Neuro-Behçet's disease: epidemiology, clinical characteristics, and management

Adnan Al-Araji, Desmond P Kidd

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Neurology Department, University Hospital of North Staffordshire, Stoke-on-Trent, UK (A Al-Araji FRCP)**; and Department of Clinical Neurosciences, Royal Free Hospital, London, UK** (D P Kidd FRCP)

Correspondence to: Adnan Al-Araji, Neurology Department, University Hospital of North Staffordshire, Stoke-on-Trent, ST4 7LN, UK
adnanalaraji@yahoo.com

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Behçet's disease (BD) is a multisystem relapsing inflammatory disorder of unknown cause. In neuro-BD (NBD), the CNS can be involved in one or both of two ways: first, and most commonly, through the development of an immune-mediated meningoencephalitis, which predominantly involves the brainstem, but can also involve the basal ganglia, thalamus, cortex and white matter, spinal cord, or cranial nerves; and second, as a consequence of thrombosis within the dural venous sinuses. Headache is a common symptom in BD and does not necessarily indicate CNS involvement. Peripheral nervous system involvement is rare. New treatment options have recently become available, which have led to an improvement in morbidity after meningoencephalitis. Most of the reported studies on NBD are retrospective. Collaborative prospective studies of the natural history of the disease, particularly the nature and treatment of progressive neurological disease, and evidence-based studies of treatment are needed.

Introduction

Behçet's disease (BD) bears the name of a Turkish dermatologist, Hulusi Behçet, who described the triad of recurrent oral and genital ulcers and uveitis in 1937.[1] BD is a multisystem disease of unknown cause in which an inflammatory perivasculitis can arise in almost any tissue.[2,3] The highest incidence of BD is in the Middle East, the Mediterranean basin, and the Far East regions, but it is rare in Europe and North America. The nature and prevalence of the various systemic features are summarised in table 1.[4] The most widely accepted criteria for the diagnosis of BD are the International BD Study Group criteria (panel 1).[5]

Neurological involvement is one of the most serious causes of long-term morbidity and mortality in BD.[6] Although BD is rare in neurological practice in most countries, it is commonly mentioned in the differential diagnosis of inflammatory or demyelinating CNS diseases. In this Review, we summarise and describe the current understanding of the various neurological aspects of BD with a special emphasis on practical aspects of the diagnosis and management of neurological complications.

	Frequency	Comments
Oral ulcers	97–99%	..
Genital ulcers	~85%	..
Genital scar	~50%	More common in men
Papulopustular lesions	~85%	..
Erythema nodosum	~50%	..
Pathergy reaction	~60%	Predominantly in Mediterranean countries and Japan
Uveitis	~50%	..
Arthritis	30–50%	..
Subcutaneous thrombophlebitis	25%	..
Deep vein thrombosis	~5%	..
Arterial occlusion (aneurysm)	~4%	..
Epididymitis	~5%	..
Gastrointestinal lesions	1–30%	More common in Japan

*Adapted from Yazici et al,[4] with permission from Nature Publishing Group.

Table 1: **Clinical manifestations of Behçet's disease***

Epidemiology

Over the past 15 years, increasing numbers of patients have been reported in different series that have described the various clinical and epidemiological features of neuro-BD (NBD). Table 2 summarises the findings of these reports.[7–25]

The frequency of neurological involvement in BD is very variable; in hospital-based series, percentages as low as 1·3%[26] and as high as 59%[10] have been reported, but are likely to be biased for various reasons (eg, study design, definition of neurological involvement, ethnic or geographic variation, availability of neurological expertise and investigations, and treatment protocols). In a two-decade retrospective study of 387 patients with BD in Turkey,[6] the frequency was 13% in men

Panel 1: **International Behçet's Disease Study Group criteria for the diagnosis of Behçet's disease[5]**

For diagnosis, patient must have had the following symptoms:

Recurrent oral ulceration—minor aphthous, major aphthous, or herpetiform ulceration observed by physician or patient that recurred at least three times in one 12-month period

Plus two of the following:

Recurrent genital ulceration—aphthous or scarring, observed by physician or patient

Eye lesions—anterior uveitis, posterior uveitis, or cells in vitreous on slit lamp examination; or retinal vasculitis observed by ophthalmologist

Skin lesions—erythema nodosum observed by physician or patient, pseudofoliculitis, papulopustular lesions; or acneiform nodules observed by physician in post-adolescent patients not on corticosteroids

Positive pathergy test—read by physician at 24–48 h

Findings applicable only in the absence of other clinical explanations.

and 5·6% in women. Neurological involvement occurred in 5·3–14·3% of patients in three prospective studies from Turkey,[27] Iran,[28] and Iraq,[19] which looked specifically at the frequency in multidisciplinary centres with special interest in BD. The pooled average was 9·4% (43 of 459).

NBD was reported 2·8 times more often in men than in women by the studies included in table 2.[7–25] This high ratio of men to women was seen in nearly all the reports, although these findings have not been shown in three reports on western European patients[22–24] and one report from Korea.[15] Men with BD were at greater risk for morbidity and mortality than were women in a long-term outcome study.[6]

The age of onset of NBD is usually 20–40 years. Special caution needs to be applied in diagnosing NBD above the age of 50 years; exclusion of more common neurological disorders, particularly stroke and non-specific changes in white matter on cranial MRI, is very important.

