

Chapter 6

Behçet's Syndrome and the Nervous System

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Keywords Behçet's disease • Neurologic involvement • Classification • Differential diagnosis • Therapy

Introduction

Patients with Behçet's syndrome (BS) may present with different neurological problems which are either direct or indirect consequences of the systemic disease (Table 6.1) [1–3]. It is common to name the former, with documented involvement of the nervous system as a part of the systemic disease, as “neuro-Behçet's syndrome” (NBS). The most common form of neurological complication seen in BS is parenchymal-central nervous system (CNS) involvement, which is believed to be due to inflammatory small vessel disease and may present as acute disease or may have a chronic progressive form. The second common form is the cerebral venous sinus thrombosis (CVST), in which CNS-parenchymal involvement is unlikely. This pattern had led some authors to name this form of presentation as vasculo-Behçet's [4, 5]. However, as in both parenchymal CNS involvement and CVST, in varying degrees, vascular involvement is part of the picture. Therefore, we choose to name these patterns as intra-axial-NBS and extra-axial-NBS, respectively. Headache is the most common neurological symptom seen in patients with NBS, but occurs commonly in patients with BS in general, as well, and may be due to different causes and therefore deserves to be discussed separately.

The neuro-psycho-Behçet variant in which an organic psychotic syndrome is prominent is a rare form of NBS [6]. Peripheral nervous system involvement is also extremely rare, and it may be either directly related to BS or may occur as a consequence of treatments given for systemic manifestations of the disease, such as

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Table 6.1 The neurological spectrum of Behçet's syndrome*

Primary neurological involvement (neurological involvement directly related to BS)

Cerebral venous sinus thrombosis (extra-axial NBS)

Central nervous system involvement (intra-axial NBS)

 Acute intra-axial NBS

 Chronic progressive intra-axial NBS

Neuro-Psycho-Behçet's Syndrome

Peripheral nervous system involvement

Subclinical NBS

Headache (migraine-like, nonstructural)

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 colchicine)

Coincidental – unrelated (non-BS) neurological involvement

Primary headaches and any other coincidental neurological problem

*Modified from refs. [1–3]

BS Behçet's syndrome, NBS neuro-Behçet's syndrome, CNS central nervous system

colchicine or thalidomide. Other neurologic complications secondary to systemic involvement of BS or related to BS treatments are considered as indirect consequences of the syndrome (Table 6.1).

In recent years an increasing number of reports had pointed to cases, who demonstrated silent clinical signs, or neurophysiological, or neuroimaging findings without any corresponding neurological symptom. This pattern is considered as subclinical neurologic disease and its long-term implications is not currently known [1].

Diagnosis of NBS

The diagnosis of NBS is accomplished mainly by clinical means. It should be noted, however, that it is uncommon for NBS to arise in the absence of systemic features of Behçet's disease. It is therefore recommended that the satisfaction of the international diagnostic criteria for Behçet's disease is a prerequisite for diagnosis [7]. Therefore, although there is not a definite validated diagnostic criteria for NBS, in a patient who fulfills the International Diagnostic Criteria for Behçet's Disease, it seems reasonable to consider the diagnosis of NBS, when neurological symptoms develop which cannot be otherwise explained by any other known systemic or neurological disease or drugs used. To confirm the diagnosis of NBS in such a patient, objective abnormalities should be detected either on neurological examination, and/or with neuroimaging studies (MRI disclosing

findings suggestive of NBS) and/or abnormal cerebrospinal fluid (CSF) findings consistent with NBS [1].

Epidemiology of NBS

The prevalence of NBS in BS is around 5% in nonselected large series [8–10]. However, in a prospective study with two decades of follow-up the frequency of neurological involvement was 13.0% among the males and 5.6% among the females [11]. The mean age of onset for BS is around 26–27, and NBS develops after a mean of 5 years. However, when CVST is the main neurologic problem, ages of onset for both BS and the NBS are much earlier [10, 12]. Neurological involvement in BS occurs more commonly in men, with a male-to-female ratio of up to 4:1, whereas the sex ratio in BS, in general, is almost equal [1]. Such a significant male predominance has also been noted in other vascular complications of BS [11].

