Neurological involvement by Behçet’s syndrome: clinical features, diagnosis, treatment and outcome

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ABSTRACT

Neurological involvement in Behçet’s syndrome arises predominately through an inflammatory meningoencephalitis characterised by perivenular inflammation due to activation of Th-17 immunological pathways. The brainstem is involved in 50% of cases, the diencephalon and other areas of the brain in 30%, and the spinal cord in 10%. Movement disorders and epilepsy may occur. Psychiatric syndromes may arise with brain and brainstem involvement, and cognitive disorders relate to the brain disease, to circulating inflammatory factors, and to fatigue and despondency. Eighty per cent of cases begin with a relapsing disease course, of whom 70% have only one attack, and 30% have a progressive disease course either from onset or following an initially relapsing course. Venous thrombosis leading to intracranial hypertension and cerebral venous infarction is less common and caused by inflammation in affected veins and a circulating prothrombotic state. Arterial involvement is rare and relates to an arteritis affecting large-sized and medium-sized vessels within the brain leading to infarction, subarachnoid and parenchymal haemorrhage, aneurysm formation and arterial dissection. There is a newly recognised disorder of cerebral cortical hypoperfusion. Cranial neuropathy, peripheral neuropathy and myositis are rare. There has been significant progress in understanding the pathophysiology and treatment of the systemic disease, leading to improved outcomes, but there has been no randomised trial of treatment in the neurological disorder.

INTRODUCTION

Behçet’s syndrome is an autoimmune disorder of unknown cause in which an inflammatory perivasculitis arises within the mucous membranes of the oropharynx, gastrointestinal tract and genital regions. Inflammation of veins leads to thrombosis and inflammation of arteries leads to vasculitis and aneurysm occurs. Ocular and neurological manifestations have the most severe consequences.

The incidence is greatest in the countries that formed the Silk Road network of trading routes between China and Europe in the 2nd–14th centuries CE. The disease presents in the 3rd–5th decades of life and lessens in severity in the seventh. Although its incidence is the same among men and women, it is overall a more severe disease in young men. The syndrome complex noting a relationship between iritis with hypopyon and orogenital ulceration was first characterised by the dermatologist Huluci Behçet in 1937, although it had been described previously by others, including the Greek ophthalmologist Adamantiades and notably Hippocrates of Kos.

Diagnostic criteria

Behçet’s disease varies greatly in its presentation and severity and there is no diagnostic test or biomarker. This has led to difficulty in creating sensitive and reproducible diagnostic criteria; in essence, it can only be diagnosed faithfully by someone who has experience in identifying and managing the disease. The International Study Group for Behçet’s Disease criteria (box 1) was considered to have sensitivity and specificity. New criteria have a higher sensitivity but a lower specificity. More helpful is the concept of ‘features helpful in the diagnosis of Behçet’s syndrome’ discussed by Yazici et al. in which the pattern of dermatological involvement, vascular complications and eye and neurological disease in the presence of a systemic disease characterised by orogenital ulceration allows greater confidence in diagnosing and treating the disease.

Epidemiology

Behçet’s disease is most prevalent in countries occupying the Mediterranean coast,
the Middle East, China, Japan and south east Asian countries; in Turkey as high as 420 per 100 000 population, in Iran 80 per 100 000 and in Japan 12 per 100 000.5–7 In European countries, the prevalence is less but probably increasing owing to a greater understanding of the disease; studies in France, Germany and the Netherlands show a prevalence of 2–3 per 100 000 in those of European ancestry and 20–78 per 100 000 in those whose families have immigrated from areas of higher incidence.4

Immunopathogenesis
The cardinal feature of Behçet’s disease is an activation of neutrophils, associated with enhancement of helper Th17 immune responses leading to chemokine release and activation of NKT and γδT cell and Th-17 cell responses.8 An ‘MHC-1-opath’, in which abnormal environmental barrier function (at the skin and mucous membranes in Behçet’s syndrome) allows a T cell response leading to neutrophilic inflammation,9 is common to other HLA-associated conditions such as ankylosing spondylitis and the arthritis associated with inflammatory bowel disease and psoriasis. Possession of the human leucocyte antigen HLA B-51 confers an OR of 5.90 for developing the disease and there is a correlation between the prevalence of B-51 in the general population and the incidence of the disease.10–12