Neurological complications can occur in children; however, the prevalence of such complications is difficult to ascertain from the available reports, mainly because of the small numbers of patients and the lack of clear details and definition of the neurological findings. The

	Country (region)	Number of patients (male/female)	Mean age at onset (years)		Mean duration (years)		Number of patients with NBD		
			BD	NBD	BD	NBD	P-NBD	NP-NBD	Other
Hentati et al[7]	Tunisia	75† (61/14)	31	34	..	..	62 (estimated)	3 IH	10 meningitis
Bohlega et al[8]	Saudi Arabia	52 (42/10)	27/22‡	..	..	2·8	36	12 CVT, 3 strokes, 1 aneurysm	2 patients with CVT had P-NBD
Nakamura et al[9]	Japan (Sapporo)	21 (12/9)	39·8§	..	..	..	21	0	..
Farah et al[10]	Kuwait	24	33·3 (for 41 patients with BD)	..	4·6‖	..	8	10 CVT, 1 IH, 3 strokes	1 trigeminal neuralgia, 1 behavioural changes
Kidd et al[11]	UK	50 (31/19)	..	..	..	3**	37	2 CVT, 2 IH	4 meningitis, 5 cranial neuropathy
Akman-Demir et al[12]	Turkey (Istanbul)	200 (155/45)	25·8	31·5	..	3·5‖	162	20 CVT, 14 IH, 3 arterial involvement (1 vertebral dissection, 1 middle cerebral artery occlusion, 1 external carotid aneurysm)	1 meningitis
Al-Fahad and Al-Araji[13]	Iraq	40 (37/3)	..	29	2·7	..	26	11 IH	3 meningitis-like presentation
Siva et al[14]	Turkey (Istanbul)	164 (130/34)	26·7	32	5·3	2·97 (at last follow-up)	124	20 CVT	1 ON, 1 psychiatric, 18 indefinite
Lee et al[15]	Korea	21 (9/12)	..	35·1	..	..	21	0	..
Yücesan et al[16]	Turkey (Ankara)	39 (32/7)	28	34	..	..	33	2 CVT, 3 IH, 1 stroke	..
Lannuzel et al[17]	West Indies	7 (5/2)	..	35·5	..	4·9‖	4	1 CVT	Patient with CVT also had P-NBD, 2 PN (1 patient also had myositis)
Sbaï et al[18]	France	161 (78/31)††	..	32/31‡	..	8·1††	109	52 CVT	2 patients with CVT developed P-NBD later, 1 patient with P-NBD developed CVT later
Al-Araji et al[19]	Iraq	20 (14/6)	..	34·1	3·25	1·7‖	10	6 CVT	4 had both P-NBD and CVT
Turker et al[20]	Turkey (Samsun)	12 (10/2)	..	33	..	..	8 (estimated)	1 CVT, 2 IH	1 ON, 1 choroid plexus
Borhani-Haghighi et al[21]	Iran	18 (15/3)	..	34·7	..	..	12	4 CVT, 1 stroke	1 PN, 1 P-NBD and PN
Lo Monaco et al[22]	Italy	27 (7/20)	27·7	34·7	13	..	26	1 vascular	..
Barros et al[23]	Portugal	15 (8/7)	29·6	..	..	..	9	1 CVT	1 ON, 4 meningitis
Joseph and Scolding[24]	UK	22 (11/11)	..	30	..	12‖	17 (2 ON)	1 CVT, 1 IH	5 meningitis, 4 had overlap of P-NBD and NP-NBD at onset
Houman et al[25]	Tunisia	63 (46/17)	29·7	..	6·1¶	..	47	13 CVT, 1 IH, 6 strokes, 2 cerebral haemorrhages	4 PN, 13 psychiatric, 13 mixed P-NBD and cerebrovascular involvement
Total	..	1031 (2·8:1)	..	..	..	..	772 (74·9%)	183 CVT/IH (17·7%)	..

All studies were retrospective, except for Al-Araji et al,[19] which was prospective. BD=Behçet's disease. CVT=cerebral venous thrombosis. IH=intracranial hypertension. NBD=neuro-Behçet's disease. NP-NBD=non-parenchymal NBD. ON=optic neuropathy. P-NBD=parenchymal NBD. PN=peripheral neuropathy. ..=not available or not reported. *Studies included case series of NBD since 1993 that had seven or more patients and had sufficient demographic and clinical details. †Definite NBD only. ‡Males/females. §Not mentioned whether at onset of BD or NBD. ¶Before onset of neurological manifestations. ‖Duration of follow-up. **70% were followed for a median of 3 years. ††Data for patients with P-NBD only.

Table 2: **Demographic features and patterns of presentation of patients with BD and NBD (1993–2007)***

Panel 2: **Classification of neuro-Behçet's disease**

CNS

Parenchymal

- Brainstem
- Diffuse ("brainstem plus")
- Spinal cord
- Cerebral
- Asymptomatic ("silent")

Non-parenchymal

- Cerebral venous thrombosis: intracranial hypertension
- Intracranial aneurysm
- Extracranial aneurysm/dissection

Peripheral nervous system (relation to Behçet's disease uncertain)

- Peripheral neuropathy and mononeuritis multiplex
- Myopathy and myositis

Other uncommon but recognised syndromes

- Acute meningeal syndrome
- Tumour-like neuro-Behçet's disease
- Psychiatric symptoms
- Optic neuropathy

prevalence of neurological involvement was higher in juveniles than in adults in two studies[29,30] but lower in juveniles in a third study.[31]

Neurological manifestations commonly develop a few years after the onset of the other systemic features of BD; the mean duration between onset of BD and development of NBD ranged from 3 to 6 years in three major studies.[11,12,14] However, the first systemic symptoms of BD might coincide with neurological presentation. Four studies reported that neurological presentation preceded other systemic features of BD (~6% of patients).[12,13,24,32] In such cases, diagnosis can be difficult or delayed, especially in areas with low prevalence. Some cases might never develop mucocutaneous manifestations.[33]

Classification

The CNS is the major target of neurological involvement in BD. There are two categories of CNS involvement in BD that have been generally accepted (panel 2): parenchymal and non-parenchymal involvement.[8,11–14,19,22,25,34–36] In the parenchymal category, meningoencephalitis occurs, whereas in non-parenchymal NBD, vascular complications involving thrombosis within large veins and occasionally arteries occur. Involvement of parenchymal tissue either does not occur in non-parenchymal disease or occurs secondarily to the thrombosis. This clinicopathological classification has clinical, laboratory, neuroradiological, pathological, and prognostic characteristics. Patients with neurological complications of the systemic disease are defined as having NBD if the clinical syndrome is closely compatible with the neurological syndromes known to arise in the disease, after other causes, particularly infective and neoplastic, have been ruled out. Patients with BD who have headache without other neurological symptoms and signs or abnormalities on neuroimaging or in the cerebrospinal fluid (CSF) are not defined as having NBD.