Extra-axial NBS

CVST is seen in 10–20% of NBS patients with neurologic involvement [8, 10, 13–15]. Thrombosis of the venous sinuses may cause increased intracranial pressure with severe headache, papilledema, motor ocular cranial nerve (sixth nerve) palsies, and mental changes, but in some patients the only manifestation may be a moderate headache [8, 10, 13–15]. CVST in BS evolves relatively slowly in most cases, but acute onset with seizures and focal neurologic signs have also been reported [4]. Superior sagittal sinus is most frequently involved with a substantial number of these patients also having lateral sinus thrombosis. Intracranial hypertension with initially normal neuroimaging with subsequent finding of CVST has been reported where patients might have CVT that couldn't be visualized due to technical problems such as being beyond the resolution of the imaging techniques or as the CVT developing very insidiously – being still partially patent early in the disease.

The onset of CVST in patients with BS tends to occur earlier than the clinical onset of parenchymal CNS involvement and this difference is significant mainly among the male patients [4, 12, 16]. Focal venous hemorrhagic cerebral infarction commonly seen in patients with CVST due to other causes is uncommon in BS, and the occurrence of CVST together with primary CNS involvement in the same patient is also rare [10, 14, 15]. CVST in BS is strongly associated with systemic major vessel disease, such as thrombosis of major veins, and systemic arterial disease, such as pulmonary aneurysms, whereas such an association isn't the case in patients with intra-axial NBS [12, 14, 16]. BS patients with CVST have a better neurological prognosis than the patients with intra-axial NBS, as recurrence and neurologic deficits are less likely to occur. However, due to an

increased association with major systemic vessel disease they may have a higher overall morbidity and mortality, and therefore a diagnosis of CVST in a patient with BS may not be always associated with a favorable outcome [1]. All these observations support the notion that the two major forms of neurological disease (*intra- and extra-axial NBS*) in BS might have different pathogenic mechanisms [10, 14, 15].

Intra-axial NBS

Parenchymal involvement in BS may present with symptoms and signs consistent with focal or multifocal CNS dysfunction with or without headache. The most common presentations are pyramidal weakness, brainstem and cerebellar signs, and cognitive/behavioral changes [1]. The onset of a subacute brainstem syndrome in a young man, especially of Mediterranean, Middle-Eastern, or Oriental origin, with cranial nerve findings, dysarthria, corticospinal tract signs and a mild confusion with severe headache should promptly raise the probability of “NBS.” Such a patient 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 recurrent oral aphthous ulcers and some other systemic manifestations of the disease. Emotional lability, seizures, a self limited or progressive myelopathy, may be seen but are less common, whereas isolated optic neuritis, aseptic meningitis, and extrapyramidal syndromes are rare presentations [1, 13, 17]. Patients with intra-axial NBS may remain with a single neurologic attack or initially have a relapsing-remitting course, with some of them developing a secondary progression later, while a few will have a progressive CNS dysfunction from the onset [1–3]. The latter progressive manifestation may be referred to chronic progressive NBS, which is discussed below.

Classification of Intra-axial NBS

Intra-axial NBS can be classified into acute NBS and chronic progressive NBS forms [2, 3]. Thus, acute NBS is characterized by an acute CNS syndrome, which responds well to corticosteroids and is usually self-limiting [2]. As already mentioned, a significant number of patients with acute NBS will remain with a single attack, while roughly a third will continue to have further attacks [8–10]. By contrast, chronic progressive NBS is characterized by intractable, slowly progressive neuro-behavioral changes and ataxia, along with persistent marked elevation of CSF IL-6 (usually more than 20 pg/ml) [2]. These patients with a chronic progressive form are also considered to have intra-axial NBS with a primary or secondary progressive course with gradual neurologic deterioration leading to significant disability [8–10].

