena cava syndrome, as well as neurologic complications related to BS treatments such as CNS neurotoxicity with cyclosporine and peripheral neuropathy with the use of thalidomide or colchisin are considered as secondary neurological complications of this syndrome. As the neurological involvement in this syndrome is so heterogeneous, it is difficult to predict its course and prognosis, and response to treatment. Currently, treatment options are limited to attack and symptomatic therapies with no evidence for the efficacy of any long term preventive treatment.

Key words Behçet's disease · neurologic involvement · differential diagnosis · therapy

Introduction

Behçet's disease, originally described in 1937 by Hulusi Behçet as a distinct disease with oro-genital ulceration and uveitis [11] known as the "triple-symptom complex", is an idiopathic chronic relapsing multisystem vascular-inflammatory disease of unknown origin. The disease 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, etc. As a result of this multisystem involvement and wide range of clinical manifestations and presentations, many prefer to call it Behçet's syndrome rather than Behçet's disease [103].

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Epidemiology

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 [104]. 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 in patients from Northern Europe and the US, than the Mediterranean region and Japan [104].

Its prevalence has been reported to be less than $1/10^5$ in northern and central Europe and the US, and goes up to $2.5/10^5$ in the north-western Mediterranean region, and then increases considerably in the eastern Mediterranean region. Prevalence rates between 4 and 420 per 100,000 have been reported in Turkey [104], and 10–$20/10^5$ for Japan, China and Korea [78]. Most of these rates come from hospital based series, with the exception of the higher rates coming from Turkey, which are from population-based studies. The prevalence in Turkish immigrants living in Germany is lower ($21/10^5$) than that reported in Turkey, but is still higher than the native German population ($0.6/10^5$) [107]. Similar decline in prevalence rates is observed between northern and southern Japan, and Japanese immigrants living in Hawaii and the USA, suggestive of an "immigration effect" similar to multiple sclerosis.

The usual onset of the BS is in the third or fourth decade; however, although rare, onset in children has also been reported [66, 104]. The gender distribution is almost equal. However, the reported increased tendency to affect men more than women may be explained by the higher incidence of systemic complications and more severe disease in men, possibly bringing them to earlier medical attention.

Etiopathogenesis

Despite broadened clinical understanding of this disease, the etiologic factors remain obscured and speculative; viral agents, bacterial factors, immunological factors, genetic causes, and fibrinolytic defects have all been implicated [34, 102]. The vessel wall and perivascular mononuclear cell infiltration consistent with vasculitis involving both arterial and venous systems has been shown in histo-pathologic studies and it was postulated that a genetic susceptibility together with a possible trigger by an extrinsic factor, such as an infectious agent may be responsible for the observed vasculitis [34, 53, 64]. But it is also known that direct injury to the vessel wall that can be observed in most of the lesions in BS is not always apparent in some, such as the acne lesions of the skin and in some brain parenchymal lesions [104].

Three major pathophysiologic changes have been reported in BS and these are excessive functions of neutrophils, endothelial injury with vasculitis and autoimmune responses, although that these are not always universal. Histopathologic and immunohistochemical studies of the biopsy lesions obtained from patients with BS were reported to reveal typical features of "vasculitis" with perivascular infiltrations of T lymphocytes, B lymphocytes and neutrophils [34, 78]. These cells secrete proinflammatory cytokines such as TNF-α, IL-1, IFN-γ, IL-6 and IL-18, cytokines that may cause vascular endothelial injury and dysfunction leading to a thrombotic tendency [49, 78, 103]. The uniformity of such a relationship, however, needs to be confirmed, as it has not been studied yet in different clinical forms of BS. It should be kept in mind that BS does not have the features of a classical autoimmune disease. There is no female predominance, and other clinical features of autoimmunity, as well as the absence of disease-specific autoantibodies. These features lead to the debate that focuses on whether or not BS belongs to a newly designated group of autoinflammatory diseases [104].

Behçet's syndrome has the hallmarks of a complex genetic disorder; however, the inheritance pattern of Behçet's syndrome is not Mendelian. The most consistently reported HLA association has been with HLA-B51, a molecule that has an important role in innate immune processes, but the role of HLA-B51 in the pathogenesis of BS is still unknown. In some recent studies tumor necrosis factor-a-1031C allele and polymorphisms in endothelial nitric oxide synthase (eNOS) gene, interleukin-10, IL-8 and CD28 genes were reported to be associated with disease susceptibility, but these findings were found only in some ethnic groups or in limited populations and need to be confirmed [49]. In addition a long list of polymorphisms and genes have also been studied, but none have been definitely linked to pathogenesis of Behçet's syndrome [104].

Diagnosis and systemic manifestations of Behçet's disease

Currently the most widely used diagnostic criteria 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 [31, 32] (Table 1).

Table 1 Criteria for diagnosis of Behçet disease*

Finding	Definition
Recurrent oral ulceration:	Minor aphtous, major aphtous, 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:	Aphtous 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 hours.
For a clinical definite diagnosis of BS patient must have recurrent oral ulceration plus at least two of the other findings in the absence of any other clinical explanations.	

* International Study Group for Behçet's disease (1990) Criteria for diagnosis of Behçet's disease. Lancet 335:1078–1080 [31]

Oral aphthae

The presence of recurrent oral ulcers are required for the diagnosis of Behçet's disease [31, 32]. It is quite unlikely to see cases without oral ulcers and almost all our patients with neuro-Behçet's disease (NBS) had a history of oral ulcers by the time that their neurological symptoms developed. However, 1 to 3 % of patients can have several other features of the syndrome without ever having aphthae. Aphthae are frequently the first manifestation of the syndrome and it is not uncommon for some patients to have only oral ulcers for many years before other signs appear. The majority of oral ulcers in Behçet's syndrome are indistinguishable from those seen in recurrent oral ulceration, but tend to be multiple and occur more frequently. These ulcers, are small, round or oval, with a sharp, erythematous border, and painful. They appear in the gingiva, tongue, palate, and buccal and labial mucosal membranes, and usually heal without scars. Large (major) ulcers are less frequent and herpetiform ulcers are rare.

Genital ulceration

External genital ulcers, which have the next highest sensitivity for the diagnosis of BS, are deeper, painful, have irregular margins, and leave scars, producing an objective sign even in the absence of active lesions. They usually occur on the scrotum in men, and on the labiae in women.

Skin lesions

The skin lesions of Behçet's disease are folliculitis, papulopustular lesions and acneiform lesions, which occur more commonly in men, and erythema nodosum, which are more common in women. These lesions all represent various forms of vasculitis. The other forms of skin lesions are leukocytoclastic vasculitis, necrotizing arteritis of the small and medium arteries, superficial thrombophlebitis, and unclassifiable papules and pustules.