Neuropathology

The neuropathology of parenchymal NBD in the acute phase involves meningoencephalitis with an intense inflammatory infiltration including polymorphs, eosinophils, lymphocytes, and macrophages, with areas of necrosis and apoptotic neuronal loss.[37] Intense inflammatory infiltration of small vessels can occur, but fibrinoid necrosis is not seen. NBD is therefore not a cerebral vasculitis (as blood vessel walls are not infiltrated and there is no evidence for endothelial cell necrosis); rather, it is an inflammatory perivasculitis,[37–39] although fibrinoid necrosis within small post-capillary venules has been reported.[40]

The structures within the brainstem, thalamus, basal ganglia, and white matter are all seen to be affected to varying degrees, which has been confirmed by MRI in patients. In the progressive phase, inflammatory infiltration remains, although immunohistochemical staining for lymphocytes and cytokines is less prominent.[37] Concentrations of interleukin 6 are persistently raised in the CSF, and axonal loss and gliosis are also seen at this stage.[37–39] These findings correlate with the striking atrophy seen on MRI, particularly in brainstem structures, in advanced stages.[15,41] In the rare case of aneurysm formation, an obliterative endarteritis of the vasa nervorum is seen in both peripherally located aneurysms and those found within the brain,[42] and is therefore related to spread of perivasculitis to the vasa nervorum. There is no evidence of fibrinoid necrosis in this circumstance either.[43]

Diagnosis

The diagnosis of neurological involvement in BD is done mainly by clinical means; the ancillary investigations noted below help to suggest alternatives, and especially infective complications of treatment, but there is no diagnostic test for NBD. In a patient with a clinical syndrome characteristic of systemic BD, with, for example, retinal vasculitis, orogenital ulceration, pathergy, and joint involvement, the presence of a sagittal venous sinus thrombosis or an inflammatory brainstem lesion is likely to be related to the underlying condition. Although the onset of disease might be heralded by the neurological syndrome, it is uncommon for BD to arise in the absence of systemic features. Thus, the signs of systemic disease in patients who present with neurological disorders compatible with BD are important.

No validated criteria for the diagnosis of NBD exist. Whether diagnostic criteria would help to reduce the risk of incorrect diagnosis or failure to identify an infective complication, for example, is not clear. Diagnostic criteria are usually helpful to determine standards for research or treatment trials, but are less

helpful for clinicians faced with difficulty in diagnosis. Previous attempts at developing a set of criteria have not clarified the issue, and neither set has been validated.[7,14]

Blood tests

Erythrocyte sedimentation rate has been found to be associated with disease activity.[4] Blood count and biochemical screening is used to identify the nature and severity of the systemic disorder and to identify signs of a superimposed infective complication.

HLA type B51 has been reported to be present in 60–70% of Turkish and Japanese patients, although in only 10–20% of European patients.[4] Patients with HLA-B51 have a six-times increased risk of BD,[4] and the disease is usually more severe in such patients. HLA-B27-related disease also seems to exist. Anterior uveitis is more common in these patients, and the disease course might be less severe.

In the case of cerebral venous thrombosis (CVT), a thrombophilia screen should be undertaken. Early reports suggested a higher prevalence of anti-phospholipid antibodies and factor V Leiden mutations, but these findings have not been confirmed.[44,45]

CSF

CSF constituents are altered in around 70–80% of patients with parenchymal complications.[11–13] CSF protein is modestly raised in most cases, sometimes to over 1 g/dL,[11–14] and oligoclonal bands are usually absent.[11,12,24] The CSF cell count is often prominently raised (range 0–400×10^6 cells/L) and there is usually a CSF neutrophilia in the early stages, replaced later by a lymphocytosis.

There are too few published studies on the relation between NBD and CSF cytokines from which to draw conclusions, particularly on whether abnormal cytokine populations exist that might have diagnostic use. One study from Turkey has shown a preponderance of CXC cytokines 2, 8, and 10, as well as increased concentrations of interleukins 12 and 17,[46] and increased CSF concentrations of interleukin 6 have been shown in patients with relapsing-remitting and progressive disease.[47–49]

Patients with CVT or intracranial hypertension have normal CSF constituents. However, in some series, up to 20% of patients present with coexisting parenchymal and vascular complications.[19,24,25]

MRI

The characteristic MRI lesion in parenchymal involvement is an upper brainstem lesion that extends into the thalamus and basal ganglia on one side (figure 1).[15,41] Bilateral lesions are less common, but do occur. Such lesions can be seen as hyperintense T2 lesions with enhancement and are often associated with oedema. These lesions diminish in size after treatment and can even disappear altogether on conventional low-strength MRI.[50] Patients with a more diffuse meningoencephalitis show hyperintense T2 lesions within the subcortical white matter of the temporal, frontal, and hypothalamic regions, but the scan might also be normal. The presence of MRI abnormalities and the degree of alteration to CSF constituents is correlated in such cases (Kidd D, unpublished).