Changes to the microbiome of the oropharynx and gut with colonisation of streptococcus and other bacteria may exert a stimulating role on activation of the disease13 14; indeed, there are T cell responses to heat-shock proteins of bacteria including Streptococcus species and Mycobacterium tuberculosis.15 16

Clinical features of the systemic disease
About 98% of cases have aphthous ulceration of the mucosa of the side and dorsal surface of the tongue, the lips, cheek and oropharynx.17 It is painful and often associated with an increase in constitutional symptoms. Genital ulcers occur in 75%, are painful and large and affect the vaginal mucosa and labia, and the skin of the scrotum and penis. Scarring often develops, and loss of tissue leading to pharyngeal and vaginal constriction may occur. Ulceration of the gut from oesophagus to rectum may arise; an ileocaecal ulcer is characteristic but most features seen endoscopically cannot differentiate from other inflammatory bowel diseases.18 The prevalence of gastrointestinal involvement is greater in south east Asian than Mediterranean populations.5

The skin is involved in 85%; most have acneiform papulopustular lesions of the arms, legs and chest. Erythema nodosum arises in 50%, and pathergy is more common in Mediterranean and south-east Asian populations than Europeans; its prevalence is thought to be decreasing, possibly related to improved hygiene. When pathergy occurs, it is considered to be both sensitive and specific for Behçet’s syndrome, although it may occur in other inflammatory disorders. However, the utility of formal testing with needle prick is uncertain. Ocular inflammation leads to a relapsing non-granulomatous anterior uveitis and pan-uveitis, less commonly a retinal vasculitis leading to ischaemia, glaucoma and irreversible sight loss. Rheumatological involvement is common but non-destructive; a relapsing oligoarthropathy of large joints occurs in 50%, and widespread aching and joint pain is a common systemic feature of the disease.
Vascular involvement

Venous thrombosis occurs in 30%. It is much more common in men (90%:10%). Most (87% of one series) have thrombosis of a leg vein; thrombosis in a deep vein of the arm (2%), the vena cavae (8% each), cerebral venous sinus thrombosis (7%), the hepatic veins (3%) and the pulmonary arteries (2%) is less common and intracardiac thrombosis may occur. Relapse occurs in 30% with a cumulative risk over 5 years of 38.4%. Thromboembolism is rare; the thrombus is tightly

Figure 2  MR brain scan characteristics of brainstem meningoencephalitis. (A, B) axial FLAIR images of a lesion on the left midbrain extending into the thalamus, (C) axial b=100 s/mm² image of the thalamic lesion showing high signal intensity, (D–F) axial FLAIR images of another patient with a lesion extending from the pons to the basal ganglia on one side with (G) high apparent diffusion coefficient within the lesion and (H, I) axial and coronal T1-weighted images following administration of contrast showing a patchy pattern of enhancement within the lesion.

Figure 3  MR scan of brain (A) axial FLAIR and (B) axial T1-weighted image showing a lesion within the caudate on the right with enhancement, (C) bilateral symmetrical temporal white matter lesions in a patient with headache and cognitive changes which resolved with treatment.
adherent to the vessel wall and the veins become obliterated by organisation and fibrosis. Arterial aneurysm develops in 5% of cases, predominately of the pulmonary arteries, in which young men with a more aggressive systemic disease present with haemoptysis and breathlessness, which carries a high mortality without treatment. Aneurysms of peripheral arteries (figure 1), the external carotid and vertebral arteries, renal arteries and the abdominal and thoracic aorta, also occur. There is a patchy neutrophilic vasculitis involving the vasa vasorum with medial necrosis and adventitial fibrosis.

Neurological disease
A 2009 review summarised the clinical features and prevalence of neurological complications in 1031 patients. The incidence of neurological complications was 9.3%. Seventy-five per cent had a meningoencephalitis and 18% vascular complications. Patients may present with the neurological disorder as the heralding symptom, but in most the neurological disorder developed 3–6 years after developing the systemic features. Men were more commonly affected.

Clinical features of parenchymal neurological disease
The neurological syndrome is heralded by a subacute worsening (or first development) of the systemic features of mucosal ulceration, fatigue, aching joints and skin lesions. A headache develops, worsens over several days and becomes meningitic. The neurological symptoms arise a week after onset and worsen subacutely. Drowsiness is common and may progress to a profound encephalopathy or stupor.