Eye involvement

This is one of the most serious manifestations and a leading cause of morbidity in BS. Males and those with younger age of onset, i.e., less than 25 years of age, have an increased prevalence. The overall prevalence is about 50 %, but in the younger male this rate goes up to 70 %. Females are less severely affected. Disease is bilateral in 90 % of the patients with ocular involvement and onset of eye disease is usually within 2 to 3 years of the development of the syndrome [78]. Eye disease in Behçet's syndrome consists of a chronic relapsing posterior and anterior uveitis, and acute panuveitis, with blurred vision, decreased visual acuity, photophobia, pain in the eye and conjuctival hyperemia being the common ocular symptoms [31, 32]. Intense inflammation (hypopyon) is seen in 20 % of patients with eye disease and as rule is almost always associated with severe retinal disease and indicates a grave prognosis associated with blindness. Optic nerve involvement can occur, but is rare [35, 40].

The pathergy phenomenon

The pathergy phenomenon is one of the diagnostic tests that is almost specific to Behçet's disease. This is a nonspecific hypersensitivity or hyperirritability reaction of the skin. It has a sensitivity that varies largely between different ethnic and geographical groups (range: 20 to 80 %). It is produced by inserting an 18 gauge needle into the dermis of the forearm of the patients. The reaction is considered positive if a papule or pustule is formed at the site of the puncture at the 48th hour. Erythema alone is considered negative.

Musculoskeletal involvement

A nonerosive, nonmigrating monoarthritis or oligoarthritis, involving the large joints, especially knees, ankles and wrists, either in the form of arthritis or arthralgia is reported in about 50 % of patients. Another musculoskeletal manifestation associated with Behçet's syndrome is aseptic necrosis of the bone. This is possibly related to vasculitis and not necessarily to steroid use [78].

Gastrointestinal involvement

Constipation, diarrhea, abdominal pain, or vomiting are common gastrointestinal symptoms but their frequency varies in different geographic populations [78, 104]. These symptoms are seen relatively frequently in Japan, but not in Turkey and other Mediterranean countries. Due to its common occurrence, oral ulcers are considered separately from the remaining gastrointestinal tract, of which any part, especially the distal ileum and cecum may also have ulcers.

Cardiovascular involvement

Major vessel involvement is a serious cause of morbidity and mortality. It manifests as arterial aneurysms or occlusions, or as pulmonary artery aneurysms with the risk of fatal hemoptysis and death. Deep vein thromboses and thrombophlebitis are among other large vessel complications, and all are expected to be seen in 25–30 % of the cases, while a possibly higher proportion do have small vessel involvement, mostly affecting post capillary venules [45]. The basic pathology is thought to be a vasculitis of the vasa vasorum [64]. BS is one of the few vasculitides, together with systemic lupus and Buerger's disease that can involve both the venous and arterial sides of the circulatory system. But it differs from the other two, as in contrast to them it can involve the vena cavae, too. In BS there is also a tendency to develop venous thromboses after venepunctures.

Although rare, myocardial ischemia associated with coronary vasculitis or with inflammation such as endocarditis, myocarditis, and pericarditis may all occur, resulting in ventricular dysfunction and intracardiac thrombi. Cases with ventricular aneurysms have also been documented.

Other ystems

Other systems reported to be involved through the course of the disease are pulmonary, urinary and the central nervous systems.

Laboratory investigations

There are no laboratory findings specific for BS. The moderate anemia of chronic disease and leukocytosis can be seen in some patients. The erythrocyte sedimentation rate is only mildly elevated, as is the C-reactive protein. None of these correlates with disease activity. In some more recent studies, it was suggested that hyperhomocysteinemia and high serum prolactin levels could serve as a marker for activation of the disease, but these findings also need to be confirmed [49]. Auto-antibodies are absent, whereas complement levels may be high [78, 104]. However, HLA testing can support the diagnosis in populations where the disease is associated with HLA B51 phenotype and may help in the differential diagnosis.

Nervous system involvement in Behçet's disease: "Neuro-Behçet syndrome"

Patients with Behçet's syndrome (BS) may present with different neurological problems, related either directly or indirectly to the disease [92] (Table 2). Cerebral venous sinus thrombosis (CVT), central nervous system (CNS) involvement secondary to vascular inflammation, the Neuro-Psycho-Behçet variant, in which an organic psychotic syndrome is prominent, are considered direct effects. As all of them demonstrate neurological manifestations, which are considered to be signs and symptoms due to nervous system involvement in BS, they will be reviewed here as "Neuro-Behçet syndrome" (NBS). A non-structural recurrent vascular-type headache that starts after the onset of the systemic manifestations of BS and is sometimes associated with their exacerbations may be seen in a subgroup of patients [77]. Neurologic complications of BS treatments, tension type headache and depression are among indirect neuro-psychiatric consequences of the disease. Peripheral nervous system involvement is extremely rare, despite that neurophysiological studies may demonstrate non-specific findings in some patients.

The suggested diagnostic criteria for NBS in a patient that fulfills the International Diagnostic Criteria for Behçet's Disease is the presence of neurological symptoms not otherwise explained by any other known systemic or neurological disease or treatment, and in whom objective abnormalities are detected either on neurological examination, and/or with neuroimaging studies (MRI disclosing findings suggestive of NBS) and/or abnormal cerebrospinal fluid findings consistent with NBS [92] (Table 3).

The prevalence of NBS in BS is around 5 % in non-selected large series [3, 40, 90]. In another study from our center, however, when the frequency of neurological involvement was evaluated prospectively, the frequency

Table 2 The neurological spectrum of Behçet's disease*

Primary neurological involvement (Neurological involvement directly related to BS)
• Headache (migraine-like, non-structural)
• Cerebral venous sinus thrombosis (extra-axial NBS)
• Central nervous system involvement (intra-axial NBS)
• Neuro-Psycho-Behçet syndrome
• Peripheral nervous system involvement
• Subclinical NBS
Secondary neurological involvement (Neurological involvement indirectly related to BS)
• Neurologic complications secondary to systemic involvement of BS (i. e., cerebral emboli from cardiac complications of BS, increased intracranial pressure secondary to superior vena cava syndrome)
• Neurologic complications related to BS treatments (i. e., CNS neurotoxicity with cyclosporine; peripheral neuropathy secondary to thalidomide or colchisin)
Coincidental – unrelated (non-BS) neurological involvement
• Primary headaches and any other coincidental neurological problem

* Modified from Siva A, Altintas A, Saip S (2004) Behçet's Disease. Curr Op Neurol [92].
BS Behçet syndrome; *NBS* Neuro-Behçet syndrome; *CNS* central nervous system

Table 3 Suggested diagnostic criteria for Neuro-Behçet syndrome*

A) Fulfilling the International Diagnostic Criteria for Behçet's Disease
B) Onset of neurological symptoms not otherwise explained by any other known systemic or neurological disease or treatment
C) Presence of at least one of the following:
1) Objective abnormalities on neurological examination (clinical evidence)
2) Abnormal neuroimaging findings suggestive of NBS (imaging evidence)
3) Abnormal cerebrospinal fluid findings suggestive of NBS (laboratory evidence)
4) Abnormal neurophysiological (electromyography or evoked potentials) studies consistent with the current neurological symptoms (neuro-physiological evidence)

* Modified from Siva A and Altıntaş A (2000) [88]

became 13.0 % among the males and 5.6 % among the females after two decades of follow-up [51]. The mean age of onset for BS and NBS was found to be 26.7 ± 8.0 and 32.0 ± 8.7 years, respectively, in our Behçet's Disease Research Center cohort [90]. Neurological involvement in BS occurs more commonly in men, with a male to female ratio of up to 4:1 [92]. Such a significant male predominance has also been noted for other vascular complications of BS [51].

