

## Neurological complications of Behçet's syndrome

### Introduction

Behçet's syndrome is an episodic disorder of unknown aetiology or pathogenesis characterised by recurrent oral and genital ulceration and panuveitis. Skin involvement manifest as erythema nodosum, pustular eruptions or pseudofolliculitis, is common and pathergy occurs in some 50% of cases. An oligoarthropathy of large joints (knees, ankles and shoulders) can also be a feature of the illness along with lung, gastrointestinal and renal involvement, although this is rare. Malaise, fatigue and loss of weight are frequent associated symptoms<sup>1</sup>.

Behçet's syndrome is most common in the countries around the eastern shores of the Mediterranean Sea and Eastern Asia. In Japan the prevalence was 7/10<sup>5</sup> in 1974<sup>2</sup> although in Turkey<sup>3</sup> in 1988 the prevalence was found to be higher in rural than urban areas at 37/10<sup>5</sup> vs 8/10<sup>5</sup> respectively. There has been only one published survey of the disease in the UK<sup>4</sup> in which the prevalence in part of Yorkshire was found to be 0.4/10<sup>5</sup>, although more recently the prevalence in Hertfordshire<sup>5</sup> has been found to be higher at 5/10<sup>5</sup>.

This latter study<sup>5</sup> identified a prevalence of neurological complications of 0.75/10<sup>5</sup>, whilst previous studies, using retrospective data, have shown a much higher prevalence of neurological involvement at 5.3% to 25%<sup>6-8</sup>, the latter figure being supported by an autopsy series in which 20% of 170 cases of patients with Behçet's syndrome showed pathological evidence for neurological involvement<sup>9</sup>.

The diagnostic criteria<sup>10</sup> are summarised in the table and although it is specified that recurrent oral ulceration is a prerequisite, cases do exist in which pathologically proven Behçet's syndrome occurs without oral ulceration; Nevertheless the criteria are said to exclude only 3% of patients in whom recurrent oral ulceration is not a feature.

### Clinical syndromes

Neurological involvement occasionally arises at the time of first presentation of the systemic disease<sup>12</sup> and more rarely precedes it<sup>2,14</sup>, but typically presents during the course of established disease. These neurological syndromes occur either as a result of the development of inflammation within the central nervous system – so-called parenchymal involvement – or as a result of vascular complications within the nervous system.

The neurological syndrome which develops most frequently is due to a lesion within the brain stem<sup>11,12</sup>, and

accounts for 25%-50% of all parenchymal lesions in large published series<sup>11,12,14,15</sup>. This often arises in the midbrain or pons (figure) with the patient developing a subacute ophthalmoplegia with ataxia. Involvement of the medulla is less common and whilst isolated cranial neuropathies also occur<sup>11</sup>, optic neuropathy is rare.

Hemispheric involvement due to inflammatory infiltration of white and grey matter structures may lead to hemisensory symptoms or hemiparesis but only a minority of patients develop seizures<sup>13</sup>. A subacute encephalopathy frequently complicated by psychosis may also arise.

Spinal cord involvement may be severe with transverse myelitis or with partial involvement and an isolated sensory syndrome. Involvement of muscle, peripheral nerves, and nerve roots with a polyradiculopathy have all been reported, although these are rare features of this condition (reviewed in<sup>(11)</sup>).

Symptoms of meningitis are more rare than was once thought; isolated aseptic meningitis arose in only 4/50 patients in one series<sup>11</sup> and 3/40 in another<sup>14</sup>, but headache and photophobia often precede and coexist with the symptoms of the lesion. Indeed headache is an exceedingly common symptom which is independent of vascular complications (see below) and the presence of abnormalities on MRI scans<sup>21</sup>. The headache syndrome is typically migrainous in nature with a high prevalence of visual and sensory aura<sup>22</sup>.

Vascular complications as a result of dural venous sinus thrombosis occur in about 16% of cases<sup>11,12,14,15,16</sup>, and is found in 80% of cases with isolated intracranial hypertension<sup>17-19</sup> and the CSF is in general inactive<sup>11</sup>. Arterial thrombosis is more rare, and aneurysm formation has been reported<sup>20</sup>.

### Investigation results

MRI findings show a close clinico-radiological correlation<sup>23</sup> with a single lesion being the most common abnormality seen. Frequently the lesion diminishes strikingly in size following treatment and recovery<sup>24</sup>.

The cerebrospinal fluid is often abnormal during an acute attack with a raised protein and a CSF leucocytosis which can be in excess of 100 cells per ml. Neutrophils are common early in the illness, with lymphocytes predominating later<sup>11,12</sup>. Oligoclonal bands are not found.

### Neuropathology

The neuropathology is of a chronic meningoencephalitis, with inflammatory cell infiltration and circumscribed



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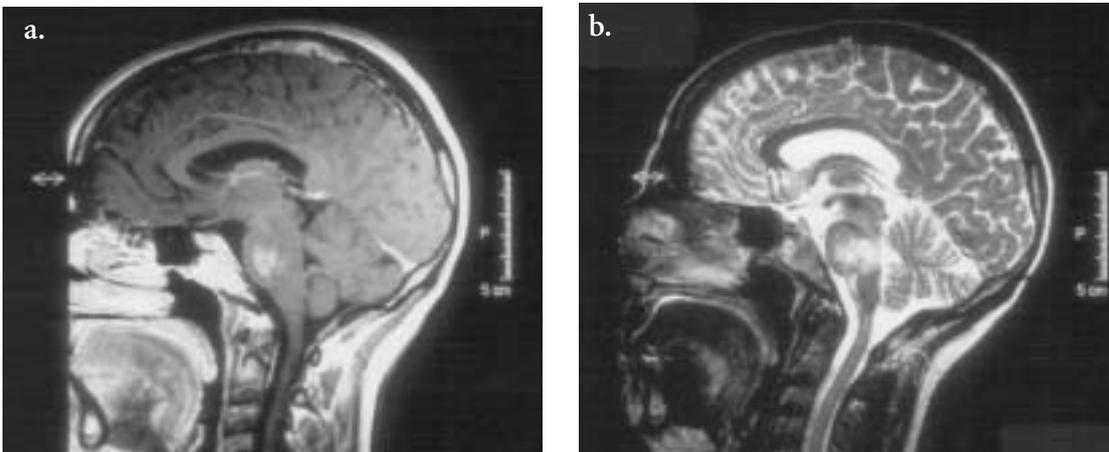