Brainstem involvement
All large series note that 50% of cases are associated with an inflammatory lesion of the brainstem. Any region may be affected, the midbrain most frequently, with a lesion extending into the diencephalon, usually on one side. Most have a midbrain lesion with ataxia, ophthalmoparesis and pyramidal and/or sensory signs (figure 2). Lower lesions are associated with dysarthria, dysphagia and long tract signs. Rarely the whole brain may be affected.

Hemisphere
Thirty per cent have cerebral hemisphere lesions. Patients present with an increasing encephalopathy with focal neurological signs determined by the site and extent of the inflammatory lesion(s), including cognitive dysfunction such as dysnesia, dysphasia and visual field defects (figure 3). Seizures may occur.

Tumefactive lesions
Lesions of the diencephalon on one side, which enlarge and simulate primary or secondary tumours, are uncommon. Patients may present with contralateral signs and seizures. Lesions can become very large, with necrotic centres and ring enhancement. The neuropathological features are the same as seen in smaller parenchymal lesions, without evidence for vasculitis. Fewer than 30 cases have been reported (ref 66 and those reviewed and cited in refs 58 and 60).

Cranial neuropathy
Isolated cranial neuropathies are rare and occur either as a result of a lesion within the brainstem small enough to cause the neuropathy alone or a lesion of the nerve itself in association with an underlying meningitis, in which imaging is normal, or shows dural enhancement.

Optic neuropathy
Optic neuropathy is uncommon; a visual disorder is more often associated with retinal vasculitis, macular oedema or glaucoma in ophthalmic disease. About 45% develop a subacute optic neuritis in which pain is uncommon (20% of cases) with disc swelling. In one series, relapse occurred in 20%, and two-thirds returned to normal acuity following treatment; the nadir acuity was the determinant of visual outcome following treatment. Another one-third had other neurological features of the condition. Two papers using 3T MRI have shown that there is enhancement of the optic nerve sheath rather than the nerve itself, implying that the disorder is a perineuritis.

Audiovestibular complications
There is a high prevalence of hearing loss and vestibular imbalance. The hearing disorder is at cochlear level in 54%–73%, in vestibular function measurement identifies that one-third of patients studied have a peripheral disorder; caloric reflexes are unimpaired but tests of nystagmus and imbalance are abnormal. Imaging is normal in those studied. Around half those studied were asymptomatic.

Movement disorders
Chorea is associated with lesions in the brainstem or putamen, or brainstem atrophy, on imaging studies. More are bilateral, and dystonic tremor and posturing may also occur. Basal ganglia antibodies have not been found when sought. The movement disorder may resolve with treatment, unless associated with a widespread and atrophic neurological disease. Oculopalatal tremor has been described (ref 90 and others cited therein). An area postrema syndrome has also recently been reported.
Parkinsonism is reported although the extrapyramidal syndrome accompanies a widespread and severe neurological disorder including tremor, myoclonus, pseudobulbar palsy and rigidity of the limbs with imaging features of the chronic progressive disease course.92

Spinal cord involvement

Spinal cord disease occurs in 10% of published cases.37 38 49 50 55 56 Cervical and dorsal lesions may occur. They tend to be single and may be small and multifocal but more commonly are longitudinally extensive.93 95 99 101 102 103 104 105 106 107 108 109 110 111 The spinal fluid is active. In one series of 17, four had relapsing disease.101 Outcome of treatment is worse in those with long lesions.95 99 101 Cord involvement forms part of the progressive form of the disease.38 49 50 95 99 102

Neuropathology of parenchymal disease

The typical pathological feature is a lymphocytic meningoencephalitis with perivascular cuffing and inflammation of the adjacent parenchyma with accumulation of lipid-laden macrophages, and areas of necrosis and gliosis.27 103–111 Perivascular cuffing arises around small veins (figure 4).27 64 103–112. Autopsy cases noted atrophy and involvement of both white and grey matter structures.107 108 Later studies noted the presence of neutrophils and eosinophils as well as lymphocytes within the parenchyma and the perivascular spaces.109 110 Immunocytochemical stains show low concentrations of B cells with a predominance of CD3 positive T lymphocytes, CD68 positive macrophages, and gliosis.111 The pathological features are less active in patients with progressive long-standing disease compared with those with more recent-onset disease. There has been no reported case with features of fibrinoid necrosis (figure 4).

