Neurological manifestations of Behçet's disease

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ABSTRACT

Objectives: To determine the prevalence, clinical manifestations, and laboratory features of Neuro-Behçet's disease.

Methods: This prospective study was carried out in the Behçet's Research Clinic in Shiraz (south-west Iran) and included the patients referred from 1990-1999. The patients' clinical records, images, CSF analyses, and electrodiagnostic studies were reviewed.

Results: Eighteen (15 males and 3 females) out of 690 Behçet's patients (2.6%, 95% CI = 1.4-3.8%) were found to have neurological involvement. The mean ± standard deviation age of these patients was 34.7±8.6 years. All fulfilled the criteria of the International Study Group of Behçet's Disease. Central nervous system involvement was more common than peripheral nervous system manifestations. Headache, weakness, tingling, and numbness were the most common symptoms. Hyperreflexia, upward plantar reflex, and somatosensory findings were the most frequent signs. Hemispheral and brainstem stroke-like syndromes and cerebral venous thrombosis were the major neurologic presentations. There were also cases of myelitic, pure meningoencephalitic, amyotrophic lateral sclerosis-like, multiple sclerosis-like, and Guillain Barre syndromes.

Conclusions: Neuro-Behçet's disease must be considered in the differential diagnosis of stroke in young adults, chronic meningitis, intracranial hypertension, multiple sclerosis, myelopathies, and peripheral neuropathies.

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Behçet's disease is a multisystem inflammatory disorder with a chronic course. Its cause is still unknown, but vasculitis is found as the major pathological feature. Due to the involvement of almost all organs of the body, different subspecialties of medicine may be involved in caring for patients with Behçet's disease.[1,2] Although the neurological involvement is less frequent than other major presentations, it is important because it produces severe disabilities and it causes grave prognosis.[3] Herein, we present 18 patients with definite neuro-Behçet's disease (NBD) and discuss their clinical, paraclinical, and radiological manifestations, and try to simplify them as a few main neurological syndromes.

Methods. We reviewed the clinical records of 694 patients referred to the Behçet's Disease Clinic at the Nemazee Hospital, Shiraz, southern Iran, from 1990-1999. Neuro-Behçet's disease was defined as a constellation of neurological symptoms, signs, or both, presenting as particular neurologic syndromes, usually confirmed by ancillary investigations. This was a direct result of Behçet's disease (fulfilling the criteria of the International Study Group for Behçet disease[4]) and was not consistent with any other medical, neurological or psychiatric entity other than Behçet's disease. Patients with positive rheumatoid factor, anti-double strand DNA, antinuclear antibodies, anticardiolipin antibodies, antineutrophil cytoplasmic

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antibodies, brucella agglutination test, major risk factors for atherosclerosis, echocardiographic findings correlating with cardiogenic embolism, and neurologic side effects of drugs were excluded. Patients with pure headache or psychiatric problems of whom we had no pathological or radiological confirmation were also excluded from the study. The results of the CSF analysis, EEG, electrodiagnostic studies, and neuroimagings were studied from the clinical records. The Statistical Program for Social Sciences (SPSS) package Version 13 (SPSS Inc, Chicago, Illinois 60606), was used for all statistical analysis.