Arterial-NBS

Arterial involvement resulting in CNS vascular disease is rare in BS, but an increasing number of cases with bilateral internal carotid artery occlusion, vertebral artery dissection or thrombosis, aneurysms, intracranial arteritis, and intra-axial small arterial occlusions are being reported [16–22]. These observations suggest that arterial involvement may be a subgroup of NBS [1], but whether this subdivision has any pathognomonic or other meaning is currently not known. Intracranial hemorrhages may occur but are extremely rare, most occurring within ischemic lesions [23, 24].

Headache in BS

Headache can occur as the presenting symptom of NBS either due to CNS involvement or CVST. It can also be seen in association with ocular inflammation. Headache is the most common neurological symptom seen in patients with BS. It usually is not associated with intracranial disease [1, 25]. In several studies on headache in BS, the most common type of headache was reported to be migraine [26–29]. When BS patients with headache are studied in detail, it will be found that some report a bilateral, frontal, moderate paroxysmal migraine-like pain, which is not a true idiopathic migraine, since it generally starts after the onset of BS and commonly accompanies the exacerbations of systemic findings of the disease, such as oral ulcerations or skin lesions, though this is not always the rule [25]. It may be explained by a vascular headache triggered by the immunomediated disease activity in susceptible individuals. Finally, coexisting primary headaches such as migraine and tension type headaches in patients with BS also are seen.

Neuro-Psycho-Behçet's Syndrome

Some patients with BS may develop a neuro-behavioral syndrome, which consists of euphoria, loss of insight/disinhibition, indifference to their disease, psychomotor agitation or retardation, with paranoid attitudes and obsessive concerns not associated with glucocorticosteroid or any other drug use, we name as “neuro-psycho-Behçet's Syndrome” [6]. This form of presentation has been suggested to be closely associated with the chronic progressive subgroup of intra-axial NBS [30].

Cognitive Changes Observed in Patients with NBS

Memory impairment was found to be the major cognitive function problem in patients with NBS with delayed recall being the most severely affected memory process, seen in all patients either in the verbal and/or visual modalities [31].

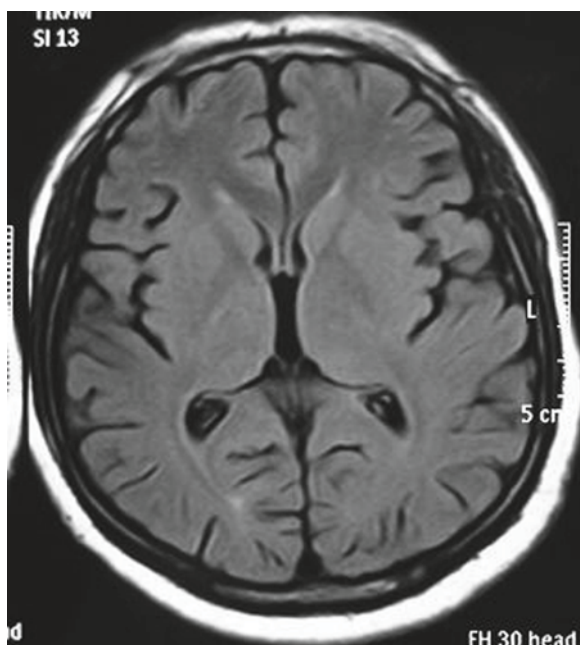


Fig. 6.1 An MRI image showing moderately enlarged third ventricle and mild sulcal enlargement in a patient with neuro-psycho-Behçet's Syndrome, who had mild cognitive deficits and behavioral changes

An impairment in the process of acquisition and storage; attention deficit and deficits of executive functions of frontal system were the other cognitive functions involved in the declining order. Neuropsychological status deteriorated insidiously, regardless of the neurological attacks during the follow-up period in most of the patients. 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 and this was correlated with memory loss (Fig. 6.1). This form of presentation might be also closely associated with the chronic progressive subgroup of intra-axial NBS [30].