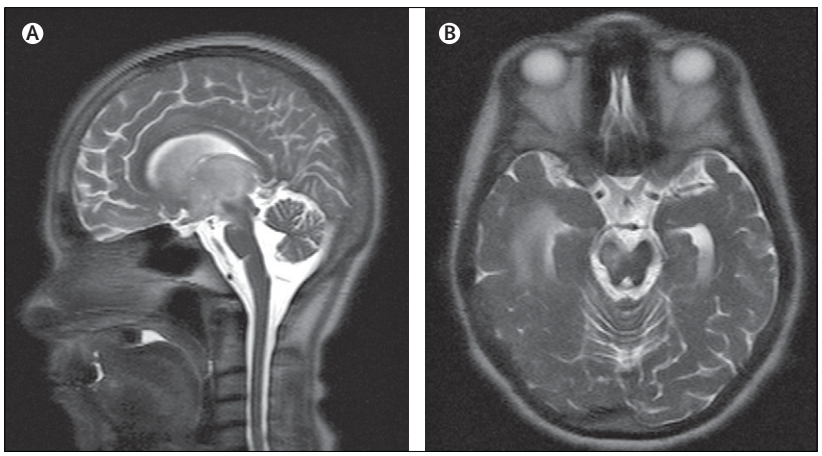

Figure 1: **MRI scans of a patient with ophthalmoparesis and hemisensory loss due to neuro-Behçet's disease**
(A) T_2-weighted sagittal MRI showing an inflammatory mass arising from the diencephalon. (B) T_2-weighted axial MRI after recovery. Evidence for residual lesion is shown, but there is also atrophy of the midbrain and cerebellum.

Diffusion-weighted imaging is useful in the case of stroke-like episodes in which an increase in the diffusion coefficient is seen, by contrast with restriction in diffusion, which would be seen if the lesion were due to cerebral infarction.[51,52] One study has attempted to define the extent to which the lesions of NBD are pathognomonic on MRI.[53] In the acute phase, most patients have single lesions; however, in the chronic phase, more widespread involvement is seen, which can make it more difficult to differentiate the condition from multiple sclerosis on radiological grounds.[53] The presence of atrophy of the brainstem in NBD can thus be used as a powerful discriminator.

Patients with spinal cord involvement show a single lesion, which might look like a demyelinating plaque, but might extend over two or three segments. Enhancement and surrounding oedema is also common. Brain MRI is usually normal if the clinical syndrome is isolated to the spinal cord.[54,55] Venous sinus thrombosis is readily seen on magnetic resonance venography (figure 2) and brain CT venography.[56,57] Patients who present with idiopathic intracranial hypertension have normal imaging studies.

Other diagnostic methods

Nerve conduction studies, electromyography, and evoked potentials, and their applications in the assessment of the disease, have specific uses if peripheral or neuromuscular involvement is suspected. In parenchymal involvement, electroencephalographic recordings show non-specific abnormalities in keeping with the presence

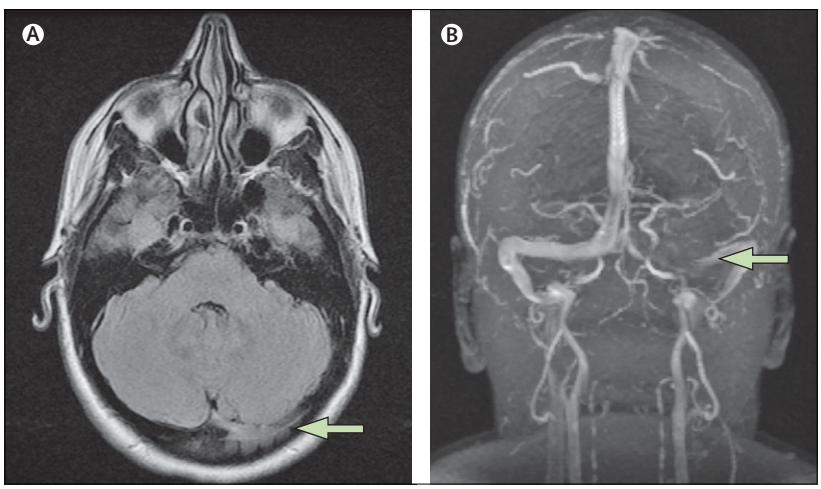

Figure 2: **Right-sided transverse venous sinus thrombosis in a patient with non-parenchymal neuro-Behçet's disease**
(A) Axial T_1-weighted MRI of lesion. (B) Magnetic resonance venogram of the same lesion.

of meningoencephalitis and should be used to help to differentiate NBD from acute viral encephalitis.

Single photon emission computed tomography (SPECT) has been studied in detail,[58] and abnormalities are commonly seen in patients with and without overt neurological involvement. These abnormalities involve asymmetries in metabolic function, often in the temporal regions. One study suggests that SPECT is a more sensitive indicator of neurological involvement,[59] but this investigation is not used in clinical practice.

Clinical characteristics

Parenchymal NBD

Subacute meningoencephalitis accounts for 75% of cases in parenchymal NBD (table 2). Onset is commonly subacute,[11–13] and often associated with exacerbation of the systemic features of BD, including fever, malaise, orogenital ulcers, skin lesions, or uveitis.[11,19,24,60] Headache is common before and during the attack. The symptoms and signs take a few days to reach a peak and last for several weeks, depending on the extent of the lesion and on how rapidly treatment is initiated. Less commonly, onset might be slower and occasionally cannot be determined with any certainty (eg, in the asymptomatic form). Spontaneous resolution even before initiation of therapy has been reported,[61,62] as has a progressive disease course.[11–13]

Different syndromes might be encountered during the course of parenchymal NBD (panel 2). First, symptoms and signs of brainstem involvement (figure 1) include ophthalmoparesis, cranial neuropathy, and cerebellar or pyramidal dysfunction. Second, in addition to the brainstem signs and symptoms, there is evidence for additional cerebral or spinal cord involvement. A subgroup of patients with a progressive form of the disease has been reported to present with a worsening subcortical dementia, usually accompanied by ataxia, and accounts for 10% of cases of NBD in Japan.[63] Third, symptoms and signs suggestive of cerebral hemispheric involvement include encephalopathy, hemiparesis, hemisensory loss, seizures, and dysphasia, and mental changes include cognitive dysfunction and psychosis. Fourth, symptoms and signs of spinal cord involvement include pyramidal signs in the limbs, sensory level dysfunction, and, commonly, sphincter dysfunction. Finally, asymptomatic (silent) parenchymal NBD is diagnosed if there are no neurological symptoms, but neurological signs on examination (usually pyramidal signs) for which there is no better explanation (eg, previous head injury, old perinatal brain damage, or underlying cerebrovascular disease).

