# PERIPHERAL NEUROPATHY IN BEHCET'S DISEASE: CLINICAL AND NEUROPHYSIOLOGICAL STUDY

By

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# ABSTRACT

**Background:** Behçet's disease (BD) is a chronic idiopathic relapsing condition, whereas multiple organs are affected as a sequential effect of the vascular and inflammatory process. Based on the neurophysiological studies, 20-40% of BD patients may have silent neurological involvement (SNI) with no or very mild clinical manifestations.

**Objectives:** Assessing clinically and electro physiologically the prevalence of symptomatic and asymptomatic peripheral neuropathy (PN) among BD patients along with the potential predictors of PN among BD patients.

**Patients and Methods:** All patients with clinically established BD according to the International Criteria for Behçet's Disease (ICBD) were involved in the current study. All patients were submitted to clinical evaluation, neuropathy symptom score (NSS) along with electrophysiological nerve conduction studies including sensory and motor nerve conduction assessment.

**Results:** An overall 30 participants who fulfilled the inclusion criteria were enrolled in the study. There were 22 (73.3%) males and 8 (26.7%) females with a mean age of  $37.9\pm8.31$  years. Based on the electrophysiological studies, 16 (53.3%) patients had the evidence of peripheral neuropathy in the terms of mixed (23.3%), motor (6.6%), and sensory (23.3%) nerve affection. The most affected peripheral nerve was sural nerve (46.6%) succeeded by peroneal (43.3%) and ulnar (20%) nerves. The univariate regression model showed that the age of the patients and the duration of the disease were independent predictors of peripheral neuropathy.

**Conclusion:** PN is a considerable complication of BD, whereby health care providers should employ a routine follow up protocol for early detection of even the subclinical PN.

Keywords: Behçet's disease, peripheral neuropathy, electrophysiological studies.

## **INTRODUCTION**

Behçet's disease (BD) is a chronic idiopathic relapsing condition, whereas multiple organs are affected as a sequential effect of the vascular and inflammatory process (*Emmi et al., 2018*). The burden of BD differed geographically, whereby countries along the silk road, apart from Japan to the Mediterranean area, showed a high prevalence of BD (*Uygunoglu et al.*, 2018). Subsequently, BD patients usually presented in the third decade of life with an equal proportion of males and females; however, males often showed more progressive disease course (Mazzoccoli et al., 2016).

Of note, BD is associated with clinical abundant manifestations counterpart eye inflammation, mucocutaneous lesions, vasculopathy, cardiac, pulmonary, musculoskeletal, gastrointestinal and neurological insults (Yusuf Yazici et al., 2009). The diagnosis of such condition is based mainly on the clinical evaluation according to the International Criteria for Behçet's Disease (ICBD), whereas the serological assessment is usually limited in the diagnosis of BD (Siva and Saip, 2009).

Approximately, 5-10 years after the onset of BD, Neuro-Behçet's syndrome (NBS) could be evolved among 4-50% of BD patients, whereby males had a triple risk of affection relative to females (Al-Araji and Kidd, 2009). Interestingly, 5-20% of the patients nearly are presenting with a neurological insult as the initial presentation instead of oral which is the predominant ulcers presentation of BD (Siva and Saip, 2009). Unfortunately, the involvement of the nervous system carries bad prognosis (Dutra et al., 2012).

In contrast, primary neurological insult cerebral includes venous sinus thrombosis, headache, arterial NBS, intraaxial NBS, subclinical NBS, (PN) (Kalra 2014). Subsequent to that, al.. et secondary neurological insult occurred as an eventual effect of the systemic consequences of BD such as cerebral embolic events from cardiac affection and the neurological manifestations related to BD treatment (Uygunoglu et al., 2018).

The burden of PN among BD patients is deeply rare (*Kalra et al., 2014*).