Vascular complications

Cerebral venous sinus thrombosis

Thrombosis of the intracranial venous sinuses occurred in 18% of cases in the 2009 study. It is far less prevalent in studies from Japan, China and Korea at 1%–3%.49 50 52 53 56 113 The incidence in northern European and Mediterranean patients with Behçet’s syndrome is 3.1 per year and 7.8% of a large Behçet’s syndrome cohort in France.19 114 In one study, 9.4% of Behçet’s syndrome cases had associated cerebral venous sinus thrombosis and there is no difference in the clinical or radiological features in those without Behçet’s syndrome.115–117 In 140 cases, the superior sagittal sinus was affected in 64%, the transverse venous sinus in 61% and the sigmoid and straight sinuses rarely. Over 60% have dual or multiple sinuses thromboses (figure 5).19

There is an association with venous thrombosis elsewhere.19 113 118 which may present synchronously.114 Relapse is associated with the presence of venous thrombosis elsewhere.114 Twenty per cent have prothrombotic factors such as lupus anticoagulant or prothrombin gene mutations,114 115 119 but their presence does not influence the severity or outcome of the disorder.

Patients present with a subacute headache with nausea, and features of raised intracranial pressure.19 113 117 118 120 Ten per cent have a sixth nerve palsy.117 118 The spinal fluid is under pressure, but inactive unless there is a concurrent meningoencephalitis.114 Venous infarction occurs in 10%–20%37 113–115 120; haemorrhage appears not to occur.114–116

Shi et al.113 noted that disease severity as measured by the Behçet’s disease current activity form was greater in their series in patients with cerebral venous sinus thrombosis than those without. The outcome is good; Sorgun cited an mRS of 0.117 An early study found that the venous sinuses recanalised ‘frequently’.120 The main adverse consequence is optic neuropathy due to high intracranial pressure.114

Intracranial hypertension without radiographic signs of cerebral venous sinus thrombosis

An intracranial hypertension syndrome without radiological signs of venous sinus thrombosis occurs in 3.4% of cases.26 The cerebrospinal fluid (CSF) pressure is raised but its constituents normal. Recommendations were to treat the underlying systemic disorder, and to treat the CSF pressure with diuretics, while monitoring the visual fields. A study of eight patients from three centres in Turkey showed similar features, although a CSF cell count of over 5/µL (normal≤5) was seen in two.121 Each was treated not only with acetazolamide but also methylprednisolone, and the outcome was good. The pathogenesis remains obscure.

Mixed parenchymal and venous disease

Several reports have shown that cerebral venous sinus thrombosis may arise simultaneously to a parenchymal...
lesion, with a prevalence in large series of 3.3%–9.5%.44 45 48 54 57

**Arterial disease and stroke**

Our 2009 study of Behçet’s disease found a stroke prevalence of 1.5%. There are several case reports of cerebral infarction or intracerebral haemorrhage; in one,122 there was fusiform enlargement of the internal carotid artery, anterior cerebral artery and middle cerebral artery (MCA); in others,123 124 there was beading of the MCA, which resolved following treatment with corticosteroids and cyclophosphamide, and there are three reports in which the basilar artery was occluded, but recanalised after treatment with corticosteroids and immunosuppression.125–127

A postmortem case found occlusion of medium-sized arterial branches of the MCA with a panarteritis of several small-sized and medium-sized branches of that vessel in a patient with infarction of the tissues beyond.128 A more recent report described high-resolution MRI that showed thickening and enhancement of the vessel walls of terminal branches of the MCA.129

**Aneurysm**

A recent report identified 24 cases previously published.130 Most presented with subarachnoid haemorrhage, two were incidental findings without bleeding and two were found to be associated with an adjacent cerebral infarction. The internal carotid artery and the circle of Willis and its proximal branches were involved. Nine cases had
multiple aneurysms. It appears that endovascular treatment and clipping is safe in ruptured aneurysms. One further case has been reported since in which aneurysms resolved with prednisolone and azathioprine.

Pathological examination of an aneurysm removed following subarachnoid haemorrhage showed vasculitis with disruption to the muscular layer within the aneurysmal wall. The walls of the parent artery were normal.

