The Spectrum of Clinical Symptomatology in Patients with Neuro-Behcet's Disease

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ABSTRACT

Objective: To understand the pattern of neurological symptoms in patients diagnosed with Neuro-Behcet's disease.
Study Design: Cross-sectional study.
Duration and Place of Study: Pak Emirates Military Hospital Rawalpindi, from Jun 2013 to Jun 2018.
Methodology: Cases diagnosed with Behcet's disease (BD) based on international criteria for Behcet's diseases (ICBD) were considered. Those cases of BD who presented with certain neurological manifestations were further analyzed for clinical symptomatology regarding the type of neurological symptoms. Moreover, data include cerebrospinal fluid (CSF) analysis, laboratory tests, and magnetic resonance imaging (MRI) findings.
Results: A total of 79 cases fulfilled the ICBD diagnostic criteria. The mean age of the cases was 36.78 ± 11.85 years. Central nervous system involvement occurred in 46 (58.2%) cases. Out of 46 patients with Neuro-Behcet's disease (NBD) with central nervous system manifestations, non-parenchymal involvement was common in 23 (50%) patients compared to parenchymal involvement in 16 (34.8%) patients. Among neurological features, migraine-like headaches were the most common manifestation present in 29 (36.7%) patients with Behcet's disease. The stroke-like presentation occurred in 18 patients, while 16 cases manifested with seizures clinically. Migraine like headaches, stroke-like episodes, seizures and neuropsychiatric features were significantly more common among patients with Neuro-Behcet's disease. Out of 46 patients with central nervous system involvement, MRI brain findings were present in 34 (73.91%) cases.
Conclusion: Behcet's disease can manifest with various symptoms, including a wide range of neurological involvement. Understanding such neurological manifestations can result in early recognition and treatment of this relatively aggressive and resistant auto-immune disease.

Keywords: Auto-immune disease, Behcet's disease, Neuro-behcet's disease, Oral ulcers.

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INTRODUCTION

Behcet's disease (BD) is a well-known inflammatory disease involving many systems with diverse symptomatology. BD is usually considered for diagnosis when characteristic features of this disease occur.[1] These characteristic features include recurrent ulcerations (at least more than three times per year) occurring in both oral and genital areas and uveitis in the eye. Many other features include inflammatory arthritis, various skin rashes, and a reaction to the needle prick on the skin in the form of positivity of pathergy test and thrombophlebitis of veins. Although not considered very common in BD, central nervous system (CNS) involvement usually occurs either in the parenchymal or non-parenchymal pattern. Digestive tract involvement has been reported in the form of ulcerations along the lining of the gastrointestinal system.[2,3]

The aetiology of this disorder is still largely unclear, but it is considered an inflammatory disorder. Vasculitis of all types of vessels has been demonstrated in the literature; however, inciting events of this inflammatory vasculitic disorder still needs to be explored.[4]

Behcet's disease is well known for its varied presentation in different regions and Ethnic groups. The type of the organ involved differs in various regions; moreover, the frequency of various symptoms varies greatly in different ethnic subgroups. These differences may be related to various environmental factors and the predisposition of certain genetic makeup in these ethnic regions. This could be why some consider BD a syndrome rather than labelling it a disease.[5,6]

This study aimed to analyze clinic-radiological features and to understand the demographic characteristics of patients with BD, who mainly have neurological involvement and compare these characteristics with other ethnic and geographic groups.

METHODOLOGY

This cross-sectional study was carried out in Pak Emirates Military Hospital Rawalpindi, in the Neurology Department, from June 2013 to June 2018. The sample size was calculated using the WHO

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calculator, keeping the prevalence of Behcet's disease at 5%.[2] The calculated sample size was 73 with a 95% confidence level. Approval from the Hospital Ethical Committee was obtained before the study started.

Inclusion Criteria: This study included all the diagnosed cases of BD that manifested with different neurological features and were managed by the Neurology Department. Any patient with international criteria for Behcet's diseases score of four or more than four was diagnosed as a case of BD and included in the study.