Recognition of these clinical syndromes might help clinicians dealing with BD to predict the pattern of involvement. They might also help neurologists to remember BD in the differential diagnosis of a patient who presents with one of these neurological syndromes. In addition, other clinical syndromes might arise in BD, and although uncommon, it is important that these syndromes are recognised.

Stroke

Ischaemic stroke is uncommon in BD, and occurred in only 15 (1·5%) patients reported by the studies included in table 2. Although confirmed strokes are usually thought to be indicative of non-parenchymal NBD, stroke-like presentation in patients with BD more commonly indicates parenchymal involvement. In patients with BD with significant risk factors for cerebrovascular disease, care must be taken before considering whether a stroke is due to NBD. Diffusion-weighted MRI is helpful in differentiating between the two conditions, as discussed above.

Epilepsy

Epileptic seizures and epilepsy were reported as manifestations of NBD in 2·2–5% in large series.[13,14,64] Partial seizures were a presenting feature of NBD in one report,[65] and epilepsia partialis continua was reported in another.[66] Generalised seizures are the predominant type.[64] The relatively low prevalence of epilepsy in NBD is compatible with the low prevalence of cortical involvement seen on cranial MRI[41,67] and in neuropathological studies.[68,69] Seizures can of course arise in CVT, although this is uncommon, possibly because of the lower prevalence of haemorrhage in this complication.[57]

Brain tumour-like NBD

We could identify fewer than 15 patients with NBD in the literature who were initially thought to have brain tumours. The earliest was in 1987,[70] and the most recent was thought to have multiple metastatic tumours involving the pons and the left parietal cortex.[71] Matsuo and colleagues[72] have reported a case and reviewed previous reports. These are predominantly large lesions (figure 3), involving the commonly affected areas in

NBD (brainstem, diencephalon, basal ganglia, and internal capsule),[72–74] but occasionally can involve other areas, such as the frontoparietal lobe,[75] temporal lobe,[76] or cerebellum.[77] Most patients are known to have BD or are found to have BD symptoms and signs on further assessment. Most cases have been diagnosed after lesion biopsy, and respond to treatment with corticosteroids.

Movement disorders

Extrapyramidal manifestations are rare in most series of patients with NBD despite the common basal ganglia abnormalities on cranial MRI and in autopsy series.[41,54,67–69] Paroxysmal focal dystonia,[78] Parkinsonian syndrome,[79] and chorea have been reported,[12,24,29,80] and these usually arise alongside other manifestations of NBD.

Acute meningeal syndrome

Meningeal signs and symptoms are relatively common in parenchymal NBD.[11–13] The pathological process is one of meningoencephalitis, and the meninges are frequently involved in post-mortem studies.[68,69] However, isolated meningitis might only rarely be the presenting feature of NBD.[11,13] In such cases, care should be taken to exclude an infective meningitic process, particularly in patients who are on immunosuppressants (panel 3).

Optic neuropathy

Optic neuropathy is rare in BD, and was reported in only four (0·4%) patients in the studies included in table 2. However, there are many case reports in the literature.[81–85] Optic neuropathy occurs particularly around the time of systemic flare-up of BD. It can be bilateral and can be recurrent over many years. The severity of the visual loss and its recovery can be very variable, even in the same patient.[86] Clinical presentation and course most often simulates an optic neuritis.[82,85–88] Optic neuropathy can present as part of parenchymal NBD[81,89] or in isolation. It can be secondary to invasion of the optic nerve in retinal vasculitis[82] or as a consequence of destruction after glaucoma and uveitis. Early recognition and appropriate treatment might limit the degree of permanent visual loss, and there is usually a significant response to steroids, particularly if administered early.[86]

Spinal cord involvement

Isolated transverse myelitis is an uncommon presentation of NBD, whereas involvement of the spinal cord as part of the diffuse type of parenchymal NBD pattern is not. Spinal cord involvement was reported in about 10% of NBD cases in some series,[8,11,24,90] whereas 28% of autopsy cases of NBD showed spinal cord lesions.[54] The cervical and/or dorsal areas can be involved.[41,55,91,92] Patients with transverse myelitis are less likely to respond well to treatment than those with lesions elsewhere within the nervous system. Spinal cord involvement is thus a bad prognostic factor in parenchymal NBD.[90]

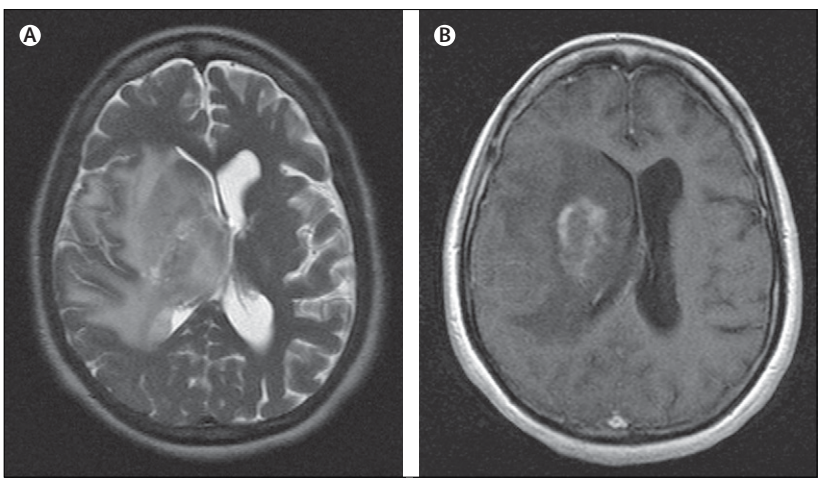

Figure 3: **Large tumefactive lesion involving the right hemisphere and causing mass effect and midline shift**
(A) T_2-weighted axial MRI. (B) T_1-weighted axial MRI after intravenous paramagnetic contrast agent showing enhancement of the lesion.