As already mentioned, in addition to isolated headache due to different causes, NBS may be manifested either in the form of central nervous system (CNS) involvement or cerebral venous sinus thrombosis (CVST), the two major neurological presentations of BS. Neurological manifestations clinically are related commonly to brainstem or corticospinal tract syndromes in the former and to increased intracranial pressure in the latter form. There is a tendency to designate only CNS parenchymal involvement as NBS and include cerebral venous sinus thrombosis within the spectrum of so-called vasculo-Behçet [85, 101]. However, as both have significant neurological consequences they will be identified as "intra-axial NBS" and "extra-axial NBS", respectively, in this review.

Clinical and neuroimaging evidence also confirm this sub-classification of NBS. CNS-NBS or intra-axial NBS is due to small vessel disease and causes the focal or multifocal CNS involvement manifested in the majority of patients. The second form, CVST or extra-axial NBS, which is due to large vessel disease presenting with thrombosis of the major cerebral venous sinuses, has limited symptoms, a better neurological prognosis and generally an uncomplicated outcome [90]. These two types of involvement occur in the same individual very rarely, and presumably have a different pathogenesis. Many of the 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 a progressive CNS dysfunction from the onset. In our series of patients with neurological manifestations related with BS, the rates of intra-axial (CNS) – NBS and CVST were 75.6 %, and 12.2 %, respectively, with the remaining having other or indefinite diagnoses [90].

Headache in BS

The most common neurological symptom among patients with BS is headache and may be due to different

Table 4 The differential diagnosis of "headache" in patients with Behçet's syndrome

- The non-structural headache of BS
- Headache due to central nervous system parenchymal involvement
- Headache due to cerebral venous sinus thrombosis
- Headache in association with ocular inflammation
- Co-exiting primary headaches (i. e., migraine; tension type headache)

causes (Table 4). In several studies on headache in BS, the most common type of headache was reported to be migraine [9, 21, 41, 59]. However, in our prospective randomized study we have observed that some patients with BS report a paroxysmal migraine-like pain, which is bilateral, frontal, of moderate severity and throbbing. It starts after the onset of the systemic findings of BS and may be seen during exacerbations of the systemic findings, such as oral ulcerations or skin lesions, though this is not always the rule [77]. Despite that this type of headache shares some features with migraine, it is not "true" migraine and it is quite likely that its inclusion together with migraine has lead some investigators to consider migraine as being more common in the Behçet population. This non-structural headache of BS is not associated with primary neurological involvement in BS and it is not specific for this disorder, but may be explained by a vascular headache triggered by the immune-mediated disease activity in susceptible individuals [77].

In our unselected cohort of 228 patients with BS, the prevalence of migraine and tension-type headache were close to the population in general, 14.9 % and 23.6 %, respectively [77]. Headache due to uveal inflammation was seen in 3.9 %, and due to NBS in 5.2 %.

A substantial number of patients with BS may report a severe headache of recent onset not consistent with a co-existing primary headache or ocular inflammatory pain. These patients require further evaluation even if they do not have neurological signs, as such a symptom may indicate the onset of NBS.

Extra-axial NBS

Cerebral venous sinus thrombosis is seen in 10–20 % of BS patients in whom neurologic involvement occurs [3, 90]. Thrombosis of the venous sinuses may cause increased intracranial pressure with severe headache, mental changes and motor ocular cranial nerve palsies, but in some patients the only manifestation may be a moderate headache. It is well known that the clinical manifestations resulting from thrombosis of the intracranial venous system vary according to the site and rate of venous occlusion and its extent. Our experience suggests that the CVST in BS evolves relatively slowly, as in none of our patients have we observed a fulminating syndrome of violent headache, convulsions, paralysis and coma. But acute onset cases are reported in whom seizures and focal neurologic signs occurred besides headache [101]. Papilledema and sixth nerve paresis are the most common signs reported, and hemiparesis may develop in some [3, 90, 101].

There is a tendency for CVST to occur earlier in disease course compared to the parenchymal type of CNS disease and this difference is significant in male patients [99]. In the pediatric age group affected with BS, the neurologic involvement is mostly in the form of CVST (unpublished observation). Any of the 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. Intracranial hypertension without any demonstrable neuro-imaging abnormality have been reported, with some of them developing neuroimaging findings consistent with CVST in further attacks later [2].

Parenchymal CNS involvement in BS patients with CVST is unlikely. The extension of the clot into the cerebral veins causing focal venous hemorrhagic infarction is uncommon, and also the occurrence of CVST with primary CNS involvement (co-existence of intra- and extra-axial NBS) is extremely rare [90]. We have also observed 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 [100] confirming some other works [29, 101]. We believe that these observations also support the notion that the two major forms of neurological disease (intra and extra-axial involvement) 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 always with a favorable outcome.

Intra-axial NBS

The onset of a subacute brainstem syndrome in a young man, especially of Mediterranean (or Middle East, or oriental) origin, that includes cranial nerve findings, dysarthria, uni- or bi-lateral corticospinal tract signs with or without weakness, ataxia and a mild confusion should raise the probability of "NBS". Such a patient (if a reliable history can not been obtained from the patient, then his family member(s)) needs to be interviewed for the presence of systemic findings of BS. In the case of BS, it will be very likely to obtain a past or present history of oral aphtous ulcers and some other systemic manifestations of the disease. Many patients may have never con-

sulted a physician because of the mild nature of their systemic symptoms, or may be missed because of not reporting a full-blown picture of the disease. As mentioned above it will be quite unlikely to see NBS cases without oral ulcers. The MRI findings of the disease are almost pathognomonic, and this will further support the diagnosis [46]. However, it should be kept in mind that parenchymal-NBS (intra-axial NBS) does not always present with brainstem signs and symptoms. Cognitive-behavioral changes, emotional lability, a self limited or progressive myelopathy, urinary sphincter dysfunction and to a lesser extent other CNS manifestations such as extrapyramidal signs and seizures have been reported [3, 8, 12, 13, 14, 37, 68, 105]. There are also a few cases with isolated optic neuritis or recurrent peripheral facial paresis [23, 35].