Results. Of 694 Behçet's patients referred to our clinic, 18 patients (2.6%, 95% CI = 1.4-3.8%) had confirmed neurological manifestations. These patients included 15 men and 3 women. The age of the neuro-Behçet's patients was between 18-50 years (mean age ± SD = 34.7 ± 8.6 years). Five patients developed neurological symptoms before the diagnosis of Behçet's disease was made. In the rest of the patients, the disease lasted for 5.4 years on average, before neurological complications developed. By convention, we considered the time of diagnosis of Behçet's disease by medical professionals as the time of onset of Behçet's disease and calculated the duration of disease since then. All the patients had recurrent oral ulcers and recurrent genital ulcers. Of other presentations of Behçet's disease, cutaneous lesions (n=16), superficial and deep vein thrombosis (n=10), uveitis (n=8), and arthritis (n=7) were more frequently associated with NBD. Pulmonary (n=4), urogenital (n=4), cardiac (n=1), and gastrointestinal (n=1) symptoms were weakly associated. Fifteen patients had positive Pathergy test, 2 patients had negative test, and one response was equivocal. **Table 1** shows the neurological symptoms and signs of patients with definite NBD. For categorization of these neurological manifestations of Behçet's disease, some particular neurological syndromes were considered to cover all presentations of NBD (**Table 2**). In 16 patients, the CNS was involved. One patient had peripheral nervous system (PNS) disease, and one showed signs of concurrent involvement of both central and PNS. Of 17 patients with CNS manifestations, 12 patients had parenchymal CNS involvement and 5 patients had involvement of major blood vessels (dural sinus thrombosis in 4 patients and posterior cerebral artery occlusion in one patient). Of the 4 patients who had cerebral venous thrombosis, 3 developed non-neurological vascular complications later. All the patients with dural sinus thrombosis had subacute onset and a monophasic course. The patient with posterior cerebral artery occlusion presented with acute stroke-like onset without recurrence. In patients with parenchymal CNS involvement, 5 patients had acute onset, 5 patients had subacute onset, and 2 patients had chronic disease. Of patients with parenchymal CNS involvement, 5 patients had monophasic courses, 5 patients had relapsing-remitting courses, and 2 patients had a progressive course. One patient had acute monophasic predominantly motor neuropathy resembling Guillain-Barre syndrome. All except one patient had neuroimaging studies, including CT and MRI. The MRI findings included single or multiple tiny ischemic/demyelinative lesions (iso/hypointense in T1 weighted images and hyperintense in T2 weighted images and FLAIR) (**Figure 1**), mass like infarctions with the same intensity pattern (in the patient with posterior cerebral artery occlusion), delta sign and cord sign of sinus thrombosis (in the patients with dural sinus thrombosis) (**Figure 2**), and

Table 1 - Neurological symptoms and signs of patients with Neuro-Behçet's disease (n = 18).

Neurological symptoms or signs	No.	(%)
Symptoms		
Headache	13	(72)
Weakness	12	(67)
Paresthesia	11	(61)
Urogenital symptoms (incontinence, retention, impotence)	5	(28)
Facial palsy	5	(28)
Dizziness	5	(28)
Diplopia	5	(28)
Dysphagia	3	(17)
Ptosis	2	(11)
Unsteadiness	2	(11)
Seizure	1	(6)
Hearing loss	1	(6)
Dysarthria	1	(6)
Signs		
Hyperreflexia	12	(67)
Babinski's sign	10	(55)
Somatosensory signs	10	(55)
Hemiplegia	9	(50)
Papilledema	3	(17)
Visual field defects	3	(17)
Cerebellar signs	3	(17)
Optic atrophy	3	(17)
Ophthalmoparesis	2	(11)
Nystagmus	1	(6)
Hyporeflexia	1	(6)
Muscle atrophy	1	(6)

Table 2 - Neurological syndromes of patients with Neuro-Behçet's disease (n = 18).

Neurological syndromes	No.	(%)
Hemispheral syndrome	4	(22)
Brainstem syndrome	4	(22)
Dural sinus thrombosis	4	(22)
Myelitis	2	(11)
Amyotrophic lateral sclerosis-like	1	(6)
Multiple sclerosis-like	1	(6)
Guillain Barre syndrome	1	(6)
Meningo-encephalitis	1	(6)

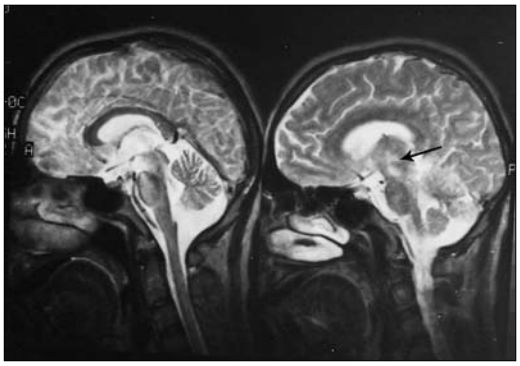

Figure 1 - T2-weighted MRI (0.5T, TR: 3620 ms, TE: 120 ms) of a patient who presented with brainstem syndrome, showing characteristic lesions in cerebellar peduncles, midbrain (arrow), thalami, and subcortical white matter.