Exclusion Criteria: Any suspected case of Behcet's disease with international criteria for Behcet's disease score of less than four was not considered for this study. Moreover, any case of BD in which neurological manifestations were better explained with an alternative diagnosis was also excluded from the study.

The non-probability consecutive sampling techniques were used for patient selection. Selected BD patients fulfilled the international criteria for Behcet's disease score system.

Record of all BD patients, who met the inclusion and exclusion criteria, was collected directly from the patients presenting in the outpatient department.

The cases were analyzed for clinical symptomatology regarding the type of neurological symptoms. Moreover, data such as cerebrospinal fluid (CSF) analysis, laboratory tests, magnetic resonance imaging (MRI) findings, and demographic data, such as gender and age, were also obtained.

Statistical Package for Social Sciences (SPSS) version 20 was used for the data analysis. Results were expressed as the mean ± standard deviation (SD) for continuous variables such as age and frequencies and percentages for categorical data such as gender, the type of neurological manifestations, laboratory tests, and MRI brain findings. The chi-square test was used to see any significance of different neurological manifestations. The *p*-value of ≤0.05 was considered significant.

RESULTS

The total no of cases treated for BD in the Neurology Department was 119 over five years, but out of these cases, only 79 cases were selected for this study who fulfilled ICBD diagnostic criteria as per inclusion and exclusion parameters. All these cases had an ICBD score of four or more four. The mean age of patients was 36.78 ± 11.85 years. BD was more common among females (45, 57%), whereas 34 (43%) males had this disease. Oral ulcers were the most common manifestation in 76 (96%) cases. However, only 46 (58.2%) cases occurred with central nervous system involvement. In 41 (51.80%) patients, ocular manifestations were present (Figure-1).

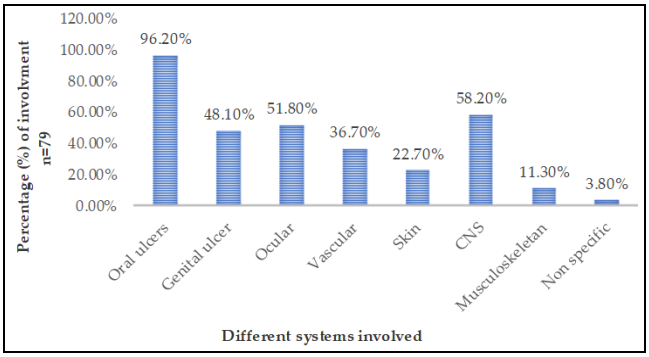

Figure-1: Percentage of different systems involvement in Becher's disease (n=79).

However, uveitis was present in 30 (37.97%) patients among BD patients, documented by the consultant ophthalmologist. Frequencies of different neurological manifestations in Behcet's disease patients were depicted in Table-I.

Table-I: Frequency of different neurological manifestations in Behcet's disease (n=79).

Neurological Manifestations	n (%)
Migraine-like Headache	29 (36.7%)
Stroke	18 (22.7%)
Seizures	16 (20.7%)
Behavioral/Neuro-Psychiatric Symptoms	15 (18.9%)
Intracranial Hypertension	12 (15.1%)
Papilledema	10 (12.6%)
Cranial Nerve Palsies	5 (6.3%)
CVST	4 (5%)
Optic Atrophy & Optic Neuritis	4 (5%)
Extrapyramidal features	2 (2.5%)
Aneurysm	2 (2.5%)
LETM	1 (1.2%)
Myasthenia Gravis	1 (1.2%)

Among 46 cases, 18 (39.1%) patients had single, while 28 (60.8%) patients had multiple neurological manifestations. Out of 46 patients of Neuro-Behcet's with CNS manifestations, non-parenchymal involvement was common in 23 (50%) patients compared to parenchymal involvement in 16 (34.8%) patients. However, only seven patients (15.2%) had parenchymal and non-parenchymal brain involvement.

Migraine-like headaches were the most common manifestation present in 29 (36.7%) patients with Behcet's disease. Moreover, the migraine-like headache was significantly more common in patients with Neuro-Behcet's disease, with the *p*-value of 0.001.