Isolated progressive ataxia with cerebellar atrophy on MRI have been reported in a few patients with BS and it was suggested that this form of presentation may be novel manifestation of NBS [16]. However, since the relationship between the neurological presentation and BS was not clear in those cases and co-morbidity could not be ruled out, further observation is needed before such a conclusion may be reached.

Aseptic meningitis was reported previously to be a relatively frequent form of neurological involvement in patients with BS, in studies, which was based on CT scans as the primary imaging modality [83]. Our experience has not been such, and we suspect that in some patients, parenchymal disease was misclassified as aseptic meningitis due to lack of sensitive imaging data. As a matter of fact in a more recent update from the same institution [3], aseptic meningitis was reported only in 1 out of 200 cases studied. Similarly, in another study of 50 patients from the U.K. [40], 4 cases were reported to have meningitis symptoms, while 2 of these patients had parenchymal lesions and 2 had normal MRI. There was no discussion of meningeal enhancement and the CSF findings were within the same range as with patients who had brainstem parenchymal involvement. In support of this, we have always observed inflammatory findings in CSF together with parenchymal disease in MRI. Taken together, we conclude that pure aseptic meningitis is very rare within the clinical spectrum of neurological involvement in BS [90].

Arterial-NBS

Arterial involvement resulting in CNS vascular disease is rare, consistent with the systemic arterial involvement which is also infrequent in BS. Observations in cases with bilateral internal carotid artery occlusion, vertebral artery thrombosis, vertebral artery dissection, intracranial aneurysms and intracranial arteritis with their corresponding neurological consequences [4, 10, 29, 44, 46, 50, 69, 75] suggested that arterial involvement may be a subgroup of NBS [92]. Intracranial hemorrhages may occur but are extremely rare, with most occurring within ischemic lesions [42, 46].

It is noteworthy that the arterial involvement affects mostly large arteries located at the extracerebral sites of the cranio-cervical arterial tree, suggesting that an extra-axial arterial pattern of NBS may exist, as well as an intra-axial arterial NBS pattern related to intracranial arteritis and intra-axial small arterial occlusions. An analogy with the patterns of venous involvement seen in NBS may be made, but whether this subdivision has any pathognomonic or other meaning is currently not known.

Neuro-psycho-Behçet syndrome

Some patients with BS develop a neurobehavioral syndrome, which consists of euphoria, loss of insight/disinhibition, indifference to their disease, psychomotor agitation or retardation, with paranoid attitudes and obsessive concerns. We have observed the development of these psychiatric symptoms either at the onset of other neurological symptoms of NBS, or independently. They were not associated with glucocorticosteroid or any other therapy. We have named this syndrome "neuro-psycho-Behçet syndrome" [86]. A similar personality change was observed by others as well [65].

Cognitive changes observed in patients with BS

In a prospective neuropsychological study of 12 patients with neuro-Behçet syndrome (NBS), memory impairment was found to be the major finding [65]. The most severely affected memory process was delayed recall, being impaired in all of the patients either in the verbal and/or visual modalities. An impairment in the process of acquisition and storage; attention deficit and deficits of executive functions of frontal system were other cognitive functions involved in a declining order. Neuropsychological status deteriorated insidiously, regardless of the neurological attacks during the follow-up period in most of the patients, and the presence of cognitive decline was not directly related to detectable lesions on neuroimaging at early stages of the disease. However, an enlargement of the third ventricle and atrophy of the posterior fossa structures were observed in the late stages of the disease, which was correlated with memory loss [65].

Peripheral nervous system involvement in BS

Peripheral nervous system (PNS) involvement, with clinical manifestations are extremely rare in BS. How-

ever, 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 PNS involvement [55]. The limited number of BS patients including the Caribbean cases, who have been reported with PNS involvement, had clinical and electrophysiological findings consistent with mononeuritis multiplex, a peripheral neuropathy prominent in the lower extremities and poly-radiculoneuritis, a sensorimotor axonal neuropathy and an axonal sensory neuropathy with recurrent episodes of myositis [7, 55, 61, 98]. Isolated muscle involvement with focal or generalized myositis have been reported but these are extremely rare [80, 85].

Electroneuromyographic studies disclosed demyelination, chronic denervation, and even myogenic involvement in the reported cases [61, 85, 98]. However, electroneuromyographic studies may disclose a subclinical neuropathy in patients who do not report symptoms suggestive of neuropathy [1, 7, 85]. In addition, it should be kept in mind that the neuropathy may develop secondary to a various drugs used in the treatment of BS, such as thalidomide or colchicine [7], or may also be coincidental.

Subclinical NBS

The incidental finding of neurological signs in patients with BS without neurological symptoms was reported in some series, with a minority of these patients developing mild neurological attacks later [3, 5]. In another study looking at silent neurological involvement in BS, the authors also concluded that this group of patients represent a milder form of the disease, since the mortality and disability rate was found to be significantly lower when they were followed prospectively [106].

Brainstem auditory and somatosensory evoked potentials, and transcranial magnetic stimulation were studied in patients with intra-axial (CNS) NBS in several studies and showed a wide range of abnormality, mainly due to the involvement the basal parts of the brainstem and corticospinal tracts. The demonstration of subclinical involvement by detection of abnormal responses in examined areas without corresponding clinical symptoms and signs in some of these patients is noteworthy in providing information for the extent of the CNS involvement. In another study subclinical involvement was investigated by using P300 in Behçet's patients without neurological manifestations [39]. The findings suggested that the P300 measures and motor response time may reflect subclinical neurologic involvement in Behçet's disease.

Electroneuromyographic studies, as already mentioned had also shown a subclinical neuropathy in some patients who do not report symptoms suggestive of neuropathy and also silent muscle involvement was reported in patients without overt muscle involvement, who were studied with electron microscopy [85]. Autonomic nervous system involvement was also reported in asymptomatic patients with BS [38]. On the other hand subclinical CNS involvement was also detected by SPECT studies as described below.

The detection of abnormalities on neurophysiological studies, as well as by neuroimaging in asymptomatic patients further suggests that the subgroup of patients with subclinical CNS and PNS involvement may not be so uncommon [99]. However, the clinical and prognostic value of detecting abnormalities in such diagnostic studies in this subgroup of patients currently is still not clear.

Diagnostic studies in NBS

Neuroimaging

Neuro-imaging studies in intra-axial-(CNS)-NBS have shown that cranial magnetic resonance imaging (MRI) is both specific and more sensitive than computerized tomography in demonstration of the typical reversible inflammatory parenchymal lesions. Lesions are generally located within the brainstem, occasionally show an extension to the diencephalon and are less often within the periventricular and subcortical white matter [46].

The most commonly affected region is the mesodiencephalic junction, followed by the pontobulbar region [3, 46]. Most patients who do have mesodiencephalic junction lesions also show an upward extension involving the diencephalic structures and basal ganglia and/or a downward extension (Figs. 1 and 2). Hemispheric lesions are not common and when they are present they 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 [46, 92]. 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 intra-axial-(CNS)-NBS [28, 33, 93]. The authors concluded that their findings were suggestive of vasogenic edema 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. There are also a number of reports of NBS cases whose MRI images showed mass lesions that mimicked brain tumors, some necessitating histological diagnosis [56, 70, 82]. Despite that the inflammatory nature could not be shown in all cases [19], these lesions are likely to be acute inflammatory edematous lesions that following IVMP show significant resolution [20, 46].