Figure: (a) T1 weighted (490ms, TE 20ms) sagittal MRI scan of brain showing an enhancing mass within the pons with high signal on T2 weighted images (TR 2000ms, TE 130ms) (b).

areas of necrosis with loss of all tissue elements, accumulation of lipid-laden macrophages and gliosis<sup>25</sup>. There is a marked infiltration by neutrophils and eosinophils as well as lymphocytes, and there is at times marked axonal degeneration within lesions<sup>26</sup>. No evidence for vasculitis has been found in this or other pathological studies aside from one report of fibrinoid necrosis within small post-capillary venules. This was not however seen in adjacent arterioles<sup>27</sup>.

### Natural history and prognosis

Four papers provide reasonable details on the natural history of the disorder; which taken together reviews 454 patients seen over ten years<sup>11,12,14,15</sup>. The majority (77%) had parenchymal disease in which there was involvement of the brain, brainstem or spinal cord. 41% had only single attacks<sup>11,15</sup>, most others went on to have further attacks or to develop a progressive disease course (some 25%), often with superimposed relapses<sup>11,12,15</sup>, although approximately 10% of patients present with a primarily progressive disease course, without relapses. Others have "silent" lesions; patients without symptoms of neurological involvement who nonetheless have abnormal neurological signs which are not attributable to an alternative disease process (about 20% in one series)<sup>12</sup>.

The prognosis in this condition seems to be related to number of attacks, the degree to which recovery occurs with each attack, whether there is brainstem involvement and the presence of a progressive disease course<sup>12,15</sup>. In two studies<sup>11,12</sup> CSF white cell count at the time of presentation was correlated with subsequent outcome, although this remains unproven.

In one series the median time to death or dependent disability in those followed for three or more years was only 115 months<sup>12</sup>, although in another<sup>15</sup> the ten year survival was 96%.

The prognosis for neurological complications related to vascular disturbances is in general much better; those presenting with intracranial hypertension on its own when treated tend not to develop recurrences, nor do patients with vascular occlusive complications. Formerly it appeared that such patients did not develop other neurological complications and vice versa but new data suggest that patients may at different times develop both forms of neurological complication and indeed some may present with parenchymal and vascular complications simultaneously (Al-Araji and Akman-Demir, personal communications).

**Table:** International Study Group for Behçet's disease (ISG) criteria; patients who fulfil these criteria must have two or more of the features noted.

Recurrent minor or major aphthous or herpetiform ulceration of the mouth

<i>plus</i>	recurrent genital ulceration
	erythema nodosum
	pseudofolliculitis
	papulopostular eruption
	aceiform nodules
	positive pathergy test
	anterior or posterior uveitis
	retinal vasculitis

### Treatment

No reasonable treatment trial has been carried out for any neurological complication of the syndrome, however uveitis has been studied carefully, and there are many histological and immunological similarities. These studies have shown that use of corticosteroids is often helpful but that other immunosuppression is usually also required. Azathioprine, methotrexate, Cyclosporin A, Chlorambucil and Cyclophosphamide have all been used with success in ocular complications. More recently Interferon/ 2a<sup>28</sup> and infliximab<sup>29</sup> have been used with success even in patients seemingly resistant to other immunosuppressants. These two new drugs are currently being tested in large blinded trials in Europe and the US.

### Concluding comments

Neurological complications of Behçet's syndrome are rare; the majority arise as a result of inflammation of parenchymal structures, the others as a result of vascular complications. Most patients recover well and suffer only single attacks although others develop increasing impairments due to repeated attacks and/or to a progressive disease course. Immunosuppression can stabilise the disease in some but not all patients. Further studies are required which identify more clearly the pathophysiology of neurological involvement in this uncommon condition.

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## Adamantiades-Behçet's Disease

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Proceedings of the 10<sup>th</sup> International Conference on Behçet's Disease, held June 27-29, 2002 in Berlin, Germany.



Benediktos Adamantiades

This book is entitled "Adamantiades-Behçet's Disease" to honour both pioneers, Benediktos Adamantiades and Hulüsi Behçet, who studied patients with the disease in the first half of the 20<sup>th</sup> century and who both published their data describing signs of a new disorder.

The book presents the state-of-the-art in historical perspectives, epidemiology, diagnostic criteria, prognostic parameters, methods for assessment of disease activity and quality of life, clinical investigation, etiopathology including the genetics and immunology of the disease, basic research, therapeutics, and physician-to-patient relations. Furthermore the manuscripts arising from a patient / physician session have also been included. The intensive exchange among expert physicians and patient representatives on scientific and personal levels which took place during the conference may be of great advantage for our patients and their families.



Hulüsi Behçet

### Contents

**History • Epidemiology • Diagnostic Criteria, Prognostic Parameters, Assessment of Disease Activity, and Quality of Life • Pathogenesis • Genetics • Immunology • Concepts for Research • Mucocutaneous Manifestations • Ocular Manifestations • Neurological Manifestations • Cardiovascular Involvement • Various Clinical Manifestations • Treatment • Patient - Physician Relationships •**