All the twelve neuro-Behcet's cases with intracranial hypertension had migraine-like headaches at presentation. Moreover, stroke-like episodes, seizures and neuropsychiatric symptoms were also significantly more common in patients with Neuro-Behcet's patients shown in Table-II.

Table-II: Clinical Manifestation of the patients.

		Present	Absent	*p*-value
Migraine Like Headache				
Central Nervous System Involvement	Present	29 (36.7%)	17 (21.5%)	0.001
	Absent	5 (6.3%)	28 (35.4%)	
Ischemic Stroke				
Central Nervous System Involvement	Present	18 (22.7%)	28 (35.4%)	0.001
	Absent	0 (0.0%)	33 (41.7%)	
Seizures				
Central Nervous System Involvement	Present	15 (18.9%)	31 (39.2%)	0.001
	Absent	1 (1.2%)	32 (40.50%)	
Neuropsychiatric Symptoms				
Central Nervous System Involvement	Present	15 (18.9%)	31 (39.2%)	0.001
	Absent	0 (0.0%)	33 (41.7%)	

MRI brain was done in 75 patients with Behcet's disease, while four patients did not undergo MRI due to contraindications to MRI. Out of 46 patients with CNS, involvement MRI brain findings were present in 34 (73.91%) cases, while in 11 patients, MRI brain was normal despite certain neurological features. Subcortical white matter T2WI hyper-intensities were the commonest findings on the MRI brain (Figure-2).

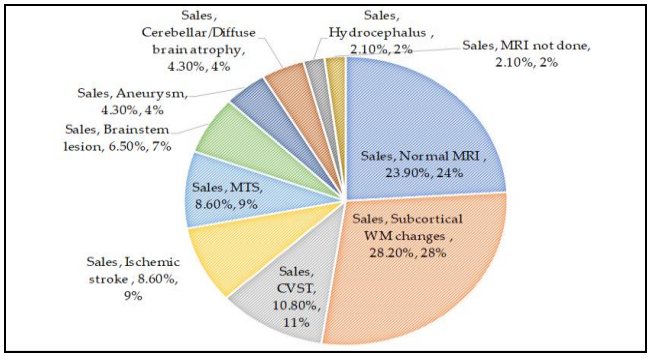

Figure-2: Magnetic Resonance Imaging Brain Findings in Neuro-Behcet's disease patients (n=46).

DISCUSSION

According to our study, Behcet's disease can manifest with various symptoms, including a wide range of neurological involvement.

This study reports the clinical features of 79 adult Pakistani patients with BD seen in the Neurology Department of Military Hospital Rawalpindi over five years. This is perhaps the largest study sample of BD patients in Pakistan. Patients were given the Behcet's disease diagnosis using international study group (ISG) classification criteria,[3] which have a sensitivity, specificity, and accuracy of 79.4%, 99.4%, and 89.8%, respectively.[4] This same classification criterion has been used previously in several population-based studies.

The result of our study regarding the high frequency of Neuro-Behcet's disease (58.2%) was consistent with the various studies done in the past few decades.[5,6] A high frequency of (58%) has also been documented previously in the Kingdom of Kuwait. Moreover, a variable frequency of 38% in Italy and 23% in the United States has been reported.[2,7,8] On the other hand, in Iranian, Turkish and Iraqi populations, Neuro -Behcet's disease is significantly less frequent.[9-11] In a study carried out on 412 Japanese patients of Behcet's disease, central nervous system involvement was reported to be 13%.[12]

In the cohort of 387 patients of BD in the Turkish population in the last two decades, the frequency of men and women with NBD was 13% and 5.6%, respectively.[9] A study was conducted on 140 patients with BD by Al-Araji *et al*,[10] in the Iraqi population. They observed the NBD in 14.3% of patients in their multidisciplinary BD clinics. However, in our neighbouring country Iran, in a large cohort of 6500 patients with BD, central nervous system manifestations were observed in only 3.7% of patients, which is quite different from our study.[11]

Our study's high frequency of neurological manifestations is perhaps caused by the selection of only neurology out and in-patient department patients, which might have resulted in some bias. The other explanation for the high frequency of NBD could be the higher rate of referral of these patients from all over Pakistan to the neurology department of tertiary care facility.

