CLINICAL PICTURE

30 Years old male patient presented clinically with bilateral pyramidal tract signs, pseudo-bulbar palsy, with orogenital ulcerations. The patient also gave a history of nonspecific relapsing headache. Examination of sensation did not show any abnormality.

RADIOLOGICAL FINDINGS

Figure 1. Precontrast MRI T1 images showing focal signal hypointensity in the left basis pontis, left crus cerebri (cerebral peduncle) and the posterior limb of the internal capsule. The focal hypointense lesions has no or very mild mass effect and they are apparently continuos cephalocaudally. Contralaterally, the pontine basis is showing a very small hypointense lesion in the right side. The lesions are located in the presumed anatomical area of the corticospinal (pyramidal) tract.
Figure 2. Postcontrast MRI T1 images showing enhancement of the hypointense lesions shown in figure 1. The lesion in the right anterior pontine zone is more definite now and is better delineated by contrast enhancement. All enhanced areas are surrounded by a hypointense edema area with mild mass effect. Also notice contrast enhancement of the meningeal covering of the pons and midbrain which indicates the existence of a meningitic element.

Figure 3. Postcontrast coronal MRI T1 images showing that the pontine, midbrain and capsular lesions described in figure 1,2 are continuous cephalocaudally as a linear long lesion, the lesion is surrounded by a hypointense edema area and is located in the presumed anatomical area of the corticospinal (pyramidal) tract. The corticospinal tract was actually mapped by contrast enhancement. The contralateral side is involved to a lessor degree. Notice meningeal enhancement which reflects a meningitic element. Contrast enhancement of the corticospinal tract in this case is due to break down of the blood brain barrier along the course of the corticospinal tract and it is a good sign of vasogenic edema which is mainly due to break down of the blood brain barrier (70). Notice middle line crossing of the lesions suggesting its venous rather that arterial origin. Also notice the mild mass effect induced by the pyramidal tract lesion in the left side which could be due to edema.
Figure 4. Postcontrast sagittal MRI T1 images showing that the pontine, midbrain and capsular lesions described in figure 1, 2, 3 are continuous cephalocaudally as a linear long lesion in the anterior parts of the pons and midbrain, the lesion is located in the presumed anatomical area of the corticospinal (pyramidal) tract and is seen surrounded by a hypointense edema area. The corticospinal tract was actually mapped by contrast enhancement. Also notice meningeal enhancement. Thrombosis of the superficial and deep venous systems is also seen.

Figure 5. MRI T2 image showing the capsular lesion (in the posterior limb of the internal capsule). The lesion is mainly hyperintense with some hypointense zones probably representing a hemorrhagic element.

In general the observed pathology in this case represents demyelination and edema along the cortico-spinal tract fibers (in fact the pyramidal tract is actually anatomically drawn by the MRI signal changes of vasogenic edema and contrast enhancement) and is found to be located mainly in the midbrain/thalamus (which probably constitutes the primary site of involvement) with upward extension to the posterior limb of the internal capsule and downward extension to the basis pontis. The upward and downward extension of the primary midbrain/thalamic lesions might be explained by wallerian degeneration and this was noted in some pathologic studies as well (20, 43, 44).

**DIAGNOSIS:**

**NEURO-BEHÇET SYNDROME**

**DISCUSSION**

Behçet's disease (BD) is an uncommon, relapsing and remitting, multisystem inflammatory disorder characterized by the triad of oral ulceration, genital ulceration, and uveitis. 61 A number of additional features are commonly
present, including arthritis, retinal and cutaneous vasculitis, thrombophlebitis, and gastroenteric disorders. The essential lesion is a focus of chronic inflammation, typically in the vicinity of a small blood vessel. Lesions in the CNS resemble those in other organ systems. Characteristically there are multiple small foci of softening that may eventually become confluent. These correspond to myelin loss and, to a lesser degree, drop out of neural elements with replacement by foamy macrophages. The lesions are not fundamentally demyelinating and more closely resemble minute ischemic foci. As in the periphery, lesions tend to occur near blood vessels, but vasculitis is uncommon. Pathologic findings are most extensive in the midbrain, pons (especially the basis pontis) and the medulla, and there is typically a lesser degree of involvement of the spinal cord, internal capsule, globus pallidus, optic nerves, and hypothalamus. In some cases, the cerebral white matter, cortex, hippocampus, basal ganglia, and thalamus are involved. The cerebellum is usually spared. The meninges are typically thickened and adherent to the brain surface, and acutely there may be considerable meningeal inflammation; hence the common reference to neuro-Behçet's disease as a meningoencephalitis. (The x ray room) (Print this case report)

In general the most common presentation of parenchymal CNS involvement is a subacute brainstem syndrome with cranial nerve findings, dysarthria, and cerebellar or corticospinal tract signs. More infrequent presentations include a stroke-like presentation (with the acute onset of unilateral neurologic findings and signs of cortical involvement including seizures) and psychiatric features, such as psychosis. Sinus venous thrombosis may evolve relatively slowly and results in intracranial hypertension, resulting headache, vomiting, and bilateral papilledema. Impaired memory (long-term verbal and nonverbal) and visuospatial skills occur frequently in patients with active disease who are taking large doses of steroids. Pure spinal cord or PNS involvement is rarely reported. Impairment of sensation is uncommon. (70)