There are reports of arterial dissection in the disease involving the mesenteric and coeliac arteries and the internal carotid and vertebral arteries associated with haemorrhage or infarction. The angiographic features suggest an intimal tear during the development of an aneurysm.

There are also reports of parenchymal haemorrhage; in one series, there was one haemorrhage in the brainstem and two in the caudate; another involved the cerebellum. An inflammatory lesion may be complicated by haemorrhage within; in one a lesion evolved to become haemorrhagic and the second had a series of haemorrhagic lesions associated with inflammation within the cortices on both sides. We have seen two cases in which a characteristic brainstem lesion was haemorrhagic (figure 6). The neuropathological examination of one fatal case found a lymphocytic infiltration around the vessels and post capillary venules.

Seizures

Epilepsy has a prevalence of 2–5%. Seizures arise during attacks, are focal more than generalised and become uncommon following treatment. Mesial temporal and cortical lesions have been associated. Partial-onset seizures and epilepsia partialis continua have been reported.

Cognitive disorders

Cognitive impairment develops in 50% of those with neurological disease; impairments of memory, visuospatial awareness, frontal executive function and attention are proportionately more affected than other cognitive domains. However, these features also occur in patients without neurological involvement; one study identified a correlation between cognitive impairment and disease severity, and in turn with treatment dosage (implying a more severe disease).

Over time patients with a progressive neurological disease course suffer declines in cognitive function and some have a progressive cognitive disorder as their only neurological manifestation.

The syndrome of fatigue and sleep disturbance is common in Behçet’s syndrome. Measurements of fatigue, anxiety and depression are higher in patients than in control populations and fatigue itself correlates with anxiety and depression, scores of depression and sleep quality correlate with disease severity. In another study, 64% of 117 patients studied had high fatigue scores and 63% poor quality sleep; serum concentrations of IL-6 and melanocyte stimulating hormone correlated with these clinical features.

Psychiatric disease and syndromes

There is a high prevalence of anxiety and depression, but also hypomania (summarised in Talarico et al). Several case reports describe an encephalopathy with visual and auditory hallucinations, delusional states, obsessive traits and anxiety preceding a neurological disorder associated with lesions of the brainstem and basal ganglia. In a series of 34 patients, 9 had psychiatric disorders, of

Figure 8  MR scan of brain (A) atrophy of the right cerebellum and pons following a brainstem lesion in that area, (B) linear signal lesions within the midbrain and pons following a second episode of brain stem meningoencephalitis, (C) atrophy of the sagittal extent of the cord following a longitudinally extensive lesion in cervical and dorsal regions, (D) atrophy of the left temporal lobe and hippocampus following repeated episodes of meningoencephalitis in that area.
whom 7 showed abnormalities on imaging within the brainstem or the cerebral white matter.\textsuperscript{164}

**Neurological disorders associated with reduced cerebral perfusion**

There is a subgroup of patients in whom neurological syndromes arise with normal imaging, who are found to have regional defects of cerebral cortical perfusion (figure 7).\textsuperscript{168-173} There are descriptions of patients with ‘personality change’, ‘dementia’, aphasia and mutism who have frontal hypoperfusion on SPECT imaging.\textsuperscript{168-173} Patients with hemisensory symptoms and weakness with contralateral hypoperfusion in the frontal and parietal regions.\textsuperscript{170 171} One study showed improvements in cerebral perfusion following treatment.\textsuperscript{174}

**Headache**

Headache is the most common neurological symptom in Behçet’s syndrome. A series of studies describing 553 patients identified an incidence of over 70%.\textsuperscript{26 175-180} The predominant headache type is migraine, with a high prevalence of aura.\textsuperscript{26} Tension-type headache is also common and may be associated with neuralgiform headache arising from the greater occipital nerve. Imaging is normal and the CSF studies inactive.

Headache often coincides with systemic features but may persist once the disease is rendered quiescent by treatment. Patients with isolated headache respond well to normal treatment; clinicians must take care to treat analgesic-overuse headache as well.

**Peripheral nervous system and muscle**

Peripheral neuropathy is very rare, accounting for less than 1% of cases to 2009.\textsuperscript{26} Axonal sensorimotor neuropathies, mononeuritis multiplex and a polyradiculoneuropathy have been described.\textsuperscript{33 181-188} Nerve biopsies usually show axonal changes without demyelination, inflammation or vasculitis.\textsuperscript{182-185}

An axonal neuropathy may complicate treatment with thalidomide

**Box 2** provides a guide to the other main inflammatory disorders that may simulate Behçet’s syndrome with neurological complications.