Noteworthy, some studies revealed the existence of mononeuritis multiplex, Polyradiculoneuritis, and axonal sensory neuropathy in BD. Besides, polyneuropathy may exist as a side effect of thalidomide or colchicine (*Saip et al., 2014*).

Based the neurophysiological on studies, 20-40% of BD patients may have neurological involvement (SNI) silent with no or verv mild clinical manifestations (Yesilot et al., 2006). Those patients may experience overt neurological manifestations within the course of the disease (Graham et al., 2013).

The current study aimed to assess clinically and electrophysiologically the prevalence of symptomatic and asymptomatic PN among BD patients along with the potential predictors of PN among BD patients.

# **SUBJECTS AND METHODS**

This study was implemented along with the ethical committee guidelines of the Faculty of Medicine, Al-Azhar University, Cairo, Egypt. All clinical interventions were illustrated to all participants prior to study implementation. A written informed consent after a clear explanation of all study steps was obtained.

This was an observational retrospective case-control study which was carried out at the inpatient departments and outpatient clinics of Al-Azhar Neurology and Rheumatology departments at Al-Azhar University Hospitals (Al Hussein and Bab Al-sharia) from January 2019 to end of June 2019.

with Thirty patients clinically established Behçet's disease according to the International Criteria for Behcet's Disease (ICBD) were involved in the current study. On the contrary, patients and concomitant with BD other neurological or chronic medical systemic illness that can develop or affect peripheral nerves, such as hereditary ataxias, diabetes mellitus, renal or hepatic failure were excluded from the study. Similar to that, patient subjected to substances or drugs abuse that may alter peripheral nerves like alcohol abuse, or patients with a possible mechanical nerve compression were omitted.

All patients were subordinated to meticulous history taking comprised age, sex, history of chronic diseases, drug abuse, medications, or other neurological diseases coupled with history of the present neurological manifestations to reveal symptoms of BD and peripheral neuropathy. Subsequent to that, general and neurological examinations were done to retrieve the clinical evidence of motor, sensory, or autonomic systems affection along with cranial nerves involvement.

Neuropathic symptoms and signs had been assessed based upon the neuropathy symptom score (NSS). The NSS is five multiple choice questions for measuring the severity of neuropathic symp-toms and signs. The NSS has a maximum score of 9, with a higher score indicating more severe neuropathic symptoms.

Electrophysiological studies of both upper and lower limbs were implemented at the room temperature, via Nihon Kochden electromyography machine, using surface electrodes for stimulation and recording. Sensory nerve conduction was assessed based on the antidromic method. Digit2wrist and Digit5-wrist segments were used for median and ulnar nerves conduction studies, respectively. To assess the sural nerve conduction, the recording electrode was positioned posterior to the lateral malleolus, whereas the reference electrode was placed approximately 3 cm distally.

electrodes The recording were positioned above the abductor pollicis brevis and the adductor digiti minimi muscles for the assessment of the median and ulnar nerves, respectively. In addition, to assess the peroneal nerve, these electrodes were placed over the extensor digitorum brevis muscle, whilst they were positioned over the abductor hallucis brevis muscle to assess the tibial nerve. Generally, the active recording electrode was laid on the belly of the muscle, whereas the reference electrode was positioned at the insertion of the muscle tendon.

A neuropathy was classified as predominantly or initially involving the Schwann cell, causing myelinopathy, or involving the axon itself causing Axonopathy.

The ESTEEM (European Standardized Telematic tool to Evaluate Electrodiagnostic Methods) was used as a guideline criterion for pathophysiological individual interpretation of electrodiagnostic nerve tests and classification of polyneuropathy (Tankisi et al., 2005).

## **Statistical Analysis:**

Continuous normally distributed data were illustrated in the form of mean, and standard deviation (SD), whereby nonnormally distributed data were presented using median and range. Categorical variables were expressed using the number and percentage and its particular groups were compared using Pearson's chi-square test with Fisher's exact test. Furthermore, correlation analysis was Spearman's conducted using rank correlation coefficient for non-parametric variables. The univariate regression model was accomplished to elucidate the independent predictors of peripheral neuropathy using t-test analysis. The significance is established when P < 0.05.