Between 5% and 20% of patients have neurologic disease. (70) The most common neurologic manifestation of Behçet's disease is a relapsing and remitting, but often progressive, focal meningoencephalitis that most often affects the brain stem. (70) Patients present with a host of cranial nerve and long tract signs and eventually develop spastic quadriaparesis and a bulbar or pseudobulbar palsy, frequently with rather dramatic emotional incontinence. (70) Cochlear and vestibular dysfunctions are common. Often there are additional features of impairment in frontal lobe and memory function characteristic of a subcortical dementia. A number of cases of nearly pure subcortical dementia have been reported, but typically long tract signs are prominent, and bulbar involvement eventually develops. Patients may also present initially with features of transverse myelitis, but bulbar signs characteristically appear as the disease progresses. Cerebral cortical involvement is unusual, but seizures and aphasia have been reported. The optic nerves are commonly involved, but symptoms are indiscriminable from those of uveitis, which is usually present in patients with neurologic features. CNS vasculitis is rare, but stroke caused by large artery involvement has been reported. Pseudotumor cerebri is relatively common and almost always caused by venous sinus thrombosis. Cerebral venous thrombosis may affect up to 10% of all patients with Behçet's disease and one third of those with neurologic involvement. CNS involvement generally manifests several years after the onset of systemic Behçet's disease, but occasionally it may be an initial feature and even precede other disease manifestations. As a rule, flares of neurologic disease parallel flares of systemic disease.

Neuro-Behçet's syndrome can be classified as an acute type and as a chronic progressive type (70). It should be pointed out that the two types of neuro-Behçet's syndrome are currently considered to represent different stages rather than independent clinical entities. Acute neuro-Behçet's syndrome is characterized by acute meningoencephalitis with a focal midbrain pyramidal tract lesions, the lesions are anteriorly located in the cerebral peduncles, bilateral, asymmetrical, extending up and down within the brain stem as a longitudinal linear lesion, and presenting high-intensity areas in the MRI T2-weighted images or the fluid attenuated inversion recovery (FLAIR) images (70). Acute neuro-Behçet's syndrome responds to steroid therapy, and is usually self-limiting.

By contrast, the chronic progressive type of neuro-Behçet's syndrome is characterized by intractable, slowly progressive dementia, ataxia and dysarthria, with persistent elevation of cerebrospinal fluid IL-6 activity (> 20 pg/ml) (70). Most patients with the chronic progressive type of neuro-Behçet's syndrome were HLA-B51-positive, and they had history of attacks of acute type neuro-Behçet's syndrome prior to the development of progressive neurological symptoms (70).

The neurological involvement in Behçet's disease is either caused by primary neural parenchymal lesions (neuro-Behçet's syndrome, or brain stem meningoencephalitis) or is secondary to major vascular involvement. The latter type is rarely complicated with the parenchymal lesions and should be called vascular-Behçet's disease. This vascular-Behçet's disease type generally has a better prognosis compared with the parenchymal type. (70) Both vascular and parenchymal types can coexist, as in this case, but this is not common.

- The primary parenchymal neuro-Behçet type
It is primary parenchymal neural disease, a focal brain stem meningoencephalitis affecting the midbrain primarily with selective involvement of the corticospinal tract bilaterally. The most common clinical findings are pyramidal signs. Sensory symptoms or signs are much less frequent in neuro-Behçet disease. (73,74) The corticospinal tract lesions extend cephalocaudally in a linear fashion from the mesencephalon down to the pons and less frequently to the medulla and up to the posterior limb of the internal capsule. The cephalocaudal extension of the midbrain corticospinal tract lesions could be either due to wallerian degeneration or extension of vasogenic edema along the myelinated fibers of the corticospinal tract. (70,73,74)

The corticospinal tract pathology is manifested by MR imaging as bilateral and asymmetrical longitudinal linear lesions extending from the posterior limb of the internal capsule down to the midbrain, pons and less frequently the medulla. The midbrain is more severely affected. The corticospinal tract linear lesions are hyperintense on the MRI T2 images and hypointense on the MRI T1 images and show contrast enhancement in the acute stage. Contrast enhancement is due to break down of the blood brain barrier and this is in favour of the corticospinal tract MRI signal changes being due vasogenic edema. (70,73,74)

Vascular-Behçet's type

Involvement of veins and arteries in Behçet's disease is usually called vasculo-Behçet's disease. Venous thrombosis appeared to be the major vascular involvement in 7–33% of patients with Behçet's disease, and represents 85–93% of vascular-Behçet's disease (70). The brain parenchymal involvement seen in the primary neuro-Behçet type is rarely seen in the vascular type of Behçet disease. Parenchymal involvement in the vascular type of Behçet disease is more commonly secondary to venous sinus thrombosis. Deep vein thrombosis or cerebral sinus thrombosis are significantly associated with the male gender and a positive pathergy test (70). Venous thrombosis is a reflection of thrombophilia in vascular Behçet's disease. (70,73,74). To the best of the author's information, cerebral sinovenous thrombosis in the vascular-Behçet type is indistinguishable from sinovenous thrombosis due to any other cause and is only distinct from the view point that it is commonly associated clinically with orogenital ulcerations. Probably vascular-Behçet syndrome must be put in the differential diagnosis of cases presented with cerebral sinovenous thrombosis of undetermined aetiology.