**Neurological Behçet’s syndrome in children**

The clinical features of the systemic disease in children are the same as those in older age groups,\textsuperscript{196-198} although its prevalence is much less.\textsuperscript{197} There are four series in which the prevalence of neurological complications is 3.6%–28%.\textsuperscript{196 199-201} The disease is most uncommon before puberty; the mean age of incidence of neurological complications is 12–13 years. It is clear that, in contrast to the adult population, there is a higher incidence of venous sinus thrombosis and intracranial hypertension (88% of one series).\textsuperscript{200} The clinical and imaging features of those who develop a meningoencephalitis have brainstem, diencephalic and cord lesions, which are the same as those noted in the adult population.\textsuperscript{118} The prevalence of HLA B-51 positivity and the response to treatment is similar.

**Investigations**

**Blood investigations**

There is no serum biomarker for the disease. In acute attacks the erythrocyte sedimentation rate (ESR), C reactive protein and other acute phase reactants are raised. ESR correlates with disease activity.\textsuperscript{5}

**Cerebrospinal fluid**

In meningoencephalitis, the protein is raised to around 1 g/L (0.15–0.45),\textsuperscript{37 38 50} with a leucocytosis of up to 500 cells/µL (≤5). In the early stages, there is a preponderance of neutrophils and this changes to a lymphocytosis after a few days.\textsuperscript{37} In cerebral venous...
sinus thrombosis, the CSF is usually normal; in mixed parenchymal and vascular disease the CSF is active. Oligoclonal bands are usually negative; fewer than 10% of patients have either matched or unmatched bands. This does not correlate with clinical features or severity and their presence and significance is not yet understood.

CSF IL-6 and IL-8 concentrations are higher than in controls and fall with treatment. In the progressive disease course, when other CSF variables may be normal, the IL-6 concentration is raised, although less raised than in acute attacks. In one study, CXCL10 concentrations were higher than in samples from controls and patients with multiple sclerosis, and IL-10 concentrations were the same in one study but not another. B cell activating factor concentrations are higher in the CSF in those with progressive neurological Behçet’s syndrome than those with acute episodes.

**MRI**

The characteristic finding is a lesion of the upper brainstem on one or both sides that extends into the diencephalon (figure 2). There is enhancement which may be patchy or nodular, and less often ring enhancement. The lesion correlates with the clinical features.

Over time, the high signal lesion tends to disappear and the affected structure becomes atrophic. On T1-weighted imaging, there may be areas of low signal. In some, punctured out or linear high signal lesions remain. On T1-weighted imaging, there may be areas of low signal.

In the brain, lesions arise within the diencephalon and temporal regions; they may be single or multifocal. The imaging features of tumefactive lesions have already been described. Over time, no new lesion develops unless there are new symptoms. Diffusion-weighted imaging of the lesion shows high signal intensity on $b=100$ s/mm² images associated with high ADC maps, implying vasogenic oedema rather than infarction of the affected area. Susceptibility-weighted imaging reveals small hypointense lesions compatible with bleeding from veins within a lesion (figure 6).

In the progressive phase of the disease, atrophic changes develop particularly within the brainstem and cerebellum. New lesions do not develop during the progressive phase, and there is no enhancement.

Other lesions within the cerebral white matter may be juxtacortical and periventricular. It is uncommon to see these in the absence of a more characteristic lesion elsewhere. They tend to be small, not associated with specific localising symptoms or signs and do not change over time, suggesting that they are not a direct consequence of inflammation in the brain. Some have oligoclonal bands, suggesting that there is a proportion of patients with Behçet’s syndrome whose neurological illness is multiple sclerosis.

There have been a few cases with dural thickening and enhancement but leptomeningeal enhancement is rare.