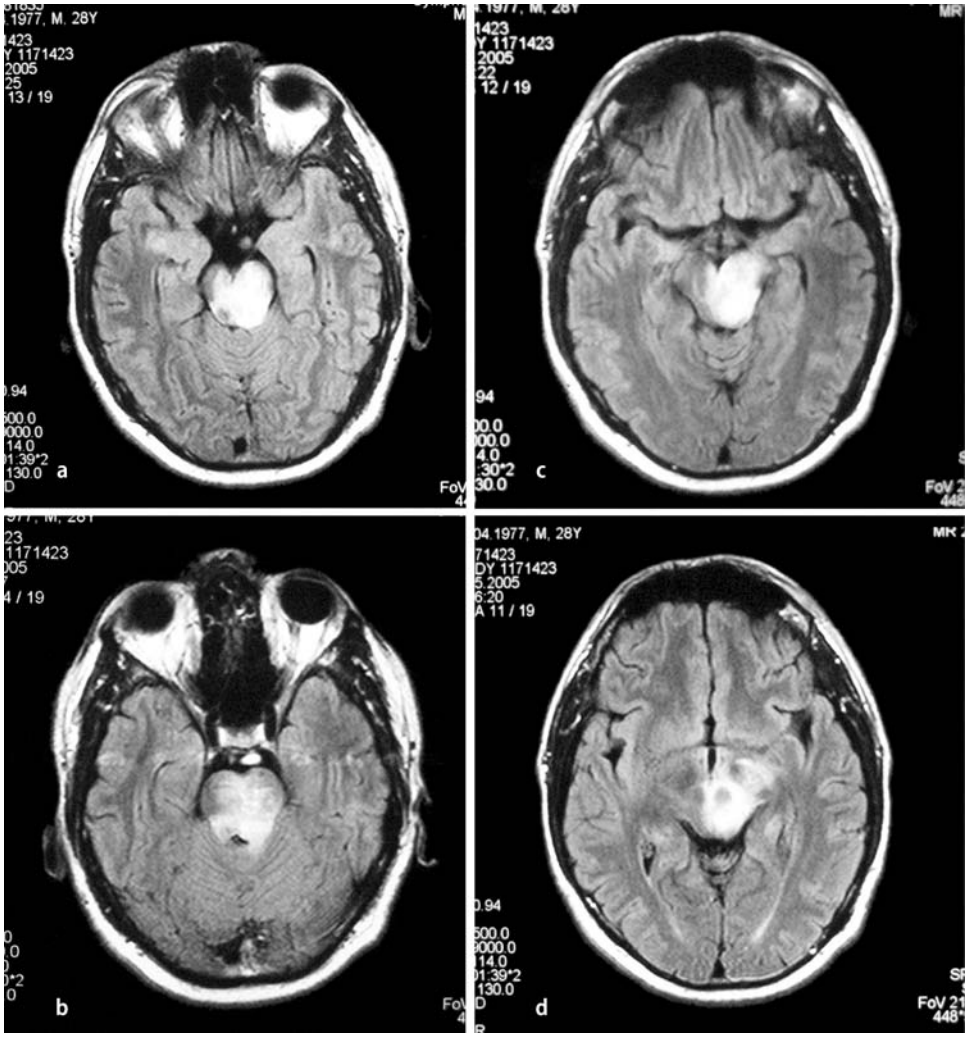

Fig. 1 **A–D** Flair MR images of a patient with neuro-Behçet syndrome showing pons and midbrain involvement extending to the diencephalic region on the left

Spinal cord involvement is not common, but can be seen. In reported cases, the major site of involvement was the cervical spinal cord with the myelitis-like inflammatory lesions continuing more than two segments, and extending to the brainstem in some [18, 46]. Single or multiple cervical and/or dorsal lesions on spinal MRIs, lesions smaller than the length of one vertebral body, resolution of these lesions, spinal cord atrophy, and gadolinium enhancement all have been reported in earlier works and also in a recent larger series [105]. We have observed two patients with optic neuropathy, with one showing an enhancing isolated optic nerve lesion. Neither neuro-myelitis optica like presentation, nor NMO-IgG have been reported in BS this far.

MR venography is the preferred study to diagnose or confirm CVST in Behçet's disease, but most of the time T1- and T2-weighted images also disclose the venous sinus thrombosis. With the exception of two cases we have not observed hemorrhagic venous infarcts or other parenchymal CNS lesions on MRI in our patients with CVST/extra-axial NBS [92, 100] and others also report a similar observation or a low rate of such changes in their patients [3, 101]. This finding together with the clinical findings as already mentioned above suggests that the cerebral venous sinus thrombosis in BS may not be acute and complete in a significant number of cases.

Cerebral or spinal arteriograpy may serve to demonstrate vasculitis, dissection or aneurysms and also may have been used to monitor treatment effects in patients with vasculitic involvement. However, the probability of detecting a significant finding in the cerebral arteriography is low, as in most cases with CNS parenchymal disease, the vascular involvement is most prominent in the postcapillary venules. Therefore it is our impression that cerebral arteriography is not a priority in NBS nor in cases with extra-cerebral vascular involvement. It should be kept in mind that not only a neutrophilic infiltration with arterial injury may occur at the site of arteriographic puncture in patients with BS, but that there may be more unfortunate consequences related to