Panel 3: **Differential diagnosis of parenchymal neuro-Behçet's disease**

Infective causes
- Viral
- Bacterial, including tuberculosis
- Spirochaetal, including *Treponema pallidum* and *Borrelia burgdorferi*
- Fungal
- Progressive multifocal leukoencephalopathy

Uveomeningitic syndromes
- Sarcoid
- Systemic lupus erythematosus
- Sjögren's syndrome
- Vogt-Koyanagi-Harada syndrome

Multiple sclerosis

Neoplastic causes
- Carcinomatous meningitis
- Lymphoma
- Glioblastoma cerebri

Complications of other systemic diseases
- Uveomeningitic syndromes (as above)
- Sweet's syndrome
- Common variant immunodeficiency disease
- Inflammatory bowel disease
- Coeliac disease

Complications of treatment for Behçet's disease
- Drug-induced meningitis
- Infections with immunosuppression
- Lymphoma and secondary tumours
- Neurological complications of ciclosporin A treatment
- Neurological complications of anti-TNF treatment

Asymptomatic and subclinical neurological involvement

Clinical reports have described patients with BD with neurological signs but no symptoms.[12,19,27] Subclinical cranial MRI abnormalities are seen to involve white matter hyperintensities, predominantly in the periventricular or subcortical area, and, as in the general population, their clinical significance is not clear.[93–96]

The finding of subclinical abnormalities in the evoked potentials is more controversial. Some studies reported abnormalities in up to two-thirds of tested patients,[96–99] whereas others found no significant abnormalities compared with controls.[94,99] A recent retrospective Turkish study reviewed 22 patients identified previously with silent neurological involvement and found that some of this group (three of 22) went on to develop symptoms and signs of NBD over time, but that the clinical course was less severe, with low mortality and disability.[100]

Non-parenchymal NBD

Non-parenchymal NBD usually involves the main vascular structures of the CNS, and is sometimes referred to as vasculo-BD or vasculo-NBD. About a fifth of patients in large case series (table 2) had non-parenchymal disease. The nature and severity of the resultant clinical syndrome depends on the structure involved and the nature of the pathological process.

CVT

In 1959, Masheter[101] reported the first case of CVT in a patient with BD who presented with headache and bilateral papilloedema. CVT constituted about 18% of NBD cases in the studies included in table 2. It has been reported more frequently from some parts of the Middle East and France, where it constitutes about a third of the reported cases of NBD.[13,25,32,102–104] The prevalence of CVT is higher in patients who have had previous venous thromboses elsewhere.[56]

There is evidence for endothelial cell activation in BD with increased concentrations of serum markers of vascular endothelial cell injury (ie, Von Willebrand's factor, tissue plasminogen activator, and antithrombin III)[105] and a reduction in flow-mediated dilatation.[106,107] Homocysteine concentrations might also be raised.[107] Recently, increased concentrations of endothelial cell activated protein C receptor have been found, suggesting that the disorder might be related mainly to endothelial cell activation by vascular inflammation, and by a local enhanced prothrombotic tendency as a result.[108]

Clinical onset is subacute or chronic in most patients. Acute onset (<48 h) has been reported in about a third of patients.[12,57] Exacerbation of the other systemic features of BD was reported in a quarter of patients in one study.[57] The clinical findings are usually confined to symptoms and signs of intracranial hypertension. A false-localising sixth or, less often, third cranial nerve palsy might be encountered.[109] Less often, focal neurological signs might be encountered that could imply associated venous infarction or concomitant parenchymal NBD involvement.[19,57] Behçet's CVT is reported to affect men more often than women, occurs at an earlier age, and presents less often with an acute clinical onset and with focal deficits and seizures than in patients with CVT due to other causes.[110] A recent review of CVT in non-Behçet's patients showed wide-spectrum clinical manifestations, including isolated headache.[111]

Intracranial hypertension

Patients who present with symptoms and signs of intracranial hypertension, but without CT or MRI signs of CVT, have an idiopathic intracranial hypertension syndrome that is identical to that seen in patients without NBD.[112,113] Although these patients might also have CVT beyond the resolution of current imaging techniques, this has yet to be proven. Treatment is the same as for idiopathic intracranial hypertension (ie, without corticosteroids or anticoagulants).

Intracranial aneurysms

There were two (0·2%) possible cases of intracranial aneurysms in the studies included in table 2. Histopathological examination of cerebral aneurysms in a few patients with BD did not show features of vasculitis, which raises the possibility of a coincidental rather than a causative association with BD.[42,114] In a review of 14 reported cerebral aneurysms, the occurrence of certain angiographic features, such as a higher frequency of multiple aneurysms, a fusiform appearance, peripheral location, signs of vasculitis on the parent artery, atypical morphology, and disappearance with steroid therapy, as well as a predominance of men with the disease, has led to the conclusion that BD has some role in the formation of cerebral aneurysms.[42,115] A few cases of extracranial arterial aneurysms or dissection involving the carotid and vertebral arteries have been reported in patients with BD.[116–120]

Mixed parenchymal and non-parenchymal disease

The two major categories of CNS involvement (parenchymal and non-parenchymal) were previously believed to represent two different underlying pathological processes, and both were rarely reported to occur in the same patient in large retrospective reports.[12,14,18] In later studies, however, a mixed pattern was reported in four (20%) of 20 patients with NBD in a prospective study in which routine cranial magnetic resonance venography in addition to cranial MRI was done.[19] In British[11] and Tunisian[25] studies, overlap was reported in 18% and 20·6% of patients, respectively. Since CVT is also due to inflammatory activation, this overlap is not surprising, and will be studied prospectively in a large worldwide collaborative study.