BD is frequently reported among men in Middle Eastern countries.[12,13] In contrast, in the Japanese population and a few European countries, it is slightly more common among females. No such gender discrimination was observed in our study of neurological manifestations in BD patients, although previously in literature NBD has been reported to be predominant in males.[14]

The parenchymal NBD generally occur in a subacute fashion. It mainly manifests with the brainstem syndrome associated with other features like spinal

cord syndrome or cerebral hemispheric involvement. Other features like pyramidal weakness, headaches, ophthalmoplegia, behavioural manifestations and sometimes sphincter disturbance have also been observed. Patients with non-parenchymal NBD usually have intracranial hypertension and quite frequently manifest with symptoms of headache and visual disturbance. This intra-cranial hypertension is one of the manifestations of cerebral venous sinus thrombosis. However, this is an uncommon manifestation of these patients presenting suddenly with a stroke-like deficit. In our study, five patients had CVST.

In BD, the parenchymal involvement of CNS was seen in 34.8% of our patients. The various largest series of NBD have reported almost similar results carried so far.[10,11,15-17] The majority of these cases in the past series with parenchymal BD presented with subacute onset of the neurological syndrome. These patients had various manifestations like headaches, strokes, seizures, cranial nerve deficit, intracranial hypertension, longitudinally extensive transverse myelitis (LETM), extrapyramidal features, and gradual behavioural neuropsychiatric symptoms.

Research carried out on the neuro-imaging aspect of central nervous system involvement in NBD demonstrated that the majority of the time, the lesions are located in the brainstem,[15,18,19] particularly at the junction of pons with diencephalon, and sometimes these do extend into to the diencephalon. However, our patients had predominantly subcortical and periventricular white matter involvement suggestive of multiple sclerosis (MS) like lesions. We also found mesial-temporal sclerosis (MTS) in patients with refractory seizures and hydrocephalus in a patient with chronic meningitis.

In our study, vasculo-Neuro-Behcet's disease was found in 23 (50%) patients with CNS involvement. Intracranial hypertension was documented in 26% of patients, while cerebral venous sinus thrombosis was seen in 8.6% of cases. These findings of our study were very different from the observations of other studies where the frequency of non-parenchymal Neuro-Behcet's disease is between 10 to 20%.[18] In recent years, in a study conducted on 54 Neuro-Behcet's disease patients in the Japanese population, only 2% had non-parenchymal Neuro-Behcet's disease.[20] In comparison to our study, intracranial hypertension was found in 17.5% of patients in a Moroccan study with NBD and was the commonest manifestation of non-parenchymal NBD. In various studies, cerebral venous sinus thrombosis frequency ranges from 10 to 12% in Behcet's disease. However, the frequency of cerebral venous sinus thrombosis in BD in Japan was much lower than in Middle-Eastern and European countries.[15,21,22]

We also found cerebral aneurysms in two patients, and one patient had an initial presentation of subarachnoid haemorrhage. Such findings have also been reported in the literature. An aneurysm should be considered during anticoagulation for cerebral venous sinus thrombosis in NBD patients.

STUDY LIMITATIONS

Although neurological manifestations have been discussed thoroughly in this study in the Pakistani population, this cannot be the true reflection of the whole population. This is due to the selection of patients from a single centre of neurology which limits the true reflection of its results. A large scale study with a large cohort of patients involving multiple centres of Neurology and Rheumatology from hospitals in different regions of Pakistan will be required to have a full understanding of neurological manifestations of BD in Pakistani patients.

CONCLUSION

Behcet's disease can manifest with various symptoms, including a wide range of neurological involvement. Understanding such neurological manifestations can result in early recognition and treatment of this relatively aggressive and resistant auto-immune disease.

Conflict of Interest: None.

Authors' Contribution

JL: WWM: SA: Direct contribution, AH: WA: Intellectual contribution.

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