The clinical picture of vascular Behçet is different from that of primary neuro-Behçet. The clinical picture of neuro-Behçet is dominated by a mainly motor clinical picture with bilateral pyramidal tract signs, pseudo-bulbar palsy, subcortical dementia, etc. and sensory symptoms are uncommon, while the clinical picture of vascular Behçet is that of acute and chronic cerebral sinovenous thrombosis and its parenchymal complications (headache, seizures, focal sensory and motor deficits, bilateral papilledema, pseudotumor cerebri).

A number of studies have explored the pathogenesis of thrombophilia in Behçet's disease. Neither deficiency in protein C, in protein S, in factor V Leiden and in antithrombin III nor resistance to activated protein C and anticardiolipin antibody levels seemed to be correlated with vascular thrombosis in Behçet's disease (75,76). There were increased thrombin generation, fibrinolysis, and thrombomodulin in Behçet's disease, but these abnormalities were not related to thrombosis (76). These results therefore suggest that thrombophilia in Behçet's disease might be related more to inflammation than to clotting disorder.

Arterial involvement, although rare, does occur in Behçet's disease. The arterial manifestations in Behçet's disease resemble those of Takayasu's arteritis, including arterial occlusion and aneurysm formation. Histopathological studies revealed that the number of vasa vasorum with infiltration of neutrophils and lymphocytes was significantly increased in vascular-Behçet's disease compared with in Takayasu's arteritis and other inflammatory aneurysms (70). It was therefore suggested that arterial involvement in vascular-Behçet (vasculo-Behçet) disease might be caused by a neutrophilic vasculitis targeting the vasa vasorum, leading to degeneration of the arterial wall. (70,73,74)

Table 1. Lesion characteristics in the primary parenchymal neuro-Behçet type

- The lesion in the primary parenchymal neuro-Behçet type is a focal brain stem meningoencephalitis affecting the midbrain primarily with selective involvement of the corticospinal tract bilaterally.

- The most common clinical findings are pyramidal signs. Sensory symptoms or signs are much less frequent...
The corticospinal tract lesions extend cephalocaudally in a linear fashion from the mesencephalon down to the pons and less frequently to the medulla and up to the posterior limb of the internal capsule. The cephalocaudal extension of the midbrain corticospinal tract lesions could be either due to wallerian degeneration or extension of vasogenic edema along the myelinated fibers of the corticospinal tract.

The corticospinal tract pathology is manifested by MR imaging as bilateral and asymmetrical longitudinal linear lesions extending from the posterior limb of the internal capsule down to the midbrain, pons and less frequently the medulla. The midbrain is more severely affected. The corticospinal tract linear lesions are hyperintense on the MRI T2 images and hypointense on the MRI T1 images and show contrast enhancement in the acute stage. Contrast enhancement is due to break down of the blood brain barrier and this is in favour of the corticospinal tract MRI signal changes being due vasogenic edema. (70,73,74)

The corticospinal tract linear lesions are sometimes surrounded by a hypointense edema area with positive mild mass effect.

Table 2. The differences between the primary parenchymal neuro-Behçet type and the vascular-Behçet's type

<table>
<thead>
<tr>
<th>Parameter</th>
<th>The primary parenchymal neuro-Behçet type</th>
<th>Vascular-Behçet's type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical picture</td>
<td>The clinical picture of neuro-Behçet is dominated by a mainly motor clinical picture with bilateral pyramidal tract signs, pseudo-bulbar palsy, subcortical dementia etc. Sensory symptoms are uncommon</td>
<td>The clinical picture of vascular Behçet is that of acute and chronic cerebral sinovenous thrombosis and its parenchymal complications (headache, seizures, focal sensory and motor deficits, bilateral papilledema, pseudotumor cerebri, etc.).</td>
</tr>
<tr>
<td>Incidence</td>
<td>More common (70-93%)</td>
<td>Less common (7-33%)</td>
</tr>
<tr>
<td>Pathology &amp; pathogenesis</td>
<td>It is primary parenchymal neural disease, a focal brain stem meningoencephalitis affecting the midbrain primarily with upward and downward extension (along the pyramidal tract fibers to the posterior limb of the internal capsule, the basis pontis and the medulla) and with selective involvement of the corticospinal tract bilaterally.</td>
<td>Venous thrombosis is a reflection of thrombophilia in Behçet's disease. Thrombophilia in Behçet's disease might be related more to inflammation than to clotting disorder.</td>
</tr>
<tr>
<td>Radiological findings</td>
<td>The corticospinal tract pathology is manifested by MR imaging as bilateral and asymmetrical longitudinal linear lesions extending from the posterior limb of the internal capsule down to the midbrain, pons and less frequently the medulla. The midbrain is more severely affected. The corticospinal tract linear lesions are hyperintense on the MRI T2 images and hypointense on the MRI T1 images and show contrast enhancement in the acute stage. Contrast enhancement is due to break down of the blood brain barrier and this is in favour of the corticospinal tract MRI signal changes being due vasogenic edema. (70,73,74)</td>
<td>The MRI picture is that of sinovenous thrombosis and its parenchymal complications (70)</td>
</tr>
<tr>
<td>Prognosis</td>
<td>Bad, higher incidence of being transformed into the progressive type with subcortical dementia, etc.</td>
<td>Better</td>
</tr>
<tr>
<td>Management</td>
<td>Steroid responsive</td>
<td>Anticoagulants, steroid may play a role</td>
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</table>