Additional features in NBD

Psychiatric and cognitive disorders

Psychosomatic symptoms, such as anxiety and depression, are the most commonly encountered psychiatric symptoms in BD. These symptoms are mostly related to the underlying systemic disease, fatigue, functional deterioration, and sociological handicap, but are only rarely due to direct involvement of the CNS.[121] Earlier reviews revealed significant psychiatric manifestations in patients with BD with and without neurological involvement.[61,122–124] In recent years, behavioural changes were common, whereas major psychiatric symptoms were less common in large series.[11–14]

Cognitive impairment in patients with BD without neurological involvement has not been studied extensively. Two small studies showed frontal and temporal inefficiencies and fatigue-related concentration problems.[125,126] Psychiatric or cognitive symptoms might be the earliest presentation of NBD. Some patients with NBD might have a special pattern of cognitive decline, with impaired memory, attention, and frontal lobe functions, and poor motivation and personality change, by contrast with relatively preserved linguistic, arithmetic, visuospatial, abstraction, and problem-solving abilities.[127]

Headache

Headache is the most common neurological symptom in patients with BD, and occurs in about 70% of patients. Table 3 summarises data from studies of the prevalence and characteristics of headaches. The frequency of headache in BD was similar to the prevalence of headache in the general population in Turkey,[131] but was higher in two UK and Italian series.[129,132]

Headache due to direct neurological involvement accounts for about 10% of patients (table 3). Primary headache syndromes (eg, migraine and tension-type headache) affect about 50% of patients with BD, and account for 70% of all causes of headaches in BD (table 3). The characteristics of these primary symptoms in BD did not differ when compared with a headache clinic population,[130] but a questionnaire-based study reported a very high prevalence of visual and sensory aurae in those whose headaches were of migraine type.[129]

Three reports describe headaches that worsened with or were triggered by systemic BD flare-up or occurred with close temporal relation to the evolution of BD, but with no other findings to suggest direct CNS involvement.[128,130,131] The features of this headache varied between migraine, migraine like, and tension type. Uveitis was the cause of headache in a small proportion of patients (2·7%). Although it can be difficult to distinguish primary headache syndromes from more serious neurological involvement, careful assessment for other neurological symptoms and signs supported by the appropriate investigations should help the differentiation.

Peripheral nervous system involvement

We found eight (0·8%) cases of peripheral nervous system involvement in the series reviewed, but none from the major centres with special interest in NBD. Others reported one or more patients with BD with Guillain-Barré syndrome,[133] sensorimotor neuropathy,[134] mononeuritis multiplex,[134,135] autonomic neuropathy,[136] and subclinical nerve-conduction abnormalities.[137] Whether these conditions represent direct involvement due to BD pathological changes is uncertain.

Muscle involvement seems to be exceedingly rare in adults but more common in children.[138] Patients present with a myositis, occasionally localised, that can be detected by electromyography.[139] The rarity of these reports should encourage clinicians to investigate extensively for alternatives before accepting BD as the diagnosis.

Paediatric NBD

Few series have described the clinical manifestations of children with BD.[29–31] One of the largest included 10 patients with neurological involvement.[140] Three

	Country	Design	Number of participants	Headache (n)							No headache (n)
				Total of any type	Migraine with aura	Migraine without aura	Tension type	Due to NBD	Uveitis headache	Due to BD	
Borhani-Haghighi et al[128]	Iran	Case–control	180	117 (65%)	3 (1·7%)	46 (25·6%)	43 (23·9%)	15 (8·3%)	6 (3·3%)	4 (2·2%)	63 (35%)
Kidd[129]	UK	Questionnaire	327 responders	270 (82·5%)	197 (73%)	91 (30%)	4 (2%)	0	0	0	57 (17·5%)
Aykutlu et al[130]	Turkey	Case–control	118	97 (82·2%)	3 (2·5%)	42* (35·6%)	26‡ (26·8%)	32 (27·1%)	0	5 (4·2%)	21 (17·8%)
Saip et al[131]	Turkey	Cohort/historical control	228	151 (66·2%)	2 (0·9%)	32 (14%)	54 (23·6%)	12 (5·2%)	9 (3·9%)	42 (18·4%)	77 (33·8%)
Monastero et al[132]†	Italy	Case–control	27	24 (88·9%)	0	12 (44·4%)	8 (29·6%)	0	0	4 (14·9%)	3 (11·1%)
Total‡	..	..	553	389 (70%)	8 (1·5%)	224 (44%)	132 (24%)	59 (11%)	15 (3%)	55 (10%)	164 (30%)

BD=Behçet's disease. NBD=Neuro-Behçet's disease. *Eight patients also had secondary headaches (included patients with NBD). †Six patients also had secondary headaches (included patients with NBD). ‡Not including UK survey because of different methodology (mailed questionnaire rather than case–control study).[129]

Table 3: **Main findings of studies of prevalence and characteristics of headaches in BD**

children had CVT, and the others had parenchymal NBD features, meningitis, and peripheral neuropathy. Although not enough data are available to draw a clear picture, in general it seems that the neurological presentation is not markedly different from that in adults. Of note, however, CVT and intracranial hypertension were mentioned frequently.[29,141–143] Necrotising myositis seems more common in children than in adults, and seems to respond rapidly and well to steroids.

Management

There have been no controlled or comparative trials of treatment of any aspect of neurological involvement in BD. There is a consensus among neurologists with experience in the management of these disorders that, in most cases of inflammatory parenchymal disease, corticosteroids should be given as infusions of intravenous methylprednisolone followed by a slowly tapering course of oral steroids. It is important to avoid an abrupt cessation of therapy to avoid early relapse. Whether immunosuppressive agents or tumour necrosis factor (TNF) antagonists should be used at the same time or later depends on the nature of the disease, its severity, the response to steroids, and whether the patient has had previous attacks. In general, patients with brainstem lesions or lesions within the hemispheres do well on steroids and make a good recovery. Retrospective studies suggest that only a third of patients relapse or develop a progressive disease course.[11–14]

Piptone and colleagues have reported a series of eight patients and reviewed earlier case reports of four patients who received infliximab for NBD.[144] Of these 12 patients, only four had relapsing or unresponsive disease. The remaining eight were treated immediately with infliximab, and although early resort to this treatment could be thought of as heavy handed, there is certainly evidence in the other four cases for an improvement when other immune suppressive agents had failed.