Statistical analysis was executed using SPSS software version 23 for Windows (SPSS Inc., Chicago, IL, USA), and MedCalc software version 14.8 (MedCalc Software, Mariakerke, Belgium).

## RESULTS

#### Patient's demographic characteristics

An overall 30 patients who fulfilled the inclusion criteria were recruited in the study. There were 22 (73.3%) males and 8 (26.7%) females with a mean age of  $37.9\pm8.31$  years. There were 22 (73.3%) patients had oral ulcers. Additionally, there were 20 (66.7%), 15 (50%), 20 (66.7%), and 17 (56.7%) patients suffered from eye affection, skin lesions, genital ulcers, and neurological manifestations,

respectively. Subsequent to that, there were 8 (26.6%) patients experienced gastrointestinal manifestations, whereas 5 (16.7%) and 3 (10%) patients experienced joint affection and major vessels affection, respectively. The duration of symptoms extended from a month up to 12 months. The mean Behcet Disease Current Activity Form (BDCAF) score was  $5.26\pm1.99$  (Table 1).

BDCAF score	5.26±1.99		
Duration of Symptoms	3 (1-12) years		
Oral Ulcers	22 (73.3%)		
Genital Ulcers	20 (66.7%)		
Eye affection	20 (66.7%)		
Neurological Manifestations	17 (56.7%)		
Skin Affection	15 (50%)		
Headache	13 (43.3%)		
Gastro-intestinal Manifestations	8 (26.7%)		
Joint affection	5 (16.7%)		
Major vessels affection 3 (10%)			
BDCAF = Behcet Disease Current Activity Form			

Table (1); Demographic and clinical characteristics in Behcet disease patients

Clinically, 7 (23.3%) of the included patients revealed symptoms of peripheral neuropathy counterpart numbness, tingling, reduced sensation, or motor weakness. On the contrary, based on the electrophysiological studies, 16 (53.3%) patients had the evidence of PN in the terms of mixed 7 (23.3%) patients, motor 2 (6.6%) patients, and sensory 7 (23.3%) patients nerve affection. In details, there were 5 (15.6%), 6 (20%), and

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5(16.6%) patients had median, ulnar, and tibial nerve affection, respectively. Consequently, 13 (43.3%) patients had peroneal nerve affection, whereby 14 (46.6%) patients had sural nerve affection (**Table 2**).

Sural nerve affection	14 (46.6%)	14 (46.6%)		
Demonant names offection	Axonal	7 (23.3%)		
Peroneal nerve affection	Demyelination	6 (20%)		
Tibial nerve affection	Axonal	3 (10%)		
Tiblai herve affection	Demyelination	2 (6.7%)		
	Axonal	3 (10%)		
Median nerve affection	Demyelination	2 (6.7%)		
Ulnar nerve affection	Axonal	3 (10%)		
	Demyelination	3 (10%)		

Table (2): Nerve	conduction stud	dv findings amon	g Behçet's disease pa	tients
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Out of the included patients, 9 patients were treated by colchicine. Of them, sex (66.6%) patients experienced peripheral neuropathy apart from mixed neuropathy (4 patients), and

sensory (2 patient). In contrast, sural and peroneal nerves were affected in six (66.6%) and 5 (55.5%) patients, respectively (**Figure1 and Table 3**).