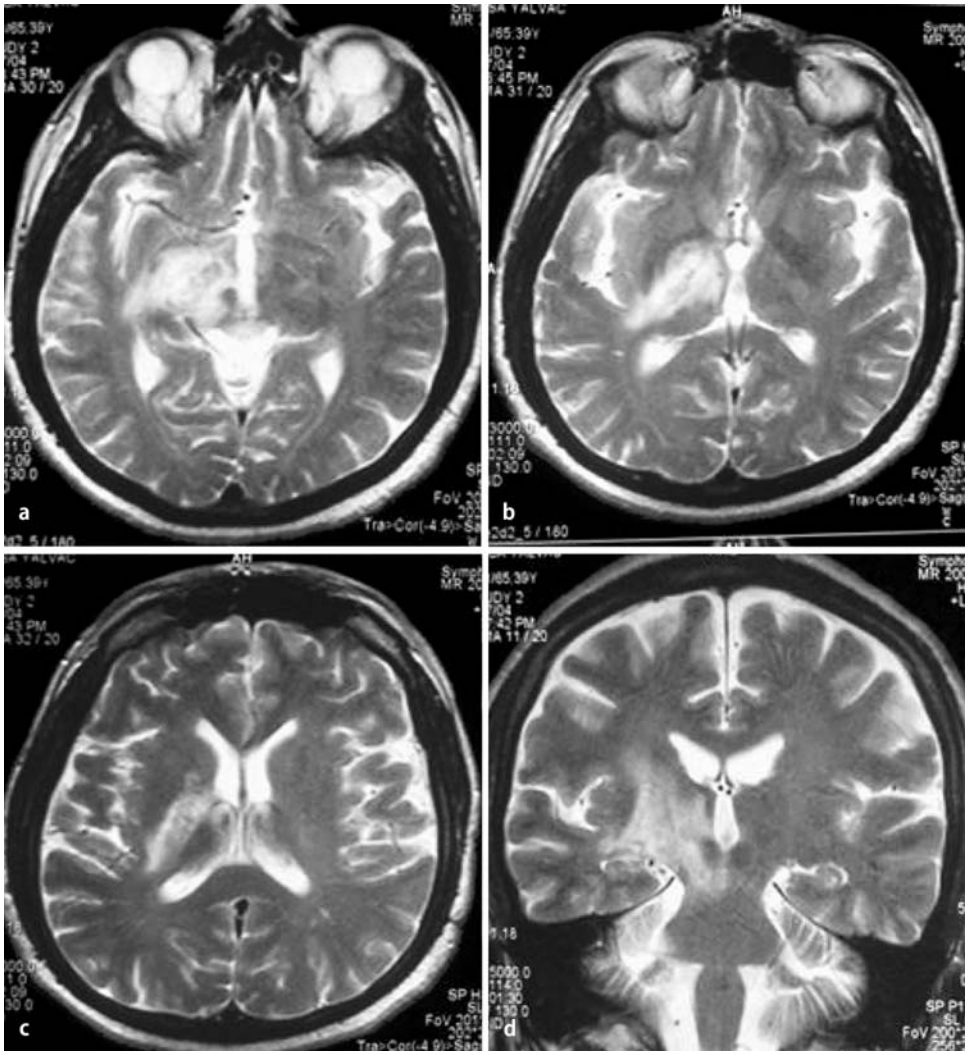

Fig. 2 Axial (**A–C**) and coronal (**D**) T2 MR images of another patient with neuro-Behçet syndrome showing a midbrain lesion extending to the diencephalic and basal ganglia regions on the right, similar to the previous patient

this procedure. Recently fatal rebleeding during the arterial injection of the contrast medium was reported in a Behçet patient with basilar artery aneurysm [4]. Since patients with BS have vascular inflammatory changes that may increase the rebleeding tendency of the aneurysm, the authors suggested that once an intracranial aneurysm is suspected or detected by non-invasive studies, further investigation of the aneurysm may be done by multi-slice computed tomography that is known to be a sensitive diagnostic tool [4].

SPECT studies in BS

SPECT studies had disclosed areas of hypoperfusion localized in the deep basal ganglia and in the frontal and temporal lobes in a group of BS patients with neuropsychiatric manifestations [30, 62]. MRI was normal in some of them and these non-specific SPECT findings, which were consistent with multiple hypoperfusion areas that correlated with decreased metabolic demand were interpreted as indicative of early functional changes in the brains of this patient population.

Cerebrospinal fluid (CSF)

If performed during the acute stage, CSF studies usually show inflammatory changes in most cases of intra-axial-(CNS)-NBS [3, 40]. Oligoclonal bands can be detected, but this will be an infrequent finding. CSF in patients with CVT may be under increased pressure, but the cellular and chemical composition is usually normal [90].

Differential diagnosis

Differential diagnosis of intra-axial (parenchymal) NBS

The major diseases to be included in the differential diagnosis of parenchymal NBS are shown in Table 5. Patients with NBS are young and frequently present with an acute or subacute brainstem syndrome or hemiparesis, as well as with other various neurological manifestations. Hence, the possibility of BS is often included in the differential diagnosis of multiple sclerosis and in the stroke of the young adult, especially in the absence of its known systemic symptoms and signs.

Multiple sclerosis is more common in women, whereas NBS is seen frequently in men. Onset age is about the same but optic neuritis, sensory symptoms and spinal cord involvement, which are common in MS, are rarely seen in NBS (Table 6). However, sometimes the clinical presentation of NBS may be confused with MS, but the neuroimaging –(MRI) findings are clearly different. The pattern of brainstem involvement in NBS, which commonly extends to involve basal ganglia and diencephalic structures are not expected to be seen in MS. Furthermore, periventricular, corpus callosum and ovoid lesions suggestive of MS are unlikely to be seen in NBS, and when hemispheric white matter lesions are present in NBS they are more likely to be hemispheric or subcortical than periventricular, and these are almost always associated with the brainstem-diencephalic lesions [46]. Brainstem lesions in MS are usually small even in the acute stage, and prominent brain stem and cerebellar atrophy without cerebral volume loss that is seen in the chronic phase of NBS is unusual in MS [57, 60]. When one considers spinal cord involvement, this rarely extends more than a few vertebral segments in MS, contrary to the more extensive lesions that were observed in the few cases of NBS [18, 46]. The CSF also reveals different patterns, with a more prominent pleocytosis and low rate of positivity for oligoclonal bands in NBS [84].

An acute stroke-like onset is not common in NBS, and MRI lesions compatible with classical arterial territories are also not expected [46]. The absence of systemic symptoms and signs will serve to differentiate the primary CNS vasculitic disorders from NBS, and the difference in the systemic symptoms and signs from the secondary CNS vasculitides, as well as the MRI findings [46, 90]. In primary CNS vasculitis cerebral angiography was reported to be abnormal in up to 90 % of patients and MRI had shown multiple infarcts that mostly involved cortical areas as well [79], both unusual for NBS.

Sarcoidosis can also be confused with Behçet disease due to uveitis, arthritis, and CNS involvement, but the absence of oral and genital ulcers, and the presence of peripheral lymphadenopathy, and bilateral hilar lymph

Table 5 The differential diagnosis of intra-axial (CNS) neuro-Behçet's syndrome

- multiple sclerosis
- Stroke in young adults
- primary CNS vasculitis
- secondary CNS vasculitis
- neuro-sarcoidosis
- CNS-tuberculosis
- brainstem glioma
- primary CNS lymphoma
- Vogt-Koyanagi-Harada syndrome
- Reiter syndrome
- Eales' disease
- Cogan's syndrome
- Susac syndrome
- Neuro-Sweet syndrome

Table 6 The differential diagnosis of multiple sclerosis and intra-axial (CNS) neuro-Behçet's syndrome*

	Multiple sclerosis	CNS neuro-Behçet syndrome
Gender	Female > Male	Male > Female
Symptoms at onset		
Common	ON; sensory; spinal cord; BS/INO; motor; cerebellar	Headache; motor; cerebellar; BS
Uncommon	Headache	ON; Sensory; spinal cord; BS/INO
MRI		
PV & SC lesions	(+++)	(±)
Brainstem lesions	small, discrete, extension (–)	large, diffuse, extension (+)
Spinal cord lesions	(++)	(±)
CSF		
Inflammatory changes	(±)	(++)
OCB (+)	> 90 %	< 20 %