Currently, the most widely used diagnostic criteria of Behcet's disease is the International Study Group's classification, which requires recurrent oral ulcerations plus two of the following in order to establish a definite diagnosis: recurrent genital ulcerations, skin or eye lesions, or a positive pathergy test (13). The epidemiology of disease shows geographic variation, encountered more commonly along the Silk Road, which extends from the Mediterranean region to Japan (15). This is coupled with a similar variation in HLA B51 (human leukocyte antigen), which has been reported to be strongly associated with the disease in the high prevalence areas (16–19). Despite broadened clinical understanding of this disease, the etiologic factors remain obscured and speculative:
viral agents, immunologic factors, genetic causes, bacterial factors, and fibrinolytic defects have all been implicated (3, 20–25). Vessel wall and perivascular mononuclear cell infiltration, which is consistent with vasculitis involving both arterial and venous systems, has been shown in histopathologic studies (20, 21). It has been postulated that genetic susceptibility together with a possible trigger by an extrinsic factor, such as an infectious agent, is responsible for the observed vasculitis (24, 26).

<table>
<thead>
<tr>
<th>Table 3. The International Study Group criteria for the diagnosis of Behcet disease</th>
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<tbody>
<tr>
<td>At least 3 episodes of oral ulceration must occur in a 12-month period. They must be observed by a physician or the patient and may be herpetiform or aphthous in nature.</td>
</tr>
<tr>
<td>At least 2 of the following must occur:</td>
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<tr>
<td>o Recurrent, painful genital ulcers that heal with scarring.</td>
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<td>o Ophthalmic lesions, including anterior or posterior uveitis, hypopyon, or retinal vasculitis.</td>
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<tr>
<td>o Skin lesions, including erythema nodosum, pseudofolliculitis, or papulopustular lesions (may also include atypical acne).</td>
</tr>
<tr>
<td>o Pathergy: defined as a sterile erythematous papule larger than 2 mm in size appearing 48 hours after skin pricks with a sharp, sterile needle (a dull needle may be used as a control).</td>
</tr>
</tbody>
</table>

Neurologic involvement in Behcet's disease, was first reported in 1941 by Knapp (27), and the term neuro-Behçet syndrome was introduced by Cavara and D'Ermo in 1954 (28). The reported rate of development of neurologic involvement among Behcet's disease patients ranges from 4% to 49% (9, 29). This rate was found to be 6.7% in our large nonselective series of patients referred from the Behçet's Disease Research Center (30).

Neuro-Behçet syndrome may present as an acute focal or multifocal CNS dysfunction, and the clinical picture of neuro-Behçet syndrome may resemble multiple sclerosis (MS) (7, 31–35). It has been observed that a substantial number of patients with neuro-Behçet syndrome will have a relapsing-remitting course while others may develop a secondary-progressive course; some neuro-Behçet syndrome patients have an insidious onset, with primary-progressive CNS dysfunction, and others may display symptoms attributable to intracranial hypertension associated with dural venous sinus thrombosis (12, 36, 37). Although non-neurologic involvement generally precedes neurologic findings, the non-neurologic involvement may go unrecognized in some cases or it may appear late in the patient's course, thus posing diagnostic difficulties (38–40). Peripheral nerve involvement, although reported in neuro-Behçet syndrome, is relatively uncommon (41).

The most common imaging lesion seen in the acute or subacute stage of neuro-Behçet syndrome is an asymmetric mesodiencephalic junction lesions (7–9, 33). These lesions extend along long fiber tracts and spare the red nucleus, suggesting that this downward extension is due to edema. The reversibility of the extension, leaving small residual lesions at the center, as observed on follow-up MR studies, further supports their edematous nature. This feature was also noted in earlier publications (9, 11, 42). Accordingly, pontobulbar involvement was an extension of lesions located at other sites, particularly the mesodiencephalic junction. The distribution and intensity of changes of the residual lesions closely corresponded to pathologic descriptions of secondary demyelination (20, 21, 43, 44). In the chronic cases, Changes may extend to the cervical cord, along the corticospinal tract, and this might be explained by wallerian degeneration. This was noted in some pathologic studies as well (20, 43, 44).

