Imaging findings of neuro-Behcet disease

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ABSTRACT

Objectives: To study the neuroimaging findings of neuro-Behcet's disease (NBD) in Saudi patients and to discuss the radiological differential diagnosis.

Methods: The clinical data and radiological findings on CT, MRI and cerebral angiography of 16 patients with NBD attending King Khalid University Hospital, Riyadh, Kingdom of Saudi Arabia, from January 1990 to February 2003 were reviewed.

Results: Out of 16 patients with NBD, 11 patients (68.75%) had cerebral venous thrombosis predominantly involving superior sagittal sinus causing intracranial hypertension, while 5 patients (31.25%) had symptoms and signs related to brain parenchymal involvement predominantly affecting brainstem.

Conclusion: Pattern of distribution of brain parenchymal lesions in NBD might help to differentiate it from other vasculitides as well as from demyelinating disease such as multiple sclerosis. Cerebral venous thrombosis is a common manifestation of NBD.

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Behcet's disease (BD) is a multi system vasculitis of unknown origin. The classical triad of oral and genital ulcerations with uveitis was originally described by a Turkish dermatologist Hulusi Behcet in 1937.[1] It is now well known that the mucocutaneous, ocular, articular, vascular, pulmonary, gastrointestinal and nervous systems are prone to develop the manifestations of the disease.[2] The prevalence of the disease varies widely, being high in the Eastern Mediterranean basin, North Africa, Iran and Japan.[3] Behcet disease is common in the Kingdom of Saudi Arabia (KSA) as many authors reported on its different clinical and neurological presentations, though the exact incidence is unknown.[4-7]

Central nervous system (CNS) involvement occurs in a variable proportion of cases ranging from 4-49%.[1,7,8] This involvement has been referred to as neuro-Behcet's disease (NBD). Neurological manifestations of BD has been categorized into 2 main types: cerebral venous thrombosis (CVT) and brain parenchymal involvement.[9]

Neuro-Behcet's disease manifests usually in the third decade and men are 4 times affected more than women.[8] Although CNS affection is one of the minor criteria, it has potentially serious consequences, including severe functional impairment or death.[8] The neurological symptoms usually begin 6 months to several years after the mucocutaneous manifestations and often occur concomitantly with exacerbations of the mucocutaneous lesions. In rare instances, however, the neurological manifestations may antedate other signs of BD.[10]

Early neuroimaging reports on NBD were based on studies with either CT or rarely cerebral angiography. Magnetic resonance imaging and magnetic resonance venogram (MRV) have been extensively used in clinical practice as noninvasive examinations for evaluation of patients with NBD.[1,7-9,11-13] The most common neuroimaging finding reported in these studies was a predilection for brain stem diencephalic involvement with a

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tendency to resolve over time. Cerebral venous thrombosis is another common neuroimaging finding reported in NBD.[1,5,14]

The aim of this work is to study the neuroimaging findings of NBD in 16 Saudi patients and discuss the radiological differential diagnosis.

Methods. From January 1990 to February 2003, BD was diagnosed in 95 patients in King Khalid University Hospital, Riyadh, KSA. All patients fulfilled the criteria of the International Study Group for Behcet's Disease.[3] The mean age was 28.5 $\pm$ 8.5 years **(**range 15-42 years**).** There were 77 male and 18 female (male:female ratio 4.2:1). The patients presented with cutaneous, ocular, rheumatologic, vascular and neurologic symptoms. The clinical and radiological data of the 95 patients with BD were retrospectively reviewed by the senior Neurologist and Neuroradiologist. Sixteen patients (12 male and 4 female) were found to have neurological manifestations either at presentation or during the course of the disease, suggestive of involvement of the nervous system. Neuro-Behcet's disease was confirmed radiologically in these 16 patients using CT (12 patients), MRI (6 patients), and cerebral angiogram (10 patients). Patients without any evidence of objective neurological involvement, namely, those with isolated headache with no abnormality on neurological or radiological examinations, were excluded and not considered as NBD in this series. Computed tomography of the brain was used with 7-10 mm slice thickness before and after intravenous injection of water soluble non ionic contrast medium. Magnetic resonance imaging was performed on 1.5 Tesla GE Sigma Horizon LX MR Unite. Sagittal T_1 weighted (T_1WI) spin echo sequence (500/16/1.5 TR/TE/NEX), axial T_2 weighted spin echo sequence (3200/90/3) axial fluid attenuated inversion recovery (FLAIR) (9000/133/2200/1 TR/TE/TI/NEX) and coronal T_2WI were obtained in addition to axial and coronal T_1WI (500/9/2) following intravenous injection of 0.1 mmol/kg gadolinium. Digital subtraction angiography (DSA) at least 2 projections late venous phase of bilateral carotid angiogram were also performed to detect CVT.