* Modified from Siva A, Altıntaş A, Saip S (2004) Curr Op Neurol [92]
CNS central nervous system; *MRI* magnetic resonance imaging; *CSF* cerebrospinal fluid; *OCB* oligoclonal bands; *ON* optic neuritis; *BS* brainstem; *INO* internuclear ophtalmoplegia; *PV* Periventricular; *SC* subcortical

nodes on chest x-ray, as well as pathological examination of the non-caseating granulomatous lesions of sarcoidosis help in the differential diagnosis. In some patients with sarcoidosis however, involvement of the nervous system may be the presenting and only manifestations of the disease [67, 76]. Cranial neuropathies (the seventh nerve is most commonly involved), seizures, diabetes insipidus and other symptoms related to chronic meningitis and hydrocephalus as well as sarcoid neuropathies and myopathies are among the nervous system manifestations of sarcoidosis [67, 71, 76]. These are not common in NBS, and MRI findings are unlikely to be confused between the two diseases.

Tuberculosis may resemble BS because of its multisystem involvement and for its potential to affect the nervous system. However, hilar lymphadenopathy and pulmonary cavities are not seen in BS, whereas its mucocutaneus manifestations are unusual for tuberculosis. Furthermore CSF and MRI findings are different and microscopic and pathological examination, as well as culture and PCR analysis of body fluids or tissue specimens will help to identify the disease as tuberculosis.

Brainstem glioma and primary CNS lymphoma may be included in the differential diagnosis of NBS in patients presenting with localized brainstem findings and whose initial MRI may disclose a large brainstem lesion, but the presence of systemic findings and the resolution of the MRI lesion following high-dose steroids will solve the problem immediately.

Due to their ophthalmologic and some other systemic manifestations rare diseases, such as Vogt-Koyanagi-Harada syndrome, Reiter syndrome, Eales' disease, Cogan's syndrome, and Susac syndrome, are other considerations in the differential diagnosis of BS. All may present with nervous system manifestations and therefore are also included in the differential diagnosis of NBS. However, a complete ophthalmologic examination will reveal the true nature of eye involvement in each of these syndromes, which have differences from the eye involvement seen in BS.

The Vogt-Koyanagi-Harada syndrome (VKH) is a bilateral, diffuse granulomatous uveitis associated with poliosis, vitiligo, alopecia, and central nervous system and auditory signs [17]. Symptoms of meningeal irritation and occasional encephalopathy are most common in the prodromal phase of the illness and a CSF pleocytosis has been noted to be even more common than symptomatic meningitis, but it rarely causes significant focal neurologic disease [17]. This inflammatory syndrome, which occurs more commonly among heavily pigmented populations such as Asians, Hispanics, Native Americans, and Indians, is probably the result of an autoimmune mechanism, influenced by genetic factors, and appears to be directed against melanocytes. Ocular inflammation, arthritis, and urethritis are seen in Reiter syndrome, but conjunctivitis is more common than uveitis in this disease and genital lesions are painless. Eales' disease, a syndrome of retinal perivasculitis and recurrent intraocular hemorrhages, is infrequently associated with neurologic abnormalities [6].

Cogan's syndrome (CS) is an idiopathic inflammatory disease in which the major symptoms are ocular and cochleovestibular. The eye inflammation consists of interstitial keratitis and uveitis, and inner ear inflammation will cause symptoms clinically indistinguishable from Meniere's disease [95]. Almost three-quarters of the patients develop systemic manifestations, and a vasculitis involving large vessels, similar to Takayasu's arteritis or involving medium vessels resembling periarteritis nodosa may develop in 10–15 % of the patients [72, 95]. Nervous system involvement is not common, but when present the neurologic manifestations are broad and include headache, psychosis, stroke, cerebral sinus thrombosis, seizures, encephalopathy, myelopathy, cranial neuropathies, mononeuropathies and polyneuropathy. Susac syndrome is an autoimmune endotheliopathy causing small infarcts in the retina, the cochlea, and the brain, resulting in the clinical triad of retinopathy, hearing loss, and encephalopathy [97].

Gastrointestinal symptoms in Behçet disease may mimic Crohn disease or chronic ulcerative colitis. Eye disease is rare and genital ulcers are absent in inflammatory bowel diseases. The diagnosis can be confirmed by intestinal biopsy. Whipple disease may be briefly mentioned here as a disease with gastrointestinal and various nervous system symptoms which may resemble BS, too.

"Neuro-Sweet disease"(NSD) is the rare CNS involvement that is seen with Sweet disease (SD), which is an idiopathic multisystem inflammatory disorder characterized by peculiar erythematous skin lesions and fever that resembles BS. It may be difficult to differentiate it from BS, but the ocular signs seen in Sweet disease are episcleritis and conjunctivitis vs the uveitis in BS, and HLA-Cw1 and B54 association has been reported for SD compared with the high frequency of HLA-B51 in BS [26, 27]. In NSD any region of the CNS can be involved without site predilection, resulting in a variety of neurologic symptoms. The neurologic events may be recurrent but the prognosis is benign, as the disease is not a true vasculitis [26, 27].

Differential diagnosis of extra-axial NBS (CVT)

In patients who present with symptoms of intracranial hypertension and in whom neuroimaging reveals thrombosis in one or more of the cerebral venous sinuses, BS needs to be included in the differential diagnosis. The presence of its systemic findings is the only clue to the association of CVST with BS, and their absence will exclude this possibility. We have not observed hemorrhagic

venous infarcts or other parenchymal lesions on MRI in our patients with extra-axial NBS, and others also report a similar observation or a low rate of such changes in their patients [3, 101].

Prognosis

Neurological involvement in BS is a remarkable cause of morbidity and approximately 50 % of the NBS patients are moderate to severely disabled after 10 years of disease. We rated the neurological disability of our patients with BS by using the Expended Disability Status Scale of Kurtzke (EDSS), which was originally devised for multiple sclerosis-associated disability [52]. Taking into consideration that the visual disability is most commonly due to uveitis in BS, the visual function was eliminated from the original scale. By 10 years after the onset of neurological symptoms and signs, 78.2 % of our patients developed at least mild (EDSS ≥ 3), and 45.1 % moderate to severe neurological disability (EDSS ≥ 6). An EDSS score of 3 represents full ambulation despite neurological moderate disability on neurological examination, and a score of 6 represents patients requiring assistance in walking, such as one-sided support to walk for 100 meters, and during other activities of daily life. However, when patients were evaluated separately, all with CVST had EDSS scores of either 1 or 2 (minimal disability) [90]. Despite the neurologic outcome is good in NBS patients with CVST, due to increased prevalence of systemic large vessel disease, the overall morbidity and mortality is significant in this group of patients [100].