Neuromuscular Disease in BS

Peripheral nervous system (PNS) involvement with clinical manifestations is rare in BS. Reported PNS involvement includes mononeuritis multiplex, a distal sensory motor neuropathy, an axonal sensory neuropathy and isolated muscle involvement with focal or generalized myositis [5, 10, 13, 33–36]. However, electroneuromyographic studies may disclose a subclinical neuropathy in patients who do not report

symptoms suggestive of neuropathy [5, 36]. Besides, 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 [8, 37]. In another study looking at silent neurological involvement in BS, the authors also concluded that this group of patients represented a milder form of the disease, since the mortality and disability rate was found to be significantly low when followed prospectively [38].

Brainstem auditory and somatosensory evoked potentials, and transcranial magnetic stimulation were studied in patients with intra-axial NBS in several studies and showed a wide range of abnormalities, mainly due to the involvement the basal parts of the brainstem and corticospinal tracts [1, 13]. 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 (event related potential=P300) in Behçet's patients without neurological manifestations [39]. The findings suggested that the delayed P300 measures and motor response time may reflect subclinical neurologic involvement.

Electroneuromyographic studies, as already mentioned have also shown a subclinical neuropathy in some patients who did not report symptoms suggestive of a neuropathy. Similarly clinically silent muscle involvement was reported in patients without overt muscle involvement, by electron microscopy [32]. Autonomic nervous system involvement was also reported in asymptomatic patients with BS [40]. On the other hand, subclinical CNS involvement was also detected by single photon emission computed tomography studies in some patients without prominent neurological problems [41–43].

The detection of abnormalities in 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 [44]. However, the clinical and prognostic value of detecting abnormalities in such diagnostic studies in this subgroup of patients is still not clear.

Neuropathology of NBS

The neuropathology of intra-axial NBS in the acute phase lesions is characterized by infiltration of mononuclear cells around small vessels, consisting of T lymphocytes and monocytes, but very few B lymphocytes, with most neurons undergoing

apoptosis [45]. Of note, neither fibrinoid necrosis nor infiltration of inflammatory cells in the vessel walls was noted, indicating that NBS is not strictly a cerebral vasculitis, but rather a perivasculitis [45–47]. However, fibrinoid necrosis was also reported to be observed in a few studies [48, 49]. In chronic progressive lesions of NBS, similar histopathological changes were noted in pons, cerebellum, medulla, internal capsule, and midbrain, although the degree of mononuclear cell infiltration was modest. There were also scattered foci of neurons undergoing apoptosis with formation of a few binucleated neurons [45]. It is suggested that soluble factors produced by infiltrating cells, including IL-6, might play a role in the induction of apoptosis of neurons in NBS. The most prominent feature of NBS at long-term remission for as long as 15 years, was atrophy of basal pons with formation of cystic or moth-eaten lesions, consisting of isomorphic gliosis with viable neurons although being in remission is not necessarily a prerequisite for these observations [45]. There were still scattered foci of perivascular cuffing of T lymphocytes and monocytes, emphasizing the common features throughout the course of NBS.

The most frequent CNS sites involved in NBS are the brainstem-diencephalic and pontobulbar regions. Koçer et al. suggested that the anatomic variability of venous structural arrangements at different levels of the CNS might explain this predilection [23]. On the other hand, arterial involvement resulting in CNS vascular disease is rare in BS [1]. Of note, the demonstration of the preservation of viable neurons within the parenchymal lesions with isomorphic gliosis in a patient with a long course of NBS renders unlikely the possibility that such lesions result from ischemia secondary to vasculitic involvement of arteries at least in some patients [45]. Rather, these findings suggest that a continuum of relapsing-remitting small attacks with perivascular cuffing of mononuclear cells might be taking place during the long disease course.