Results. Two types of neurologic manifestations were identified in 16 patients with NBD. Intracranial hypertension secondary to cerebral venous thrombosis (CVT) was seen in 11 patients (68.75%), while 5 patients (31.25%) had symptoms and signs related to brain parenchymal involvement.

Cerebral venous thrombosis. The symptoms and the CT, MRI and angiographic findings in 11 patients diagnosed with CVT are summarized in **Table 1**. The age of onset of the symptoms was 24-40 years (mean 32 years). Most of these patients were investigated before the introduction of MRI service in the institute, hence, many of them were studied by angiography. In 8 patients with angiographically proven CVT who also had CT, CT was positive in only 3 (38%) patients. The hallmark of CVT on contrast enhanced CT brain was the presence of filling defect within the involved sinus due to thrombus giving the empty delta sign (**Figure 1a**). The angiographic findings of CVT included occlusion or poor opacification of the involved sinus with multiple filling defects is shown in **Figure 1b**.

Brain parenchymal involvement. The clinical features and MRI findings in 5 patients with brain parenchymal involvement are summarized in **Table 2**. The age at onset of neurological symptoms was 25-38 years (mean 31.5 years). Magnetic resonance imaging was performed during the acute illness and was abnormal in all cases. All showed abnormal high-signal-intensity areas on T_2 weighted and FLAIR images. In all the 5 patients, brain stem was affected. Pons was the site of predilection in brain stem involvement (affected in 4 out of 5 patients). Computed tomography scanning was carried out in 4 patients, only one showed equivocal findings suggestive of brain stem lesion.

Discussion. Behcet disease was originally described as a syndrome of aphthous stomatitis, genital ulceration and uveitis is now recognized as a systemic vasculitis.[9] The etiologic factors remain obscured and speculative despite the wealth of information available on the clinical manifestations of this disease. Infective and genetic causes, immunologic factors, fibrinolytic defects, or combinations of these have all been suggested as causative factors.[1] The neurological presentation and clinical course of NBD are variable. Some patients have an acute presentation followed by relapsing remitting or secondary progressive course. Others may have a primary progressive course without a clear cut attack. A small group has no neurological complaints, but shows abnormal neuroimaging findings. This group is said to have "silent neurological involvement".[11] The non neurologic manifestations of the disease generally precede the neurologic findings, however, the non neurologic involvement may go unrecognized in some cases or it may appear late in the course of the disease.[9]

Neurological manifestations of BD have been divided into 2 categories: cerebral venous thrombosis (CVT) and brain parenchymal involvement.[9] The frequency of CVT in NBD is approximately 30%.[14] Cerebral venous thrombosis is seen in higher percentage (68.75%) in our series.

Table 1 - Clinical and radiologic (CT, MRI and angiography) findings in patients with cerebral venous thrombosis.

Case	Age years	Gender	Symptoms	CT	MRI	Angiography
1	32	M	IH	ND	ND	SSS thrombosis
2	34	F	IH	Empty delta sign	ND	SSS thrombosis
3	38	M	IH, seizures	Normal	ND	Right TS thrombosis
4	26	M	IH	Normal	ND	SSS thrombosis
5	30	F	IH, monoparesis	Normal	ND	SSS thrombosis
6	24	M	IH	Normal	ND	SSS + Right TS thrombosis
7	27	M	IH, diplopia	Empty delta sign	ND	SSS thrombosis
8	40	M	IH	ND	ND	SSS thrombosis
9	29	F	IH	Empty delta sign	ND	SSS thrombosis
10	28	M	IH, hemipareses	Normal	ND	Right TS thrombosis
11	30	M	IH	ND	SSS + Right TS thrombosis	ND

IH - intracranial hypertension, ND - not done, SSS - superior sagittal sinus, TS - transverse sinus, F - female, M - male

Table 2 - Clinical features and MRI findings in patients with CNS involvement.

