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NEUROLOGICAL UPDATE

Neurological complications of Behçet's syndrome

D. P. Kidd[1]

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Abstract In this review of the neurological complications of Behçet's syndrome, the clinical features and epidemiology of the systemic disease are summarised before a discussion of the neurological syndromes which may develop is made. Neurological involvement occurs in 9% of cases, and is equally prevalent in each geographical area. Vascular complications occur in 14%, in whom thrombosis of the venous sinuses or cerebral veins occurs, and intracranial hypertension, venous infarction and parenchymal haemorrhage may develop. There is a correlation with the prevalence of peripheral venous thrombosis. Concurrent inflammatory disease of the brain is most uncommon. Inflammation may affect any part of the central nervous system, but most commonly involves a subacute meningoencephalitis of the brainstem and diencephalon. Inflammatory lesions elsewhere in the brain and in the spinal cord may occur, and tumefactive lesions may arise from the diencephalon. Cognitive dysfunction and affective symptoms, including psychosis, may occur, and there are high levels of anxiety and fatigue which are related to the severity of the systemic disease, all of which are more severe in those with neurological involvement. Imaging shows enhancing lesions which often disappear after treatment, but atrophy is common. The CSF is active when there is a meningoencephalitis, and oligoclonal bands do not occur. Treatment is with steroids and immunosuppression. Those with treatment resistant disease respond to biological agents, including TNF alpha, IL-1 and IL-6 antagonists.

✉ D. P. Kidd
d.kidd@ucl.ac.uk

[1] Behçet's Syndrome Centre of Excellence, Institute of Dentistry, Royal London Hospital, Whitechapel, London E1 1BB, UK

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Introduction

Behçet's syndrome is a relapsing systemic auto-inflammatory disease characterised by ulceration of the mucous membranes and inflammation leading to tissue destruction of other parts of the body [1]. Any system may be affected. Almost all have recurrent painful and multiple oral ulcers which begin in childhood or early adulthood and which scar the soft palate and pharynx. 90% have genital ulcers, and involvement of the gut leads commonly to a painful irritable bowel (when ulceration is present) or to a colitis which can make differentiation from ulcerative colitis and in particular Crohn's disease challenging.

Erythema nodosum, papulopustular and acneiform lesions of the skin are recurrent in 75% of cases, and an inflammatory oligoarthropathy of the large joints occurs in 60%. The pathergy response, in which a papule or blister develops within 48 h of trauma to the skin, for example venepuncture, is an inflammatory lesion of the skin with endothelial cell proliferation and identical to spontaneous skin lesions seen in the disease.

Ocular involvement is common, affecting half of all patients. The classical hypopyon (the collection of pus cells in the anterior chamber), is much less common than previously seen. Most have a pan uveitis, around a third have a non-granulomatous anterior uveitis, an isolated vitritis and retinal vasculitis is uncommon. An anterior uveitis is complicated by the development of secondary glaucoma and cataract formation [2]. When the retina is affected a sight threatening ischaemic retinal vasculitis in which there

is inflammation within and occlusion of retinal veins leading to retinal necrosis and detachment occurs [3].

Vascular involvement occurs in 20% [1, 4], most commonly manifest as a relapsing superficial thrombophlebitis or deep vein thrombosis. Thrombosis of the inferior vena cava and the hepatic veins, and as will be discussed below, the cerebral venous sinuses, is less common. There is evidence for inflammation of the vessel wall leading to thickening and occlusion [4, 5], and there is much debate on whether or not there is a role for anticoagulation in the management of these patients [6]. Arterial involvement is less common, but can be associated with aneurysm formation, particularly within the pulmonary circulation, which may be associated with life-threatening haemoptysis [1, 4].

The inflammatory disorder is to the most part a venous perivasculitis, but arterial involvement is seen leading to fibrinoid necrosis and aneurysm formation, particularly in the pulmonary arteries but also in the limbs [1, 4].

Epidemiology

The disease is more common in countries which formed the ancient Silk Route, comprising those from either side of the Mediterranean Sea, the Middle East extending to Japan. The prevalence in Turkey has been measured to be as high as 421×10^5 [1]. It is 20×10^5 in Japan, and in European countries it is less common, and the disease is probably overall less severe. There is a clear association between prevalence of the disease and the prevalence of HLA B51 in these countries [7]; in Turkey it is present in 70% of patients vs 14% of controls and in European patients much lower—perhaps 20%. It confers a greater risk of ulceration, skin, vascular and ocular involvement, but not neurological complications [8]. It is more common and more severe in men, and typically arises in the third to fifth decades, tending to diminish in severity in the sixth and seventh decades.

There is often a delay before the diagnosis is attained [9] particularly in those with a more mild disease course. Male patients and those with a more widespread systemic involvement early in the disease course have a more severe form of the disease.