Neuroimmunology of NBS

CSF analysis findings, when available, usually show abnormalities including leukocytosis and an increase in protein concentration in most patients with intra-axial NBS [8–10]. More importantly, it has been shown that the concentration of IL-6 is markedly elevated in CSF from patients with acute NBS and chronic progressive NBS, correlating with the disease activity [2, 50]. Thus, CSF IL-6 was decreased when the disease activity was successfully suppressed [51]. Previous studies also demonstrated that proinflammatory cytokines, including IL-6, play important role in the neuron damage [52–54]. Accordingly, there has been a growing appreciation of the destructive potential of elevated levels of IL-6 in the CNS. IL-6 has been found to cause neuronal degeneration and cell death also in various other disorders [55]. It is therefore most likely that high amounts of proinflammatory cytokines, especially IL-6, might be important in the induction of neuronal apoptosis in NBS.

In another study in which serum and CSF levels of cytokines and chemokines were studied in NBS, multiple sclerosis, and other inflammatory and noninflammatory

neurological diseases, the authors pointed to the importance of chemokine effects in NBS CSF, and that this pattern resembled nonspecific inflammation compared to autoimmune disorders such as MS [56].

Diagnostic Studies in NBS

Neuroimaging

In BS patients with neurological problems consistent with intra-axial-NBS, cranial magnetic resonance imaging (MRI) is usually quite diagnostic. The lesions are generally located within the brainstem, extending to the diencephalon and/or basal ganglia (Figs. 6.2a–d and 6.3a–c). They are less often at the periventricular and subcortical white matter [23]. However, the pattern of parenchymal lesions can also be suggestive of a small vessel vasculitis, reminding us that the pathological changes in CNS involvement is not always typical in NBS. As discussed above a definite vasculitis is not observed in most cases. Brainstem lesions with extension into the diencephalic and basal ganglia region in the acute phase of the disease may disclose mass effect due to vasogenic edema and therefore may resemble tumors. A number of tumefactive lesions confused with primary or metastatic tumors have been reported but only a few were located elsewhere from the brainstem and deep hemispheric structures, such as the frontoparietal lobe, temporal lobe, or cerebellum in the cerebrum [13, 57]. Spinal cord involvement is not common, but when seen the major site to be involved is the cervical cord, with a myelitis-like lesion continuing more than two segments sometimes mimicking neuromyelitis optica (NMO), with the lesion extending to the brainstem. Gadolinium enhancement of the lesions, subsequent resolution of these lesions, and thoracic cord involvement have also been reported.

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 likely to be prominent in the postcapillary venules. Therefore cerebral arteriography is not a priority in NBS, as well as in cases with extra-cerebral vascular involvement. It should be kept in mind that more than a neutrophilic infiltration with arterial injury may occur at the site of arteriographic puncture in patients with BS. Recently a fatal rebleeding during the arterial injection of the contrast medium was reported in a Behçet patient with a basilar artery aneurysm [58]. 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 noninvasive studies, further investigation of the aneurysm may be done by multi-slice computed tomography, which is known to be a sensitive diagnostic tool [58].

MR-venography (MRV) is the preferred imaging modality to diagnose or confirm CVST in BS, and T1&T2-weighted images also may disclose the venous sinus thrombosis (Fig. 6.4).