**Clinical course**

There are data from 10 studies (table 1) comprising the follow-up of 809 patients with parenchymal involvement due to meningoencephalitis. A monoclonal syndrome in which there was an attack without relapse following treatment during the study follow-up period occurred in 416 patients (51.4%). Relapse requiring further treatment leading to recovery occurred in 190 (26.5%) of 718 patients, or relapse forming part of a progressive disease course occurred in 103 (15.3% of 671 patients). A progressive disease course, in which a neurological disorder without relapse or remission arose leading to increasing neurological impairments, occurred in 153 patients (18.9% of all studies). The prevalence of these disease course subgroups is no different when studies are grouped into ‘predominately south east Asian populations’ versus ‘predominately Mediterranean’ populations versus ‘predominately northern European’ populations. Thus 80% begin with a relapsing disease course of whom 70% have only one attack, and 30% have a progressive disease course either from onset or following an initially relapsing course.
Table 2  Clinical features and response to treatment with biological therapies in 81 published cases

<table>
<thead>
<tr>
<th>Biological agent</th>
<th>Papers</th>
<th>Type</th>
<th>Disorder</th>
<th>Previous treatment</th>
<th>Reason for change</th>
<th>Outcome</th>
<th>Follow-up</th>
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<td>Licata</td>
<td>CR</td>
<td>Brain</td>
<td>S, cyclo</td>
<td>Relapse</td>
<td>Resolved</td>
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<td>Ribi</td>
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<td>Improved</td>
<td>2y</td>
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<td>S</td>
<td>first line</td>
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<td>1y</td>
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<td>CR</td>
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<td>Improved</td>
<td>ns</td>
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<td>S, cyclo</td>
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<th>Previous treatment</th>
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<th>Outcome</th>
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<td>Jade</td>
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The chronic progressive disease course

Thirty per cent of patients relapse after the first symptoms of neurological involvement; of these fewer than half develop a progressive disease course. In 20% of all cases, this course arises from onset without attack or relapse. This disease course is associated with poor outcome and greater risk of death. CSF indices such as cell count and protein concentration are less abnormal than in acute attacks, and CSF IL-6 levels are raised but less than in acute attacks. Patients develop cognitive dysfunction, ataxia, pseudobulbar palsy and spinal cord lesions leading to immobility and a requirement for long-term care.

All studies show an association between a progressive course and outcome, between brainstem involvement, more severe spinal fluid abnormalities, atrophic features on MRI and residual neurological impairments, disability or death. Measurements of outcome suggest that 35%–45% of patients become disabled over time. In these series, the incidence of death was 12% overall and 6.8% attributed directly to the disorder. A Kaplan-Meier analysis showed survival rates of 95% at 1 year reducing at 10 years to 40%.

Treatment

There is still no controlled trial of any form of treatment in neurological complications of Behçet’s syndrome. There have been trials of azathioprine, colchicine, thalidomide, interferon α2a and etanercept in the mucocutaneous forms of the disease, each with positive results (reviewed in Yazici et al and Leccese et al). Colchicine is considered first-line therapy for mucocutaneous manifestations. Corticosteroids are given topically for oral and genital ulceration, and systemically for acute attacks including skin lesions and arthritis. Second-line therapy with azathioprine, mycophenolate mofetil and cyclosporine A is used in relapsing or treatment resistant cases, or with ocular disease. In uveitis, a series of controlled trials (reviewed in Ozguler et al) has shown benefit with azathioprine, methotrexate and cyclosporine A. Care should be taken when using cyclosporine A since patients with Behçet’s syndrome treated with the drug for uveitis have a higher than expected prevalence of neurological complications.

Interferon α2a and infliximab in comparative trials were more effective and also more rapid in provoking clinical improvement (reviewed in, refs 245 and 247–249). The rationale for using biological agents comes from studies of the immunopathology of the disease. TNFα blocking biological agents had a positive effect in 90% of cases with mucocutaneous, ocular, gastrointestinal and neurological disease.

Treatment of neurological parenchymal disease

Early series noted a response to corticosteroids and later to immunosuppression; however, many patients developed neurological involvement during immunosuppressive therapy, suggesting that these alone are insufficient to treat and prevent neurological disease.
Table 2 provides all published data on the use of biological agents in the disease; 6 of 69 responded better when switched from infliximab to adalimumab, etanercept or golimumab. The profile of adverse effects is low; 3 of 81 patients developed active tuberculosis, 1 a bacterial lung infection and another a varicella zoster infection. One developed an IgA nephropathy and one a positive ANA and lupus-like skin rash.