Taken together, the current case (case version number 1.4) and the previously reported case in version 1.3 of this publication emphasized and highlighted the following common clinical-radiological findings in neuro-Behçet syndrome:

1. In general the observed pathology in these cases represents demyelination and edema along the corticospinal tract fibers (in fact the pyramidal tract is actually anatomically drawn by the MRI signal changes of vasogenic edema and contrast enhancement) and is found to be located mainly in the midbrain/thalamus (which probably constitutes the primary site of involvement) with upward extension to the posterior limb of the internal capsule and downward extension to the basis pontis. The upward and downward extension of the primary midbrain/thalamic lesions might be explained by wallerian degeneration or vasogenic edema (which characteristically spreads along the myelinated fibers of long tracts) and this was noted in some pathologic studies as well (20, 43, 44)

2. The selective involvement of the corticospinal tract would explain the clinical picture of these patients which is dominated by pyramidal tract involvement and pseudo-bulbar palsy with absence of sensory changes. In fact the clinical picture and the MRI findings in neuro-Behçet syndrome closely resemble those of motor neuron disease with pseudo-bulbar palsy (they both shared common topographic distribution and spatial extension of
the corticospinal tract lesions), however the corticospinal tract lesion in motor neuron disease does not show contrast enhancement. (70). The corticospinal tract linear lesion appeared larger in size in acute neuro-Behçet syndrome compared with that of motor neuron disease probably due to the contribution of edema in neuro-Behçet syndrome. The corticospinal tract lesion is reversible in the acute neuro-Behçet syndrome, however it is irreversible in motor neuron disease. In general the lesion in acute neuro-Behçet syndrome has an acute onset and a regressive course, while that of motor neuron disease has a chronic progressive course. The MRI signal changes along the course of the corticospinal tract are mainly due to reversible vasogenic edema in acute neuro-Behçet syndrome, while the MRI signal changes along the course of the corticospinal tract in motor neuron disease are mainly due to wallerian degeneration. See table 4

3. Both cases (this case and the previously reported case in version 1.3 of this publication) shared common clinical (purely motor clinical presentation) and common MRI findings (selective pyramidal tract involvement). However sinus thrombosis was demonstrated only in the current case. Which simply means that the parenchymal lesion demonstrated in neuro-Behçet syndrome is a primary neuronal lesion and not secondary to sinus thrombosis (Behcet's disease is a relapsing and remitting, but often progressive, focal meningoencephalitis that most often affects the brain stem). Sinus thrombosis is probably a product of the primary pathology. In the current patient the presence of the midbrain lesions characteristic of the primary neural type of Behçet disease associated with cerebral sinus thrombosis simply means that both the primary parenchymal neural type and the vascular type of Behçet disease can coexist in a single patient, but this uncommon. Vascular Behçet is rarely associated with neuro-Behçet. The predominant histopathological features in the inflamed tissues in Behcet's disease are infiltration of lymphocytes and monocytes, and sometimes polymorph nuclear leukocytes, through small veins without microscopic changes in the vessel walls. Thrombophilia or thrombophlebitis involving small and large veins is also common, whereas arteritis is rare. In these regards, Behçet's disease is unique compared with other vasculitides.

4. The existence of meningeal enhancement at the midbrain and pontine level in this case (version number 1.4) is simply a reflection of a meningitic process at the pontine and midbrain levels. The meninges are typically thickened and adherent to the brain surface in neuro-Behçet syndrome, and acutely there may be considerable meningeal inflammation; hence the common reference to neuro-Behçet's disease as a meningoencephalitis. (70) Meningeal enhancement could not be appreciated radiologically in the previously reported case (number 1.3).

Table 4. Differences between motor neuron disease and acute neuro-Behçet syndrome, with regard to the corticospinal tract affection

<table>
<thead>
<tr>
<th>The corticospinal tract lesion in neuro-Behçet syndrome</th>
<th>The corticospinal tract lesion in motor neuron disease</th>
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<tbody>
<tr>
<td>The corticospinal tract linear lesion appeared larger in size probably due to the contribution of edema</td>
<td>Smaller in size</td>
</tr>
<tr>
<td>Reversible</td>
<td>Irreversible</td>
</tr>
<tr>
<td>Show contrast enhancement</td>
<td>Does not show contrast enhancement</td>
</tr>
<tr>
<td>Has an acute onset and a regressive course</td>
<td>Has a chronic progressive course</td>
</tr>
<tr>
<td>MRI signal changes are mainly due to reversible vasogenic edema</td>
<td>MRI signal changes are mainly due to wallerian degeneration</td>
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</table>

In presented patient, an asymmetric subcortical and deep periventricular white matter involvement (involving mainly the posterior limb of the internal capsule) without cortical involvement was observed. The patient also had concomitant mesodiencephalic junction lesions. In the majority of reported cases with hemispheric involvement, the lesions were located subcortically, particularly within temporal and occipital regions (7–11, 34, 39, 45, 46). In the acute stage the periventricular white matter changes are due to edema, while in the chronic stage these white matter changes are due to wallerian degeneration, gliosis, and demyelination (4, 20, 21, 43, 44, 47, 48).