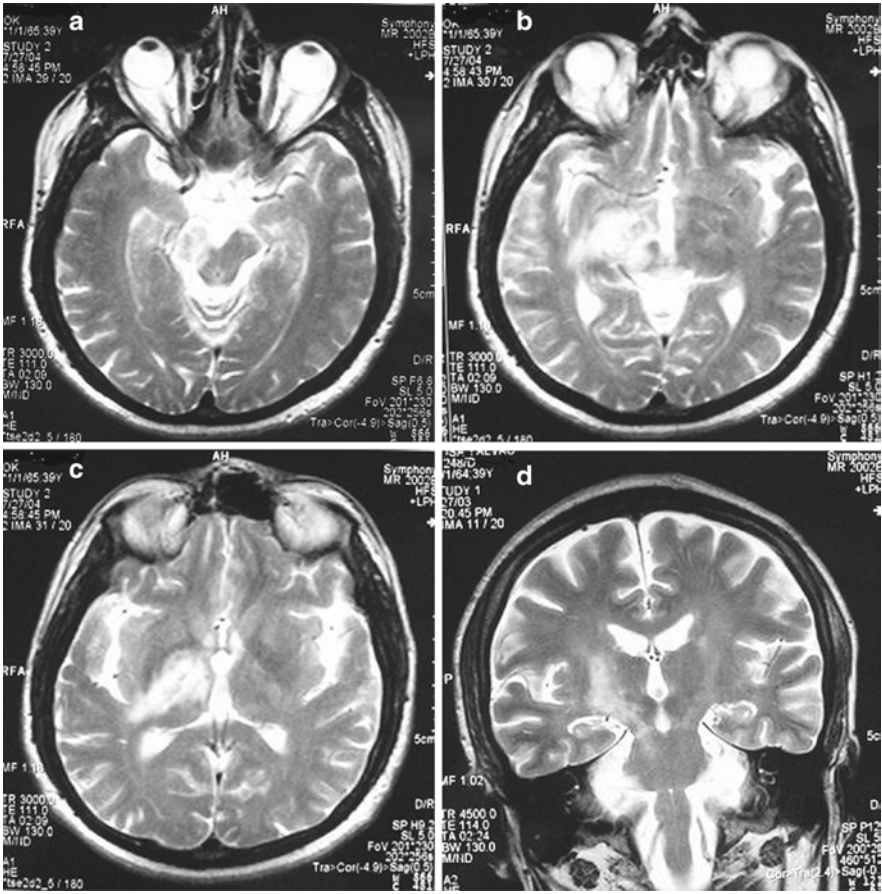


Fig. 6.2 a–d: Axial (a, b and c) and coronal (d) T2W-MR images showing an inflammatory lesion in the right meso-diencephalic region extending toward the basal ganglia in a patient with neuro-Behçet’s Syndrome

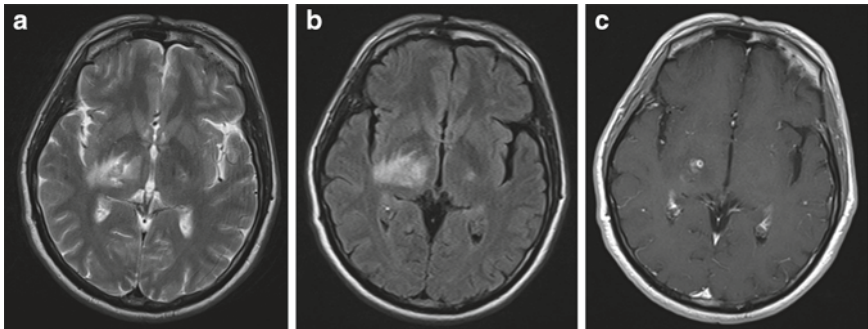


Fig. 6.3 a–c: Axial cranial T2 (a) and Flair (b) images showing an active-contrast enhancing lesion (T1 Gadolinium image, c) in the right deep hemispheric structures extending from the brainstem to the basal ganglia, posterior internal capsule and thalami of a male patient with intra-axial neuro-Behçet’s Syndrome



Fig. 6.4 A T2-weighted image showing thrombosis of the posterior part of the superior sagittal sinus thrombosis in a patient with extra-axial neuro-Behçet's syndrome

Cerebrospinal Fluid

During the acute stage, CSF examination usually shows inflammatory changes in most cases of intra-axial NBS with increased number of cells (up to a few hundred cells per ml) and modestly elevated protein levels [13]. Besides, as already mentioned markedly elevated concentrations of IL-6 in the CSF of patients with both acute and chronic progressive NBS in relation to disease activity can be found [2]. Oligoclonal bands may be seen but this will be an infrequent finding, seen in about less than 20% of cases. CSF in patients with CVST may be under increased pressure, but the cellular and chemical composition is usually normal.