Onset with cerebellar symptoms and a progressive course were unfavorable factors, while onset with headache, a diagnosis of CVST, and disease course limited to a single episode were favorable [90]. An elevated protein level and pleocytosis in the CSF were also reported to be associated with a poorer prognosis [3].

Treatment

Neurological involvement in BS is heterogeneous and it is difficult to predict its course and prognosis, and response to treatment. Therefore it is not possible to reach a conclusion on the efficacy of any treatment unless properly designed, double masked, placebo controlled studies are carried for each form. However, this is difficult to accomplish, as even in large centers the yearly numbers of new neuro-cases are very limited. Most studies, which report some kind of efficacy with various treatments in BS with neurological involvement have not included uniform cases, have not followed their patients for long periods and did not have controls. So, currently we have no evidence for the efficacy of any treatment for any form of NBS. Empirical impressions currently create the guidelines for management.

Intra-axial NBS: acute episodes

Glucocorticoids are used to treat acute CNS involvement with in BS, but their effects are short-lived and they do not prevent further attacks or progression. Acute attacks of CNS-neuro-Behçet syndrome are treated with either oral prednisolone (1 mg/kg for up to four weeks, or until improvement is observed) or with high dose intravenous methyl prednisolone (IVMP-1 g/day) for 5–7 days. Both forms of treatment should be followed with an oral tapering dose of glucocorticoids over 2 to 3 months in order to prevent early relapses [89]. There is no apparent difference between the two regimens, but our impression is that the high dose IVMP regimen is associated with earlier improvement. Our current practice is to give IVMP, 1 g/day for 7 days, followed by the oral regimen in patients with clinical and imaging evidence of CNS involvement [36].

Intra-axial NBS: long-term treatments

Colchicine, azathioprine, cyclosporine-A, cyclophosphamide, methotrexate, chlorambucil, immunomodulatory agents such as interferon-α, and, more recently, thalidomide have been shown to be effective in treating some of the systemic manifestations of BS. None of these agents have been shown beneficial in NBS in a properly designed study [36, 78, 89].

In a small, retrospective study, chlorambucil was reported to have some efficacy in meningoencephalitis of BS [63]. As most patients were treated prior to the CT/MRI era, there is no information on neuroimaging correlates of treatment. However, lessening in the CSF pleocytosis was documented in patients treated with chlorambucil. Although limited, our experience with chlorambucil in NBS is negative, and its serious side effects including increased risk of malignancy excludes it from our use. We have observed that treatment with other immunosuppressive drugs such as azathioprine, cyclosporine A and cyclophosphamide either alone or in combination for extraneural systemic manifestations of BS do not seem to prevent the development, exacerbations, or stop progression of intra-axial (parenchymal) NBS [89]. Cyclosporine was reported to cause neurotoxicity or to accelerate the development of CNS symptoms and therefore its use in NBS is not recommended [47, 48, 58]. In six patients with Behçet's disease who were judged to have progressive neuropsychiatric manifestations, an open 12-month trial with low-dose weekly methotrexate was carried out [24]. The authors had the impression that this regimen might have a beneficial effect in the

treatment of progressive NBS, but the results are not conclusive and not confirmed.

A common clinical practice is to add an immunosuppressant drug, such as azathioprine or monthly pulse cyclophosphamide to glucocorticoids in progressive NBS cases; however, the efficacy of such a combination has not been demonstrated.

Mycophenolate mofetil (CellCept) and Tacrolimus (Prograf) are other immunosuppressant/immunomodulator agents that were used to treat ocular inflammation and significant systemic manifestations in patients with BS, but there is no information regarding the potential effect of all these drugs in preventing CNS involvement or new neurologic attacks.

Successful treatment of neurologic manifestations of BS with monoclonal anti-TNF alpha antibody treatment with infliximab in a few patients has been reported recently [15, 43, 54, 73, 81]. However, the occurrence of neuro-relapses after stopping infliximab, formation of neutralizing antibodies and the probability of increased CNS auto-immunity with monoclonal anti-TNF alpha antibody treatment [74] should be also kept in mind. In a recent review on anti-TNF therapy in the management of Behçet's disease by a panel of experts, it was concluded that based on accumulated experience infliximab seemed to be more efficacious than etanercept in disease manifestations other than mucocutaneous or joint involvement, whereas the data on adalimumab was very limited [93]. The panel recommended that infliximab or etanercept could be used as an add-on therapy for selected patients with BD, who are refractory or intolerant to traditional immunosuppressive regimens, and who also have CNS involvement.

In theory, intravenous immunoglobulin (IVIg) would be expected to have a possible regulatory effect in the reported immunologic abnormalities of BS and its CNS involvement. However, in our limited experience with a few cases with progressive CNS involvement, we have not observed any significant improvement [89]. Data on the use of plasma exchange in NBS is also limited and unclear.

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 Behçet's disease-associated intracranial aneurysms and this form of treatment is suggested for ruptured, peripherally located, fusiform shaped, dissecting pseudoaneurysms and posterior circulation aneurysms [44].

Cerebral venous sinus thrombosis (CVT)

There is a tendency to treat deep venous thrombosis in BS with anticoagulants and antiplatelet agents in combination with intermediate doses of glucocorticoids [78]. However, there is no consensus on the treatment of CVT. Some authors use a combination of anticoagulation with glucocorticoids [101], while others administer glucocorticoids alone [2]. Although that we have used earlier a combination of subcutaneous low-molecular weight heparin with glucocorticoids in our treatment protocol for such cases [89], this is not our routine protocol anymore. Extreme caution is needed as BS patients with CVST, as these patients are more likely to have systemic large vessel disease including pulmonary and peripheral aneurysms. Therefore the use of anticoagulation should be considered only after such possibilities have been ruled out. Patients with CVST should be evaluated frequently, with detailed neuro-ophthalmic examination. Naturally, such an evaluation can only be carried out in the absence of ocular involvement due to BS. If the patient continues to report headache and visual symptoms, CSF analysis is repeated at week four or earlier. When the opening pressure is found to be elevated, the oral glucocorticoid treatment is continued until the patient improves and stabilizes in terms of clinical symptomatology, CSF pressure and on neuro-ophthalmic examination. Recurrence of CVST is uncommon after the initial episode. Thus, we do not recommend any form of long-term treatment in extra-axial NBS.

Summary of NBS treatment

The conclusions related to NBS of the recently published EULAR recommendations for the treatment of Behçet's disease summarize the status of the current NBS treatment. According to the panel, currently there are no controlled data to guide the management of CNS involvement in BD. For parenchymal involvement agents to be tried may include corticosteroids, interferon-α, azathioprine, cyclophosphamide, methotrexate and TNF-α antagonists. For dural sinus thrombosis, corticosteroids are recommended. Cyclosporine A should not be used in BD patients with central nervous system involvement unless necessary for intraocular inflammation [22].

Conflict of interest The authors declare no conflict of interest.

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