Neurological complications

Neurological involvement arises in around 9% of most hospital based clinical series [10]. Most have parenchymal inflammation within the central nervous system whilst the remainder has venous sinus thrombosis. Involvement of the peripheral nervous system is very rare, with occasional reports of large fibre neuropathies, acute polyradiculoneuropathy, and mononeuritis multiplex (reviewed in [10]). Myositis is more common in children than adults, and can be severe. Isolated cranial neuropathies do occur and are associated with evidence for a concurrent meningitis on CSF assessment. Optic neuropathy [11] is rare in the absence of an associated severe ischaemic retinal vasculitis.

Involvement of the central nervous system

Non-parenchymal disease

Venous sinus thrombosis occurs in 14% of summated series to 2009 [12]. The superior sagittal and transverse sinuses are affected most often, although all may be thrombosed in severe cases (Fig. 1). Thrombosis of superficial cerebral veins may also arise. 25% have had previous or concurrent venous thrombosis elsewhere. In 15% the venous sinus thrombosis heralds the onset of the systemic disease. Patients present with headache and visual obscuration, with focal signs as a result of intraparenchymal haemorrhage or venous infarction uncommon. Papilloedema is seen in 40%; blindness may ensue due to sequential optic atrophy [12, 13].

Treatment is not only with anticoagulation but with high dose corticosteroids and immune suppression. The outcome is good, with a low mortality rate and, with treatment of the systemic disease, a low risk of recurrence.

There is a subgroup of patients who present without imaging evidence for venous sinus thrombosis but with intracranial hypertension. This is uncommon and there are no conclusive data to define whether or not they too should be anticoagulated, but these patients have a benign prognosis provided the pressure is reduced adequately and vision is preserved.

It is uncommon for patients with venous sinus thrombosis also to have parenchymal involvement [12].

Parenchymal disease

Over 80% of patients with neurological complications develop inflammatory lesions of the central nervous system [14]. The neuropathology is of a meningoencephalitis in which there is infiltration of lymphocytes, neutrophils, eosinophils and plasma cells and macrophages. There is often an intense cuffing of small veins within the affected areas, but vasculitis is not seen (Fig. 2). Areas of necrosis and apoptotic neuronal loss are seen [15, 16].

Brain stem lesions

Half of all patients present with a brain stem lesion [17–21]; there is a prodrome of unwellness with fever and

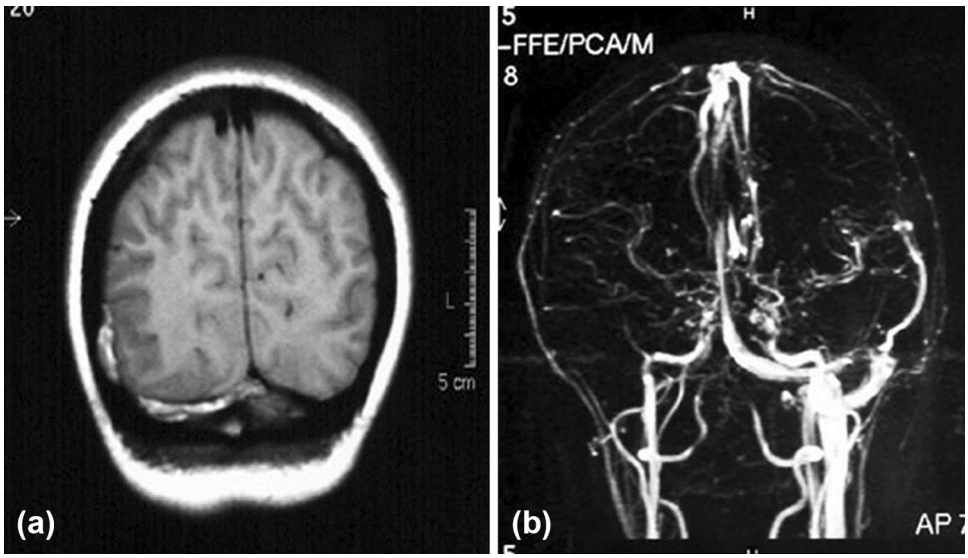

Fig. 1 **a** T1 weighted MRI and **b** MRV showing thrombosis of the right transverse venous sinus

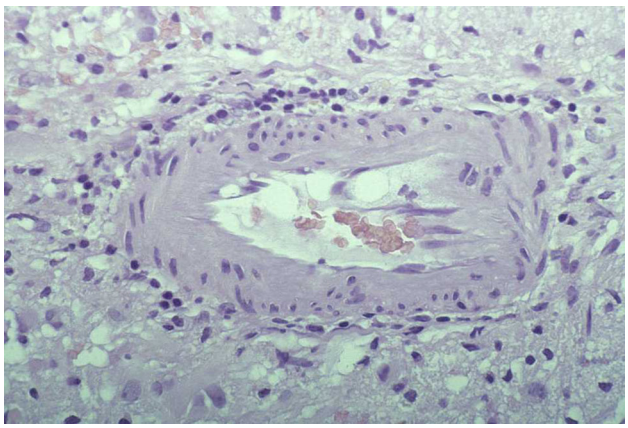

Fig. 2 H&E photomicrograph showing infiltration of inflammatory cells around a vein

escalating headache, the systemic features increase and then the focal neurological signs develop. The clinical syndrome evolves over several days. An ophthalmoparesis is common, usually associated with ataxia. Characteristically the lesion is in the midbrain (Fig. 3a) or pons, less often the medulla, associated with asymmetric long tract signs.