Differential Diagnosis

Differential Diagnosis of Intra-axial (Parenchymal) NBS

Patients with NBS are young and frequently present with a 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 [17] (Table 6.2).

Table 6.2 The differential diagnosis of intra-axial (CNS) neuro-Behçet's syndrome*Neurologic diseases*

Multiple sclerosis
 Stroke in young adults
 Primary CNS vasculitis
 Primary CNS lymphoma
 Brainstem glioma

Systemic diseases with neurologic involvement

Connective tissue diseases and systemic vasculitides with CNS involvement
 Neuro-sarcoidosis
 CNS-tuberculosis
 Vogt–Koyanagi–Harada syndrome
 Reiter syndrome
 Eales' disease
 Cogan's syndrome
 Susac syndrome
 Sweet syndrome

Optic neuritis, sensory symptoms, and spinal cord involvement, which are common in MS, are rarely seen in NBS. However, sometimes the clinical presentation of NBS may be confused with MS, but the MRI findings are clearly different. MS has more discrete and smaller brainstem lesions in contrast to the large extensive lesions of NBS. The supratentorial, periventricular ovoid lesions and corpus callosum involvement are more prominent in MS compared to the small, bi-hemispheric, and subcortical lesions of NBS [1, 17]. Spinal cord involvement is unlikely to extend more than two vertebral segments in MS, whereas more extensive lesions are reported in NBS, similar to NMO. The CSF also reveals different patterns, with a more prominent pleocytosis and low rate of positivity for oligoclonal bands in CNS-NBS (Table 6.3).

An acute stroke-like onset is not common in NBS, and MRI lesions within the classical arterial territories are also not expected. The absence of systemic symptoms and signs will serve to differentiate the primary CNS vasculitis from NBS, and the difference in some of the systemic symptoms and signs, as well as the MRI findings and specific blood tests from the secondary CNS vasculitides.

Sarcoidosis can be confused with BS 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 nodes on chest X-ray, as well as the presence of noncaseating granulomatous lesions in biopsy specimens in sarcoidosis help in the differential diagnosis.

Tuberculosis may resemble BS because of its multisystem involvement and for its potential to affect the nervous system. Hilar lymphadenopathy and pulmonary cavities are not expected in BS, and the mucocutaneous manifestations of BS are unusual for tuberculosis. Furthermore the cellular and biochemical constituent of CSF and the MRI findings are likely to be different brainstem or hemispheric tumors and primary CNS lymphoma may be included in the differential diagnosis

Table 6.3 The differential diagnosis of multiple sclerosis and intra-axial (CNS) neuro-Behçet's syndrome

	Multiple sclerosis	CNS-neuro-Behçet's syndrome
Gender	Female > male	Male > female
<i>Symptoms at onset</i>		
Common	ON; sensory; spinal cord; brainstem/INO; motor; cerebellar	Headache; motor; cerebellar; brainstem
Uncommon	Headache; brainstem	ON; sensory; spinal cord; brainstem/INO
<i>MRI</i>		
PV&SC lesions	(+++)	(±)
Brainstem lesions	Small, discrete, extension (-)	Large, diffuse, extension (+)
Spinal cord lesions	(++)	(±)
<i>CSF</i>		
Inflammatory changes	(±)	(++)
OCB (+)	>90%	<20%

From ref. [17]

CNS central nervous system, MRI magnetic resonance imaging, CSF cerebrospinal fluid, OCB oligoclonal bands, ON optic neuritis, BS brainstem, IN internuclear ophthalmoplegia, PV Periventricular, SC subcortical

of NBS in patients who present with space occupying lesions on their MRIs, but the presence of systemic findings and the resolution of the MRI lesion following high-dose steroids that will remain without expanding and/or enhancing on follow-up imaging studies will help to distinguish NBS from brain neoplasia.