Vasculitis is regarded as the key feature in neuro-Behçet syndrome (3, 26), as biopsy specimens from mucous and cutaneous lesions show those changes (54, 55). Arterial and venous large vessel involvement, such as narrowing, occlusion, and aneurysmal formation, has been reported in up to 27% to 35% of cases, with 12% arterial and 88% venous (52). An even greater proportion of patients with neuro-Behçet syndrome may have small vessel vasculitis, and recently this has been validated as the pathologic basis of various histologic changes observed in different organ systems (26).
Lesions of arterial origin may be observed in some patients, in whom these lesions, for example, may lie within the pons without crossing the midline, consistent with involvement of the penetrating arteries. Although such lesions, resulting from small or medium-sized intracranial arteries, have been reported either microscopically or radiologically in neuro-Behçet syndrome, they are not as common as the arterial lesions observed with the involvement of other systems (20, 21, 40, 43, 47, 48, 50–52). There are also a few publications concerning the involvement of large intracranial arteries (40, 51–53). Hemorrhagic lesions seen in some patients most likely resulted from "diapedesis of red cells around veins," as already reported, and are not of arterial origin (21).

Autopsy studies and biopsy specimens of the CNS lesions are consistent with vasculitis as well, and they show a clear venous predominance (20, 21, 49). Radiologic studies support this finding that lesions seen in neuro-Behçet syndrome are not compatible with arterial territories. Furthermore, significant perilesional edema with a tendency to disappear or to leave disproportionately small residua on follow-up studies has been reported. This feature is consistent with venous infarction, since not all signal intensity changes seen in venous occlusive disease necessarily represent infarction, but rather an accumulation of water within interstitial spaces (56, 57). This information, together with our observations, supports the probable inflammatory-venous pathogenesis for the CNS lesions seen in Behçet's disease.

<table>
<thead>
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<th>Table 5. Factors that support the probable inflammatory-venous pathogenesis for the CNS lesions seen in neuro-Behçet syndrome</th>
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<tbody>
<tr>
<td>Arterial lesions are unilateral and do not cross the middle line, while lesions observed in neuro-Behçet syndrome are frequently bilateral with frequent midline crossing.</td>
</tr>
<tr>
<td>Autopsy studies and biopsy specimens of the CNS lesions are consistent with vasculitis with a clear venous predominance (20, 21, 49).</td>
</tr>
<tr>
<td>Significant perilesional edema with a tendency to disappear or to leave disproportionately small residua on follow-up studies has been reported. This feature is consistent with venous infarction, since not all signal intensity changes seen in venous occlusive disease necessarily represent infarction, but rather an accumulation of water within interstitial spaces (56, 57).</td>
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</table>

If one considers the possible venous territories in which brain stem lesions have occurred in neuro-Behçet syndrome, it is clear that the affected venous structures are indeed small intraaxial veins of the brain stem (58). That particular predilection of occurrence raises the question of why these veins are affected or why occlusion of them causes symptoms. The literature on autopsy studies states no apparent tendency toward these venous channels, and brain stem veins and cerebral hemispherical veins are equally affected, although there is a clear-cut predominance of lesions in the brain stem. The question can also be addressed according to regional hemodynamic properties. It is well known that cerebral hemispherical structures are drained by superficial and deep venous systems, both of which anastomose via medullary veins. They interconnect superficial pial veins to the internal cerebral vein and the basal vein of Rosenthal, the former being more common than the latter (59), whereas in the brain stem, intraparenchymal radial and longitudinal anastomotic channels are nearly absent (58). In the spinal cord, intraaxial anastomoses are claimed to be prominent at the thoracic level (60). The particular arrangement of veins in the cerebral hemisphere permits them to flow in both directions via medullary veins, as seen with certain disorders, such as deep arteriovenous malformations, Sturge-Weber disease, and the developmental venous anomalies (60), possibly explaining the small diameter and unimportance of parenchymal lesions when such a vein is thrombosed. At the mesencephalic, diencephalic, and pontine levels, thrombosis of small veins might be accompanied by a very large, sometimes hemorrhagic lesion, since there is nearly no collateral venous pathway. The same anatomic arrangement might also explain the vulnerability of the cervical spinal cord (7, 44). It appears, therefore, that the variability of venous anatomic arrangements at different levels of the CNS might explain the predilection of lesions for different regions.

Vasculitis, like inflammation in other tissues, is caused by many different agents and pathogenic mechanisms; however, these different causes produce only a limited number of histologic expressions of injury. The major type of injury to nervous tissue in vasculitis is ischemia. Therefore, the same clinical manifestations can result from etiologically and pathogenetically different vasculitic diseases. In vasculitic processes, location, extension, and distribution of vascular involvement might point to a specific diagnosis, such as Takayasu or temporal arteritis (26, 61–65). In neuro-Behçet syndrome, lesions therefore appear secondary to the small vessel venous vasculitis, and the anatomy of those intraaxial venous structures explains the dominant involvement of the upper brain stem and diencephalic structures.