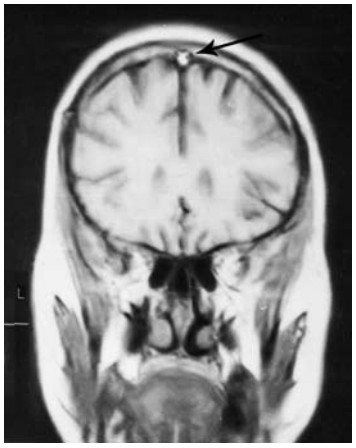

Figure 2 - T1 weighted MRI (0.5T, TE: 20 ms, TR: 540 ms) of a patient who presented with signs of increased intracranial pressure showing thrombosis of the superior sagittal sinus (arrow).

cerebral or cerebellar atrophy (associated with spinal thinning in one case). Enhancement was seen in all patients for whom contrast injection was carried out. Intravenous digital subtraction angiography was carried out in only 2 patients, which revealed aneurysm of the anterior cerebral artery in one patient and "beading appearance" in some territories of the middle and anterior cerebral arteries in the other. Only 6 patients had CSF analysis. Of 4 patients with dural sinus thrombosis, CSF analysis was carried out in 2 patients, both had elevated CSF pressure and one of them had lymphocytic pleocytosis as well. In 4 patients with parenchymal CNS involvement, 2 had lymphocytic pleocytosis and 2 were normocellular. Elevated CSF protein and hypoglycorrhachia was not seen. Nerve conduction studies and electromyography in the patient with Guillain-Barre syndrome revealed axonal type peripheral polyneuropathy. The same electrodiagnostic studies in the patient with amyotrophic lateral sclerosis-like presentations showed normal nerve conduction velocities but fibrillations, fasciculations and positive sharp waves associated with large polyphasic motor unit potentials in the upper and lower extremities. No patient expired during the study, hence, we have no autopsy confirmation.

Discussion. Diversity of neurological symptoms and signs in our study is consistent with Wolf's statement: "almost any part of the neuraxis may be involved, and there is no characteristic pattern of the disease process."[5] The prevalence of definite neurologic involvement among 694 Behçet's patients was 2.6% (95% CI = 1.4-3.8%). The frequency of NBD in different series varies between 2.5-49%.[6,7] This difference is not only due to geographic and ethnic factors (which also contribute in variations of other presentations of Behçet's disease) but also related to arbitrary definitions of NBD and inclusion or exclusion of particular neurological symptoms or signs in different studies. We accept that the prevalence of neurological manifestations of Behçet's disease is underestimated in our report. The retrospective nature of this study, referral system of our clinic, in which patients were only referred to neurologists if neurologic manifestations were elucidated by the rheumatologist, the transient nature of some presentations, and lack of some sophisticated investigatory tools may have all attributed to this underestimation. Neurological complications were significantly more frequent in our male patients, consistent with other reports.[8,9] The prevalence of patients whose neurologic manifestations antedate other signs of Behçet's disease in our study (28%) was much more than other series (3-5%).[2,8] This may be due to our convention in considering the onset of Behçet's disease as the time of diagnosis by medical professionals, and the fault of both patients and primary care physicians who neglect common initial symptoms such as oral ulcers. Headache, weakness, and paresthesia were the most common symptoms and corticospinal and sensory signs were the most common signs of NBD in our series. Our results are consistent with other reports that weakness and pyramidal signs were the most common symptom and sign in some,[8,10] but headache was the most common in others.[11]

The CNS manifestations of Behçet's disease can be categorized into 2 main groups. 1. Parenchymal CNS involvement (NBD), which include brainstem involvement, hemispheral manifestations, spinal cord lesions, and encephalitic presentations. 2. Non–parenchymal CNS involvement ("neuro-vasculo–