Others present with a progressive encephalopathy, with headache, focal signs such as hemiparesis, sensory loss, dysphasia and cognitive dysfunction, in whom the lesions are usually more widespread on MRI and involve the hemispheres. Seizures may arise.

Tumefactive lesions

Infrequently a large mass lesion may develop in one hemisphere, centred on the deep structures (Fig. 4) simulating a glioma or lymphoma. Such lesions are often biopsied [22] and resolve with treatment, but with residual neurological impairments.

Movement disorders

Chorea, dystonia and akinetic rigid syndromes have been reported, usually in association with established and longstanding neurological disease.

Isolated meningitis is uncommon since most patients have spread of inflammation into the parenchymal regions leading to other neurological signs.

Stroke due to venous or less frequently arterial thrombosis is very uncommon.

Cognitive dysfunction

Cognitive impairment is common in Behçet's syndrome; working memory and retrieval, frontal executive function and attention are predominately affected [23–25]. These are more severe in those with established neurological involvement but also those without other neurological symptoms who have abnormal imaging [24, 25]. In one study of patients without neurological involvement and with normal MRI 46% had cognitive processing disorders compared with none of the age matched controls [24]. These deficits correlated with the Behçet's current activity index and the prescription of medication (implying an active systemic disease). Another study found abnormalities in 63% of patients, associated with imaging abnormalities but also with indices of anxiety and depression [25]. This study found a protective association with prescribed medication, implying that those treated feel generally better and better within themselves. No other studies have been published, and crucially no prospective

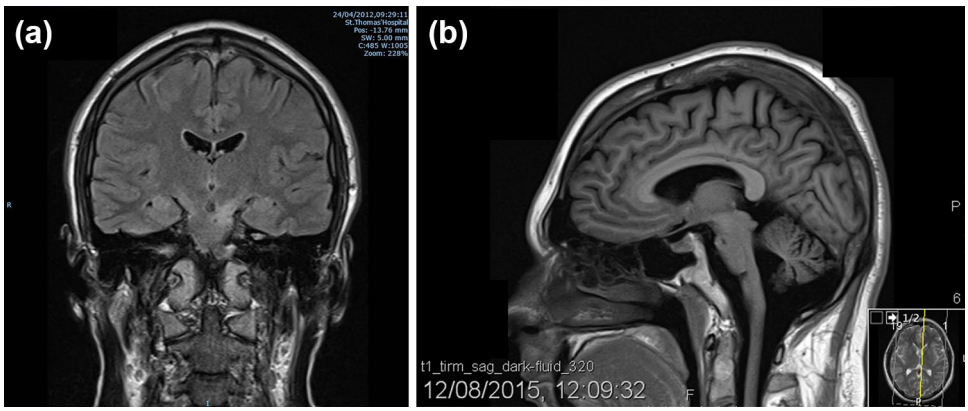

Fig. 3 **a** FLAIR sequence MRI showing a lesion of the left side of the midbrain during an acute attack and **b** T1 weighted sagittal MRI 3 years later showing atrophy of the brainstem and cerebellum

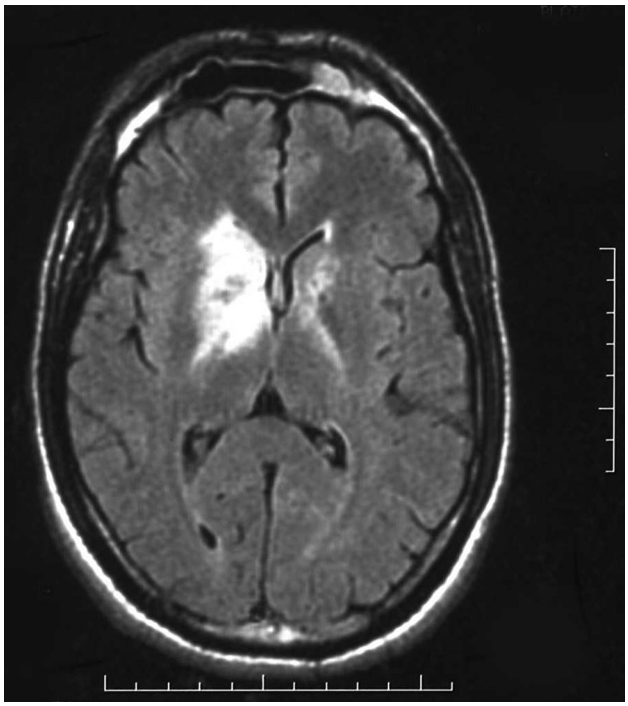

Fig. 4 FLAIR sequence MRI showing a large lesion arising from the basal ganglia and deep white matter on the right side