Pathologically proved small vessel arteritis, either alone or with venous inflammation, has also been reported in conjunction with neuro-Behçet syndrome, and it is probable that some of the cerebral hemisphere and midbrain lesions might result from small vessel arteritis (62, 63). In this case, there appeared to be at least one lesion that
Vasogenic edema is the most common type of edema associated with brain tumors, venous congestion and other causes and results from local disruption of the blood brain barrier. This leads to extravasation of protein-rich filtrate of plasma into the interstitial space, with subsequent accumulation of vascular fluid. This disruption results from loosening of the tight junctions between endothelial cells, and the neoformation of pinocytic vesicles. Once the barrier is breached, hydrostatic and osmotic forces work together to extravasate intravascular fluid. Once extravasated, fluid is retained outside the vasculature, mostly in the white matter of the brain, and within the bundles of myelinated axons of long tracts and commissural fibers. This is because axons run in parallel bundles of fibres with loose extracellular space (that offer low resistance and facilitates the extension of vasogenic edema along myelinated axons which are spreaded apart by the edema) as opposed to gray matter, which has high cell density and is enmeshed in an interwoven network of connecting fibres that offer high resistance to the formation and spread of edema. By definition, this type of edema is confined to the extracellular space. (70) In neuro-Behçet case reports of diffusion weighted imaging (DWI) of the T2 hyperintense lesions revealed elevated ADC values compared to normal subjects, indicating restricted diffusion and the presence of vasogenic edema (71,72). Contrast enhancement of the corticospinal tract in this case is due to break down of the blood brain barrier along the course of the corticospinal tract and it is a good sign of vasogenic edema which is mainly due to break down of the blood brain barrier. (70)

Anther explanation for the selective involvement of the corticospinal tract in neuro-Behçet is that the signal changes observed in the MRI study is due to vasogenic edema secondary to venous congestion, vasogenic interstitial edema spreads in the white matter along myelinated fibers of long tracts and commissural fibers (This is because axons of long tracts run in parallel bundles of fibres with loose extracellular space that offer low resistance to the formation and spread of edema as opposed to grey matter). The long tracts are anteriorly located within the brain stem in the crus cerebra, cerebral peduncle, and basis pontis. Subsequently brain stem interstitial or vasogenic edema is much more likely to be concentrated anteriorly within the corticospinal tract as vasogenic edema spreads the myelinated fibers apart and extends along them. In the presented case the MRI signal changes were maximum in the upper midbrain and internal capsule, present to a lesser extent in the pons and to a much less extent in the medulla. Anatomically the corticospinal tract remains abundant, compact and in a single bundle as it transverses in the posterior limb of the internal capsule down to the cerebral peduncle (crus cerebri) in the midbrain. The corticospinal and corticobulbar fibers gradually decreases in number as they descend down to the pons, and through the medulla to the spinal cord. Also starting from the level of pons and downward the corticospinal tract starts to fragment into scattered, irregular and isolated bundles. The corticospinal fibers, being more abundant and more compact at the internal capsule and midbrain levels, compared with corticospinal fibers at the level of pons and medulla, would explain why MRI signal changes were maximum in the internal capsule and upper midbrain.

However selective involvement of the corticospinal tract in Behçet disease still needs further explanation. Taken together, this case and the case reported in version 1.3 of this publication clearly demonstrate the selective pyramidal tract involvement in neuro-Behçet.

Concerning the differential diagnosis, hemispheric white matter lesions are not common in neuro-Behçet syndrome, and when they are present, they are more likely to be subcortical than periventricular. Furthermore, these are generally associated with brain stem--diencephalic lesions. That combination is unlikely in systemic lupus erythematosus (SLE) and non-Behçet vasculitides. CNS involvement due to SLE and other systemic vasculitides tends to involve arterial territories, and as a result, cortical involvement is frequently observed (34, 66, 67). We have not observed cortical involvement in neuro-Behçet syndrome, despite pathologic studies in which such involvement has been reported (21). These changes, however, are minor in neuro-Behçet syndrome, which may explain the radiologic-pathologic discrepancy. Periventricular and ovoid lesions suggestive of MS are not expected to be seen in neuro-Behçet syndrome.

Extensive confluent periventricular changes that are seen in MS and occasionally in sarcoidosis were not observed in this patient with neuro-Behçet syndrome. Posterior fossa lesions, particularly those located around the fourth
ventricle with or without the associated supratentorial lesions seen in MS, are not similar to the neuro-Behçet syndrome lesions described above. Brain stem lesions in MS are usually small, even in the acute stage, and prominent brainstem and/or cerebellar atrophy without cerebral volume loss, which is observed in the chronic phase of neuro-Behçet syndrome, is unusual in MS (7, 34). When one considers cervical involvement, this rarely extends more than a few vertebral segments in MS (68), unlike the more extensive lesions we observed in neuro-Behçet syndrome. Leptomeningeal contrast enhancement is a typical finding of sarcoidosis (69). We did not encounter this finding in patients with neuro-Behçet syndrome. Devlin et al (38) reported abnormal leptomeningeal enhancement in two of their patients with neuro-Behçet syndrome. Abnormal meningeal enhancement secondary to dural venous occlusion or to lumbar puncture should be excluded before attributing it to the disease itself (70).