Case	Age years	Gender	Clinical features	MRI findings			
				Site	T_1-weighted images	T_2-weighted images	Contrast enhancement
1	37	M	Meningo encephalitis Right side hemiplegia	-Brain stem (mainly pons)	Low signal	High signal	None
2	25	M	Headache, fever Bilateral pyramidal signs	-Basal ganglia -Mid brain	Low signal	High signal	None
3	34	M	Headache + right cerebellar syndrome	-Brain stem (pons and medulla) -Middle cerebellar peduncles -Subcortical white matter	Low signal	High signal	None
4	29	F	Headache, vomiting, Left cerebellar signs Left side weakness	-Brain stem (pons, midbrain and medulla) -Cerebellar peduncle -Cerebellar hemispheres -Subcortical white matter	Not seen	High signal	Ring enhancement of pontine lesions
5	38	M	Tetraparesis	-Brain stem (pons) -Basal ganglia	Not seen	High signal	None

M - male, F - female, CNS - central nervous system

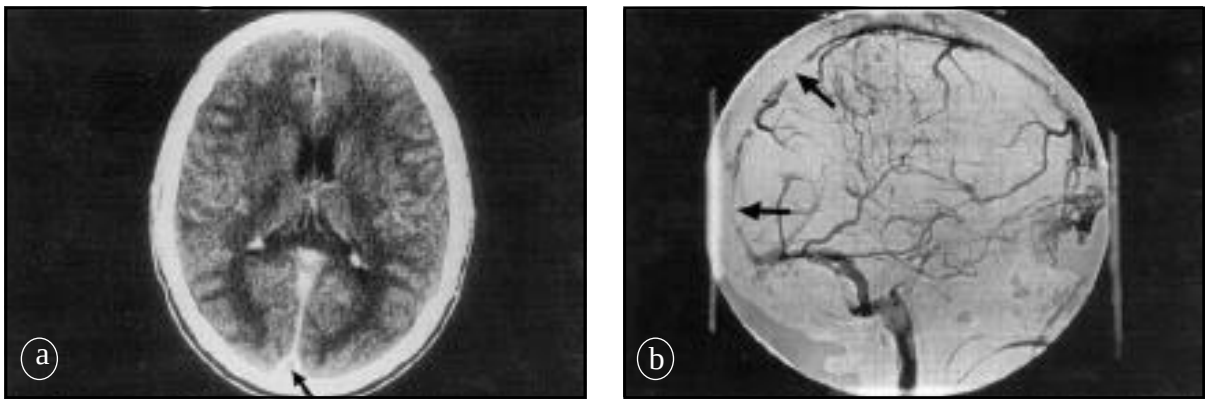

Figure 1- A 29-year-old male patient with neuro-Behcet disease and cerebral venous thrombosis. **a)** Axial contrast enhanced CT brain showing filling defect in the posterior part of superior sagittal sinus (SSS) giving the appearance of "empty delta" sign, (arrow). **b)** Lateral view of venous phase of right internal carotid arteriogram showing poorly opacified SSS with multiple filling defects (arrows) due to sinus thrombosis.

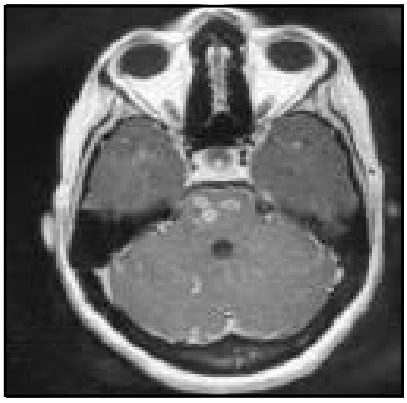

Figure 2 - A 29-year-old woman with neuro-Behcet disease. Contrast-enhanced axial T_1-weighted image showing ring enhancement of multiple pontine lesions.