longitudinal studies; it appears that those with neurological involvement have cognitive dysfunction as well, and those without have cognitive dysfunction which is related to fatigue and the psychological consequences of a chronic, painful systemic disease which may not deteriorate and may indeed be reversible.

Psychiatric disorders

Psychiatric disorders are common in Behçet's syndrome and even less well characterised. There are isolated reports of acute psychosis associated with neurological involvement which resolve with treatment [26–28]. Other reports suggest a higher prevalence of hypomania and obsessive compulsive disorder in patients, as well as anxiety, depression and problems with coping with stress (reviewed in [29]). Fatigue is common and correlates with disease activity, but also with anxiety and depression [30].

Spinal cord involvement

Involvement of the spinal cord occurs in 10% of large series [17–21]; patients have small demyelinating type rather than longitudinally extensive cord lesions on MRI. Brain imaging is usually normal. Those with partial lesions of the cervical and dorsal cord often respond to treatment and recover whereas those with transverse myelitis often do not. These lesions may be destructive and a poor recovery may be seen despite prompt treatment [18, 19].

Progressive disease

In early series, around one-third patients had a progressive disease course, of whom the majority had suffered repeated relapses of their condition prior to its onset (a secondary progressive course). A minority was seen to have suffered a primary progressive disease course, in which no acute or subacute attack had heralded the onset of the neurological disorder [18, 19]. Further prospective study is underway which will identify if the more aggressive and long-term treatments now used have altered this disease course.

Imaging features

There are lesions in the white matter which correlate with the clinical syndrome. Characteristically there is a single lesion of the midbrain which ascends to the diencephalon on one side. There is oedema and the lesion enhances. With time and treatment, the enhancement resolves, the lesion regresses and may disappear altogether on T2-weighted MR images, but focal areas of atrophy are seen where the lesion once was (Fig. 3b).

Patients with more widespread or relapsing disease show T2 hyperintensities which show a periventricular and

subcortical pattern occasionally resembling multiple sclerosis, but which are seen in the frontal, temporal and hypothalamic regions, without enhancement.

Tumefactive lesions and, when there is a venous sinus thrombosis, venous infarction and peripheral haemorrhage may also be seen.

Cerebrospinal fluid

The CSF is active in the majority of cases in which there is parenchymal involvement. The protein is raised modestly, and the cell count often considerably. Oligoclonal bands are not seen. Often there is an initial neutrophil leucocytosis, replaced within days by a persisting lymphocytosis [17, 18]. The CSF IL-6 level is raised in acute attacks and in progressive disease [31, 32]. It falls with treatment. The CSF constituents are normal in venous sinus thrombosis, unless there is co-existing inflammation within the brain.

The natural history

In early series [17–20] a third of patients had only one attack and a third had relapsing disease, the remainder having a progressive disease course. The prognosis is related to the presence of brain stem disease, the number of attacks or the presence of progressive disease and the initial CSF cell count [17, 18]. Those with venous sinus thrombosis and intracranial hypertension tend not to relapse.

Headache

Headache had a prevalence of 85% of UK patients studied [34]. The majority have vascular headaches resembling migraine, and the prevalence of aura is high. Tension type headache, analgesic-associated and chronic daily headache syndromes all occur [33–35]. Many note an association between the frequency and severity of the headaches and the systemic disease activity. Most have normal imaging, but patients with evolving neurological involvement note that an escalating headache forms part of the prodrome of the illness. Those without neurological involvement respond well to anti-migraine therapies.

Treatment

There has been no controlled trial of treatment in neurological disease in Behçet's syndrome. Corticosteroids and oral immune suppression work well and prevent relapses in the nervous system as well as settling the systemic disease [10]. Treatment trials in ocular disease have shown beneficial effects with interferon α2a [36] and TNFα antagonists [37], and treatment resistant systemic disease of all types responds to anti-cytokine therapies [38–40]. TNFα antagonists have also been shown to be effective in relapsing and progressive neurological disease [41]. There are isolated reports that Rituximab [42, 43], Anakinra [44] and Tocilizumab [45, 46] are helpful in severe and treatment resistant forms. These biological therapies must only be used in units experienced in their use and aware of potential significant adverse effects.

Compliance with ethical standards

Conflicts of interest The author has no conflict of interest.

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