Table 6. Differences between neuro-Behçet syndrome, and other similar diseases

<table>
<thead>
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<th>Pathology</th>
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<td>CNS lupus versus neuro-Behçet</td>
<td>Periventricular and ovoid lesions suggestive of MS are not expected to be seen in neuro-Behçet syndrome. Extensive confluent periventricular changes that are seen in MS and occasionally in sarcoidosis are not observed in neuro-Behçet syndrome. Posterior fossa lesions, particularly those located around the fourth ventricle with or without the associated supratentorial lesions seen in MS, are not similar to the neuro-Behçet syndrome lesions. When one considers cervical involvement, this rarely extends more than a few vertebral segments in MS (68), unlike the more extensive lesions observed in neuro-Behçet syndrome. Brain stem lesions in MS are usually small, even in the acute stage, and prominent brainstem and/or cerebellar atrophy without cerebral volume loss, which is observed in the chronic phase of neuro-Behçet syndrome, is unusual in MS (7, 34) Abnormal meningeal enhancement is unusual in MS and reported in neuro-Behçet syndrome. (38)</td>
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Inflammatory demyelinating diseases, such as MS, and inflammatory vascular disorders (vasculitides), such as neuro-Behçet syndrome and SLE, can affect the CNS primarily or secondarily, and onset tends to occur in young adulthood. Although the clinical presentation of these diseases may be similar, the radiologic findings of neuro-Behçet syndrome are quite distinct, which may help differentiate it from other disorders, even in the absence of overt systemic involvement.

The diagnosis of Behcet's disease is clinical. Patients with Behcet's disease and venous thrombosis are often heterozygotes or homozygotes for the factor V Leiden allele. The CSF in patients with neurologic involvement is typically characterized by a pleocytosis (usually less than 100/mm3) that is equally likely to be neutrophil or lymphocyte predominant. CSF protein is only slightly elevated. There have been reports of intrathecal synthesis of oligoclonal IgA and IgM. An immunofixation electrophoretic pattern of oligoclonal bands has been reported in 16% of patients. Magnetic resonance imaging in patients with CNS disease typically reveals multiple 3-10 mm in diameter sharply margined, irregular, and often confluent lesions in the spinal cord, brainstem, thalamus, basal ganglia, and deep cerebral white matter. The lesions may be quite extensive. In some cases, they may be difficult to distinguish from those of multiple sclerosis, but Dawson's fingers are not seen. (70)

High-dose corticosteroids (prednisone 60 mg/day) are effective in suppressing skin, mucosal, and arthritic manifestations of Behcet's disease. Pulse corticosteroids (methylprednisolone 1 gm/day for 3 days) are often employed effectively for acute flares of neurologic disease, but the effect of corticosteroid treatment on chronic or recurrent neurologic disease is less satisfactory. Corticosteroids are clearly ineffective in halting the progression of uveitis and chlorambucil; 0.1-0.2 mg/kg/day has been used with considerable success in treating this disabling manifestation. (70) O'Duffy, (3) also induced remission in eight of nine patients with meningocerebralitis using chlorambucil. Azathioprine (Imuran), cyclosporine A, and colchicine have been shown in prospective, randomized studies to be highly effective in halting or preventing the ocular manifestations of Behcet's disease; however, cyclosporine A is relatively contraindicated in the presence of neurologic disease. Acute neurologic symptoms are remarkably reversible and justify aggressive treatment during flares. Patients with cerebral venous thrombosis respond well to chronic anticoagulation without significant risk of intracranial hemorrhage. (70)
Thalidomide (Thalomid) is highly effective in suppressing oral and genital manifestations of Behcet's disease; however, between 6% and 50% of patients develop an axonal sensorimotor polyneuropathy that may be dose related. (70)

The parenchymal distribution of lesions in neuro-Behçet syndrome seems to support the hypothesis of small vessel vasculitis, mainly venular involvement. The known anatomic arrangement of CNS intraaxial veins explains the predominant involvement of the brain stem structures observed in these patients. This pattern of lesion distribution might help to differentiate neuro-Behçet syndrome from other vasculitides as well as from the inflammatory-demyelinating diseases of the CNS, such as MS. Our experience with neuro-Behçet syndrome has caused us to consider neuro-Behçet syndrome in the differential diagnosis of patients who have brain stem and/or diencephalic lesions that extend along the long tracts and have a tendency to resolve on subsequent imaging studies, whether or not they are associated with periventricular and subcortical lesions. CNS involvement generally manifests several years after the onset of systemic Behcet's disease, but occasionally it may be an initial feature and even precede other disease manifestations. According to the diagnostic criteria of Behcet's disease of the International Study Group's classification (13), it is very difficult to diagnose Behçet disease without oro-genital ulcerations. However and in the author experience, primary parenchymal neuro-Behçet disease with selective involvement of the corticospinal tract (and with a purely motor clinical presentation) taken together with the characteristic MR imaging findings of selective pyramidal tract involvement are highly suggestive of Behçet disease even if CNS involvement precedes other disease manifestations.

- **Addendum**
  - A new version of this PDF file (with a new case) is uploaded in my web site every week (every Saturday and remains available till Friday.)
  - To download the current version follow the link "http://pdf.yassermetwally.com/case.pdf".
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  - The case is also presented as a short case in PDF format, to download the short case follow the link: http://pdf.yassermetwally.com/short.pdf
  - At the end of each year, all the publications are compiled on a single CD-ROM, please contact the author to know more details.
  - Screen resolution is better set at 1024*768 pixel screen area for optimum display.
  - For an archive of the previously reported cases go to www.yassermetwally.net, then under pages in the right panel, scroll down and click on the text entry "downloadable case records in PDF format"

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