The data suggest that TNFα blockade works well in active currently relapsing cases and in patients with active frequently relapsing disease refractory to other immunosuppressive therapies. In chronic progressive disease (n=12) the disease may too be stabilised, although we need further, more long term, studies to investigate this. The optimum treatment duration is not yet known. There are reports of a response to rituximab and tocilizumab following failure of TNFα blockade.

Haematopoietic stem cell transplantation
Haematopoietic stem cell transplantation is effective in cases in which a neutrophil activation syndrome that simulates Behçet’s syndrome occurs in myelodysplastic syndromes, leading to bone marrow failure. It is associated with acquired trisomy 8, and mucocutaneous symptoms especially gastrointestinal ulceration predominate; a neurological disorder has not been reported (refs 259 and 260 and PubMed review). In a review of 20 cases with Behçet’s syndrome,11 had a myelodysplastic disorder and 9 had not, of whom 5 had neurological involvement.11,261–264, all cases showed a response to treatment; 3 were rendered free of relapse while 1 was improved and the other made no response leading to a second transplant. One died of infection and one had GvHD.11 Two other cases in our unit are shortly to be reported.

### Table 3 Summary and treatment recommendations

<table>
<thead>
<tr>
<th>Neurological disorder</th>
<th>Imaging appearances</th>
<th>CSF findings</th>
<th>Treatment</th>
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</thead>
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<tr>
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<td>Lesions with enhancement</td>
<td>Intravenous corticosteroid Immediate institution or escalation of immunosuppressive therapy</td>
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<td></td>
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<tr>
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<td>Cord</td>
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<tr>
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<td>Atrophy without enhancement</td>
<td>Less active, IL-6 elevated</td>
<td>Corticosteroid and immunosuppression Role of TNFα antagonists to be defined</td>
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<tr>
<td>Venous disease</td>
<td>CVST</td>
<td>Venous sinus thrombosis</td>
<td>Intravenous corticosteroid Immediate institution or escalation of immunosuppressive therapy Role of TNFα antagonists to be defined</td>
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<td>Cerebral infarction</td>
<td>Infarction</td>
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<td>Cerebral haemorrhage</td>
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<td>Treatment of the meningoencephalitis</td>
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<tr>
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<td>Careful multidisciplinary assessment to define relationship to Behçet’s syndrome Treatment of meningoencephalitis Treatment of systemic disease without brain disorder Treatment of underlying psychiatric disorder</td>
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<tr>
<td>Myositis</td>
<td></td>
<td>Corticosteroid and immunosuppression</td>
<td></td>
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</tbody>
</table>
Early reports noted that recurrent thrombosis arose despite oral anticoagulation; others showed a lower risk of relapse with immunosuppression and furthermore that concurrent anticoagulant treatment gave no additional benefit.266–269 Treatment of arterial, large and refractory venous disease with TNFα blockade shows a response of 80%–90%.270–272 The incidence of adverse events was low. There has been no trial of treatment for cerebral venous sinus thrombosis; one study117 found that the neurological outcome when treated only with corticosteroids was the same as those treated additionally with anticoagulation. Use of TNFα blockade in cerebral venous sinus thrombosis is limited to five patients reported in which all cases responded.271–273

Arteritis reflects a more severe disease with a poor prognosis. Intravenous cyclophosphamide was effective in only 38% of one series,24 and reconstructive surgery is required in half. More recently, there are reports showing infliximab and tocilizumab are effective.270 272–275

**Box 2** Differential diagnosis of the systemic disease with neurological complications

<table>
<thead>
<tr>
<th>Category</th>
<th>Conditions</th>
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</table>

*See Jung et al276

**Key points**

- Behçet’s syndrome is uncommon and the systemic features are not always prominent.
- Its neurological complications can evolve quickly and become severe.
- The keys to successful management are early diagnosis and careful exclusion of alternatives, collaborative working with a multidisciplinary team, and early institution of effective treatment.

**Further reading**


**Acknowledgements** I thank my colleagues at the Behçet’s syndrome centre of excellence for their help, support and friendship over the years.

**Contributors** Dr Kidd was responsible for the study concept and design, acquisition of data and analysis and interpretation. He performed the literature search and wrote the manuscript, composed the panels and tables and obtained the figures. He was responsible for a critical revision of the manuscript for important intellectual content. He was the study supervisor.

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Review