Our own treatment plan is to use steroids alone for the first attack and to monitor patients closely thereafter. If the systemic disease requires further treatment (except perhaps in the case of ciclosporin A in the treatment of uveitis), then it is given, although we do not use immunosuppressive therapy until the second attack occurs, unless there is a slow response to treatment or if it is clear from the outset that the disease is aggressive. A gentle oral immunosuppressant, such as azathioprine, mycophenolate mofetil, or methotrexate, is added and the patient observed closely. Whereas previously we believed that there was a role for interferon-alfa 2a, we would now recommend that patients should move on to TNF antagonists earlier with aggressive disease or disease that responds poorly to steroids, or if relapse is not prevented by regular immunosuppression.

Patients with spinal cord lesions do not seem to recover well, and it is not yet known whether early recourse to intravenous immunosuppression or biological agents is worthwhile. Evidence from one centre suggests that oral weekly methotrexate can slow down the rate of progressive neurological disease in association with a reduction in CSF interleukin-6 concentration.[145] This study has not been replicated, and there have been no other investigations of the pathophysiology of progressive disease in NBD.

Rheumatologists and ophthalmologists might become involved in management of NBD because the choice of immunosuppressive agent might be influenced by the severity of the systemic disease. However, even in systemic disease, only a small number of randomised placebo controlled trials have been done.[4,146] Colchicine and oral TNF antagonists such as thalidomide and pentoxifylline are useful for mucocutaneous features of systemic disease, but would be effective only as an adjunct therapy for neurological involvement.

Similarly, no treatment trial has been undertaken in CVT. Some neurologists do not use anticoagulants at all, choosing instead to give steroids and immunosuppressants alone.[110] The rationale, as noted above, is that venous thrombosis occurs as a result of endothelial cell activation through inflammation, and that there is a low prevalence of thromboembolism in the case of deep vein thrombosis.[56] Other neurologists prefer to use anticoagulants, but recent data show that immunosuppressants are underused, because the mechanisms of venous thrombosis in BD are still poorly understood (Kidd D, unpublished). Whether reduction in plasma homocysteine concentrations improves endothelial cell dysfunction and reduces the risk of CVT or venous thrombosis elsewhere is not known.[107] Our recommendation is to use anticoagulants, once the presence of pulmonary artery aneurysm has been ruled out, as well as immunosuppressants, to treat the disease but also to prevent extension of the thrombus within the cerebral venous system. Evidence for the best treatment of CVT is clearly still required. As patients recover, they should be referred for rehabilitation to appropriate hospital-based and outpatient facilities.

Ciclosporin A is commonly used for severe ocular BD, although it is well known to be potentially neurotoxic.[147] Three case–control studies have reported more neurological manifestations in patients with BD who have received ciclosporin A than in those who did not.[148–150] Because patients with more severe ocular disease are at greater risk of developing neurological complications, the reports might show an inherent selection bias. Whether these neurological manifestations are due to usual NBD and/or ciclosporin A toxicity is not currently known.

Clinical course and prognosis

Most patients who have an acute parenchymal inflammatory episode recover well after steroid treatment. Retrospective series from 10–15 years ago reported a mean of 20–30% of patients with residual

neurological impairments,[12,14] and a high 10-year mortality of 10%. Around a third of patients have single episodes, a third have repeated relapses with remission, and a third undergo a progressive disease course with accrual of neurological impairments.[11–14] A primarily progressive disease course has been observed in one series.[12] There are no published prospective studies of the natural history of neurological complications in BD, although one is underway in the UK.

Adverse prognostic factors include a progressive disease course, frequent relapses, and residual neurological impairments in remission. Patients with brainstem and spinal cord lesions recover less well, and those with more abnormal CSF indices have a worse prognosis.[11–13] Patients with silent neurological involvement tend to progress to have clinically apparent neurological involvement,[12,19] but with a low risk of impairment.[100] Patients with venous sinus thrombosis and intracranial hypertension tend to recover well with appropriate and prompt treatment, with a low risk of recurrence. Whether these patients are at a greater risk of the development of inflammatory neurological complications than others with systemic BD is not known.

Conclusions and further perspectives

Over the past 10 years, our understanding of the clinical features and pathophysiology of neurological complications in BD has increased substantially due to the simultaneous interest of clinical researchers around the world. We have reviewed the current understanding of the nature, pathogenesis, and management of NBD. Parenchymal complications arise due to a meningoencephalitis that might occur in the brainstem, cerebral hemispheres, spinal cord, or cranial nerves. Diffuse and progressive forms of the conditions also exist. Isolated aseptic meningitis is rare but is a common aspect of meningoencephalitis. Vascular complications due to CVT are less severe and carry less risk of associated morbidity than CVT in other patient groups. Psychiatric disorders are common and associated more with the systemic disease itself than any neurological complication, and headache is a common manifestation with and without meningoencephalitis.

Search strategy and selection criteria

References for this Review were selected by a PubMed search of English language publications and covered the period from 1946 to November, 2008, by use of the terms "Behçet's", "Behçet's disease", "Behçet's syndrome", and "neuro-Behçet's". Further articles were identified from the references cited in those articles. Abstracts were reviewed, and when relevant findings were reported, the full article was retrieved and reviewed. We also identified articles from our personal knowledge of the subject and from our own files.

Most of our information on NBD is based on retrospective data. Prospective and controlled studies are difficult to undertake for such an uncommon disease. The establishment of multicentre collaborative and prospective studies of the natural history, pathogenesis, and immunopathology of the disease, and the design and execution of controlled treatment trials will greatly enhance our understanding of the disease.

Contributors

AA-A initiated the project, developed the framework for the Review, and summarised the data. Both authors contributed to the writing, editing, and agreed on the final version of the manuscript.

Conflicts of interest

We have no conflicts of interest.

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