Behçet's disease"), which include dural sinus thrombosis, arterial occlusion, and arterial aneurysms. These 2 categories differ in clinical, paraclinical, and prognostic properties.[8,12,13] The ratio of parenchymal to non-parenchymal involvement was 4.3:1,[8] and 7.3:1[13] in some large series, and 2.4:1 in our series. These 2 types of involvement rarely occur in the same individual. However, one of our patients had tiny internal capsular infarction and aneurysm of anterior cerebral artery concurrently. Of 4 patients who had cerebral venous thrombosis, 3 later developed non-neurological vascular complications. This leads us to speculate that "neuro-vasculo-Behçet's disease" is a part of the general vascular involvement of Behçet's disease and probably has a different pathogenesis from NBD. It appears that brainstem manifestations are the most common presentations of NBD.[8,13] However, there are reports that showed equal frequency of cerebral and brainstem lesions[14] (as in our series) or greater prevalence of manifestations of intracranial hypertension.[15] However, the latter reports had fewer patients. Four of our patients presented with dural sinus thrombosis and raised intracranial pressure. Intracranial hypertension manifested as acute, or more commonly, subacute evolution of headache, nausea, vomiting, visual obscuration associated with bilateral papilledema, sixth nerve palsy and occasionally, focal neurologic deficits.[16] Dural sinus thrombosis may or may not be confirmed by radiologic investigations.[8,16] The superior sagittal sinus is the most common site of thrombosis followed by transverse sinuses, deep cerebral veins, and cavernous sinus.[16] The prevalence of spinal cord involvement in clinical studies of NBD ranges from 10-18%[7,12] (11% in our series) and a predilection for thoracic level had been noted.[17] Lesion regression paralleled to clinical improvement (which was seen in one of our patients) was also previously reported.[17] One of our patients developed a multiple sclerosis-like course. Neuro-Behçet's disease resembles multiple sclerosis in many aspects: Predilection to present in young persons, relapsing-remitting or progressive course of neurologic manifestations, perivascular infiltration of inflammatory cells, hyper-intense lesions in T2-weighted or FLAIR images of MRI, abnormal evoked potentials, response to corticosteroids and immune-suppressant drugs. In differentiation of NBD, some points must be considered: Neuro-Behçet's disease is more common in men, but multiple sclerosis is more frequent in females. In NBD, CSF pleocytosis is predominantly lymphocytic or neutrophilic whereas, lymphocytes are always predominant in multiple sclerosis. Oligoclonal bands are scarcely seen in NBD. Such abnormalities, however, are present in more than 90% of patients with multiple sclerosis. The most common site of lesions in NBD is the brainstem extending to the diencephalon and basal ganglia, but periventricular in multiple sclerosis. If periventricular lesions are seen in NBD, they will be smoother and fewer in number than the lesions of multiple sclerosis. Brain stem lesions are larger in NBD than in multiple sclerosis. In chronic cases of NBD, atrophy of the brainstem and cerebellum are seen, but generalized cerebral atrophy and ventricular enlargement is usually present in patients with chronic multiple sclerosis. The predominant abnormalities of visual evoked potential (VEP) and brainstem auditory evoked potential (BAEP) in NBD are reduced amplitudes rather than increased latencies, which are usually seen in multiple sclerosis. This difference however, is only confirmed by some studies.[18]

Peripheral nervous system manifestations in Behçet's disease mainly include subacute sensorimotor polyneuropathy,[19] mononeuritis multiplex,[20] and autonomic neuropathy.[21] In Al-Dalaan et al's[22] report, there was a patient whose manifestations resembled one of our patients with Guillain-Barre syndrome. We reported and discussed our ALS-like case in another article. Concurrent involvement of spinal cord and peripheral nerves may cause this constellation of upper and lower motor neuron manifestations.[23]

Acute onset (progression over minutes to a few days) or subacute onset (progression over several days or 1-2 weeks) and monophasic or relapsing-remitting course were the most common temporal patterns in our patients with NBD. Our findings were consistent with other major series.[8,13]

In conclusion, NBD must be considered in the differential diagnosis of stroke in young adults, intracranial hypertension and intracerebral sino-venous occlusive disease, multiple sclerosis, spinal cord syndromes and peripheral neuropathy, especially in countries where Behçet's disease is prevalent.

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References

1. Behçet H. Uber rezidirierende, aphtose, durch ein virus verursachte geschrwre am mund, am auge und an den genitalien. ***Dermatol Wochenschr*** 1937; 105: 1152-1157.
2. Davatchi F, Shahram F, Akbarian M, Gharibdoost F, Nadji A, Chams SH et al. Behçet's disease – analysis of 3443 cases. ***APLAR Journal of Rheumatology*** 1997; 1: 2-5.
3. Borhani Haghighi A, Pourmand R, Niksersht AR. Neuro-Behçet's disease: A review. ***Neurologist*** 2005; 11: 80-89.
4. International Study Group for Behçet disease. Criteria for diagnosis of Behçet disease. ***Lancet*** 1990; 335: 1078-1080.
5. Wolf SM. Involvement of Nervous system in Behçet's syndrome. ***Arch Neurol*** 1965; 12: 315-325.