Due to the presence of eye disease 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 included in the differential diagnosis of NBS, too. However, a complete ophthalmologic examination will reveal the true nature of eye involvement in each of these syndromes, which will have differences from the eye involvement seen in BS [17].

"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's disease are episcleritis and conjunctivitis rather than uveitis. HLA-Cw1 and B54 association has been reported for SD compared with the high frequency of HLA-B51 in BS [59, 60]. 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 isn't a true vasculitis [59, 60].

Gastrointestinal symptoms in BS may mimic Crohn's 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's disease with its gastrointestinal and various nervous system symptoms may also resemble BS.

Prognosis

Neurological involvement in BS is an important cause of morbidity. Approximately 50% of NBS patients are moderate-to-severely disabled after 10 years of disease [10]. Onset with cerebellar symptoms and a progressive course were found to be unfavorable factors, while onset with headache, a diagnosis of CVST, and disease course limited to a single episode were favorable [1]. An elevated protein level and pleocytosis in the CSF were also reported to be associated with a poorer prognosis [8].

Treatment

Neurological involvement in BS is heterogeneous and it is difficult to predict its course, prognosis, and assess response to treatment. Therefore, it is not possible to reach a conclusion on the efficacy of any treatment unless properly designed studies are carried for each form of NBS. However, this is difficult to accomplish, as numbers of new NBS cases seen yearly are limited even in large centers. Currently, we have no first-rate 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, but the effect is short-lived and they do not prevent further attacks or progression. Acute attacks 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 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 2–3 months in order to prevent early relapses [61, 62].

Intra-axial NBS: Long-term Treatments

Colchicine, azathioprine, cyclosporine-A, cyclophosphamide, methotrexate, chlorambucil, immunomodulatory agents such as interferon- α and thalidomide have been shown to be effective in treating some of the systemic manifestations of BS; however, none of these agents have been shown to be beneficial in NBS in a properly designed study [30, 61–63]. Cyclosporine was reported to cause neurotoxicity or to accelerate

the development of CNS symptoms and therefore its use in NBS is not recommended [64–66]. The common clinical practice is to add an immunosuppressant drug, such as azathioprine or monthly pulse cyclophosphamide to glucocorticoids in progressive NBS cases, but the efficacy of such a combination has not been proven. Although limited to a small case series in an open study with long-term follow-up of 4 years, low dose methotrexate (5–15 mg/weekly) was reported to have some beneficial effect in patients with chronic progressive NBS and the beneficial effect was reported to be correlated with the decreased CSF IL-6 concentrations [67].

Successful treatment of neurologic manifestations of BS with monoclonal anti-TNF alpha antibody (infliximab) in a few patients has been recently reported [68–73]. 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 should be kept in mind. Mycophenolate mofetil and tacrolimus 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. Data on the use of intravenous immunoglobulin and 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 [21].

Treatment of CVST in NBS

There is no consensus on the treatment of CVST in NBS. Some authors use a combination of anticoagulation with glucocorticoids [4, 14, 61], while others administer glucocorticoids alone [15]. As BS patients with CVST are more likely to have also systemic large vessel disease including pulmonary and peripheral artery aneurysms, anticoagulation should be considered only after such possibilities are ruled out to avoid the possibility of fatal bleeding [74]. However, in a recently reported large series of patients with CVST (extra-axial NBS), who were treated successfully with anticoagulation no serious side effects were observed [14], recurrence of CVST is uncommon after the initial episode.

EULAR (European League Against Rheumatism) Recommendations for the Treatment of NBS

According to the recently published EULAR recommendations for the treatment of Behçet's Disease, 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 [74].

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