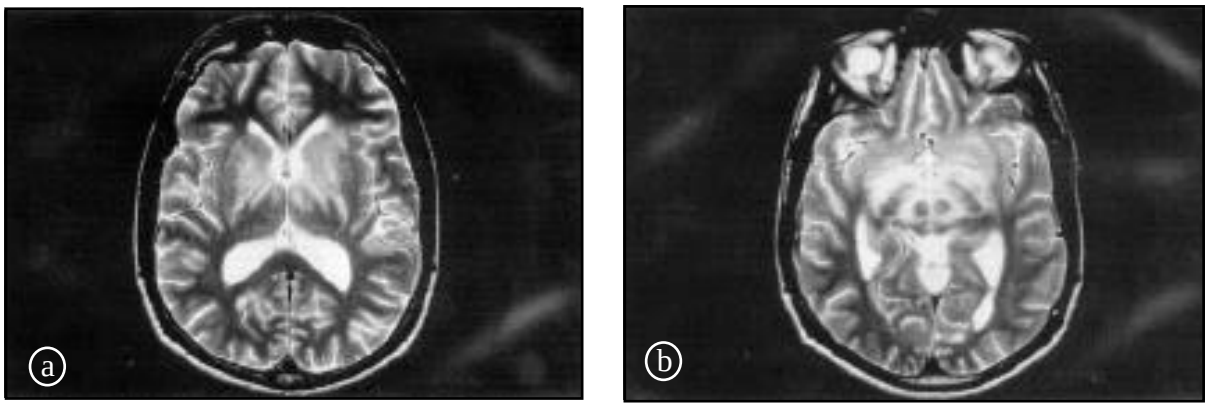

Figure 3 - A 25-year-old male patient with neuro-Behcet disease. **a)** Brain MRI axial T_2 weighted image at the level of basal ganglia showing bilateral symmetrical homogenous high signal intensity in the caudate and lentiform nuclei. **b)** Axial T_2 weighted image at the level of crus cerebri showing homogenous high signal intensity sparing the red nucleus.

The clinical and neuroimaging features of CVT in NBD are similar to those of CVT due to other causes.[14] Conventional angiography was the mainstay of CVT diagnosis, however, most of cases are now efficiently and noninvasively diagnosed by MRI.[9] More recently, MRV has proved very helpful in identifying thrombosis with good correlation with conventional angiography.[9,15] Furthermore, MRI allows reliable differentiation between dural venous sinus hypoplasia and thrombosis.[9,16] The use of conventional angiography in the diagnosis of CVT is now limited to cases with non conclusive MRI findings and patients on whom MRI is contraindicated.

Brain parenchymal involvement is a severe and devastating manifestation of BD. Magnetic resonance imaging is much more sensitive than CT in the detection of brain lesion in NBD.[9] In our patients, brain parenchymal lesions in NBD were of variable size, iso or hypointense relative to brain on T_1WI, and hyperintense on T_2WI and FLAIR images. There was a clear predilection for brain stem involvement, especially pons (**Figure 2**) and cerebral peduncles. Involvement of basal ganglia (**Figure 3**), thalami, cerebral hemispheres and cerebellum have been observed. Follow up MRI 3 months after treatment in one patient showed complete resolution of the lesions. The distribution pattern and shape of the lesions in our patients are similar to the previously published reports.[1,7,9] These MRI findings are not specific to NBD and can be observed with other causes of CNS vasculitis such as systemic lupus erythematosus (SLE), however, brain stem involvement is rare in SLE.[9,17] Neuro-Behcet disease is also considered in the differential diagnosis of multiple sclerosis (MS) when neurological features are seen in isolation.[9,17] The differentiation between MS and NBD on the basis of MRI may be difficult at times, however, lack of periventricular white matter involvement favors NBD. In addition, the pontine lesion in NBD involve the central part of pons, while in MS the pontine lesions involve the floor of the fourth ventricle and the middle cerebellar peduncles.[9] Sarcoidosis may be considered in the differential diagnosis of NBD, however, meningeal lesions and nodular enhancement of the leptomeninges particularly the basal meninges and basal midline structures (hypothalamus, infundibulum, pituitary gland and floor of the third ventricle) are not usual findings of NBD.[18-19]

Other possible differential diagnoses of NBD may include progressive multifocal leukoencephalopathy (PML), in which the subcortical white matter hyperintense lesions on T_2WI start small and eventually become large and confluent with predominant involvement of the posterior centrum semiovale, distinguishing PML from NBD.[19]

Autopsy studies and biopsy specimens of CNS lesions showed vasculitis with venous predominance.[1] This venous relation is supported by lack of arterial territorial distribution of lesions on radiologic studies. Significant perilesional edema with tendency to disappear or to leave disproportionally small residue on follow up studies has been reported. This feature is consistent with venous infarction, as signal intensity changes seen in venous occlusive disease do not necessarily represent infarction, but rather an accumulation of water within interstitial spaces.[1] Diffusion weighted imaging (DWI) seems to be useful in distinguishing acute exacerbation of NBD from acute infarction due to the ability of DWI to discriminate the 2 types of brain edema: cytotoxic edema caused by acute infarction and vasogenic edema seen in NBD. The lesion of cytotoxic edema tends to have decreased apparent diffusion coefficient (ADC) and shows hyperintensity on DWI, while that of vasogenic edema tends to have increased ADC and shows isointensity to slight hyperintensity on DWI.[18]

In view of the superior capability of MRI in the detection of brain parenchymal lesions and cerebral venous thrombosis, it should be the initial neuroimaging tool in the evaluation of patients with NBD. Presence of brain stem and diencephalic lesions that tend to resolve overtime should raise the possibility of NBD.

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