6. Kang SJ, Kim HB. Behçet's disease in Korea. ***J Korean Ophthalmol Soc*** 1992; 33: 332-341.
7. Fadli ME, Youssef MM. Neuro–Behçet's syndrome in the United Arab Republic. ***Eur Neurol*** 1973; 9: 76-89.
8. Akman–Demir G, Serdaroglu P, Tasci B and the Neuro-Behçet Study Group. Clinical patterns of neurological involvement in Behçet's disease: evaluation of 200 patients. ***Brain*** 1999; 122: 2171-2182.
9. Al–Fahad SA, Al-Araji AH. Neuro–Behçet's disease in Iraq: a study of 40 patients. ***J Neurol Sci*** 1999; 170: 105-111.
10. Serdaroglu P, Yazici H, Ozdemir C, Yurdakul S, Bahar S, Aktin E. Neurologic involvement in Behçet's syndrome: A prospective study. ***Arch Neurol*** 1989; 46: 265-269.
11. O'Duffy JD, Goldsterin NP. Neurologic involvement in Seven patients with Behçet's disease. ***Am J Med*** 1976; 61: 170-178.
12. Shakir RA, Sulaiman K, Khan RA, Rudwan M. Neurological presentation of neuro–Behçet's syndrome: clinical categories. ***Eur Neurol*** 1990; 30: 249-253.
13. Kidd D, Steuer A, Denman AM, Rudge P. Neurological complications in Behçet's syndrome. ***Brain*** 1999; 122: 2183-2194.
14. Tajima Y, Homma S, Sinpo K, Maruo Y, Moriwaka F, Tashiro K. Clinico–radiological findings of neuro–Behçet's syndrome. ***Intern Med*** 1994; 33: 136-141.
15. Farah S, Al-Shabaili A, Motaser A, Hussein JM, Malaviya AN, Mukhtar M, et al. Behçet's syndrome: a report of 41 patients with emphasis on neurological manifestations. ***J Neurol Neurosurg Psychiatry*** 1998; 64: 382-384.
16. Wechsler B, Vidailhet M, Piette JC, Bousser MG, Dell-Isola B, Bletry O, et al. Cerebral Venous thrombosis in Behçet's disease: clinical study and long–term follow-up of 25 cases. ***Neurology*** 1992; 42: 614-618.
17. Lafitte C, Servan J, Bleibel JM, Wechsler B, Delattre JY. Meningomyelite rvlatrice dune maladie de Behçet. ***Rev Neurol*** 1996; 152: 205-207.
18. Ashjazadeh N, Borhani Haghighi A, Samangooie SH, Moosavi M. Neuro-Behçet's disease: a masquerader of multiple sclerosis. ***Exp Mol Pathol*** 2003; 73: 17-22.
19. Namer IJ, Karabudak R, Zileli T, Ruacan S, Kücükali T, Kansa E. Peripheral nervous systems involvement in Behçet's disease. ***Eur Neurol*** 1987; 26: 235-240.
20. Takeuchi A, Kodama M, Takatsu M, Hashimoto T, Miyashita H. Mononeuritis multiplex in incomplete Behçet's disease a case report and the review of the literature. ***Clin Rheumatol*** 1989; 8: 375-380.
21. Aksoyek S, Aytemir K, Ozer K, Ozcebe O, Oto A. Assessment of autonomic nervous system function in patients with Behçet's disease by spectral analysis of heart rate variability. ***J Auton Nerv Sys*** 1999; 77: 190-194.
22. Al-Dalaan AN, Al-Balaa SR, El-Ramahi K, Al-Kawi Z, Bohlega S, Bahabri S, et al. Behçet's disease is Saudi Arabia. ***J Rheumatol*** 1994; 21: 658-661.
23. Borhani Haghighi A, Ashjazadeh N, Nikseresht AR, Samangooei SH. Amyotrophic lateral sclerosis in a patient with Behçet's disease. ***Ir J Med Sci*** 2005; 30: 194-196.