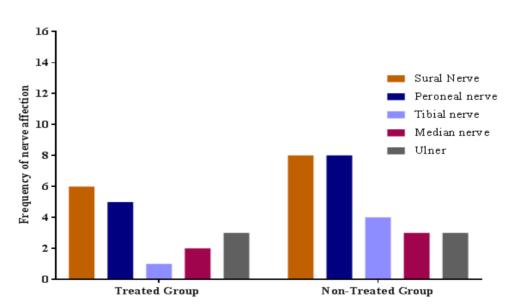


Figure (1): Bar chart displayed the pattern of peripheral neuropathy among patients received colchicine and patients not received colchicine. Table (3): The pattern of peripheral neuropathy according to colchicine treatment

Variables	Treated	Non-Treated	Fisher exact	P-value
	(N=9)	(N=21)	test	
Peripheral neuropathy	6 (66.6%)	10 (47.6%)	0.0894	> 0.05
Sural nerve affection	6 (66.6%)	8 (38.1%)	0.0512	> 0.05
Peroneal nerve affection	5 (55.5%)	8 (38.1%)	0.0695	> 0.05
Tibial nerve affection	1 (11.1%)	4 (19 %)	0.0618	> 0.05
Median nerve affection	2 (22.2%)	3 (14.7%)	0.0639	> 0.05
Ulnar nerve affection	3 (22.2%)	3 (14.3%)	0.0103	> 0.05

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Based on the clinical evaluation, only 7 (23.33%) patients revealed evidence of the peripheral neuropathy. However, on nerve conduction studies, extra nine patients were appeared to have subclinical peripheral neuropathy. Hereafter, sural nerve affection was evident in 8 (88.8%) patients among the asymptomatic group, while there were 6(85.7%) patients among the symptomatic group. Subsequently, three (42.8%) and six (66.6%) patients had peroneal nerve affection in the symptomatic and the asymptomatic groups, respectively (Figure 2 and Table 4).

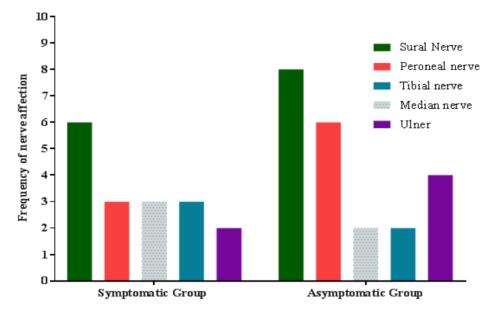


Figure (2): Bar chart showed the pattern of peripheral neuropathy among the symptomatic and asymptomatic groups.

Table (4):	The pattern	of peripheral	neuropathy	among	the	symptomatic	and the
	asymptomat	ic groups.					

Variables	Symptomatic (N=7)	Asymptomatic (N=9)	Fisher exact test	P-Value
Sural nerve	6 (85.7%)	8 (88.8%)	0.0693	> 0.05
Peroneal nerve	3 (42.8%)	6 (66.6%)	0.0318	> 0.05
Tibial nerve	3 (42.8%)	2 (22.2%)	0.0276	> 0.05
Median nerve	3 (42.8%)	2 (22.2%)	0.0489	> 0.05
Ulnar nerve	2 (28.5%)	4 (44.4%)	0.0831	> 0.05

#### Correlation and regression analysis

There was a statistically significant positive correlation between the age of the patients and the incidence of peripheral neuropathy (r=0.605. p=0.026). Additionally, BDCAF score (r=0.786, p=0.035) and the duration of the disease (r=0.565, p=0.001) showed statistically significant positive a correlation with the occurrence of the peripheral neuropathy. On the other hand, the colchicine treatment had no

statistically significant positive correlation with the occurrence of peripheral neuropathy (Figure 3, and Table 5). The univariate regression model revealed that the age of the patients (p=0.039) and the duration of the disease (p=0.021) are independent predictors of peripheral neuropathy (Figure 4, and Table 6).

There was a statistically significant positive correlation between sural nerve affection and the duration of the

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disease (r= 0.71, p=0.005) and the BCDAF score (r= 0.59, p=0.006). Conversely, the peroneal nerve affection was neither correlated with the duration of the disease (r= -0.01, p=0.93) nor correlated with BCDAF score.

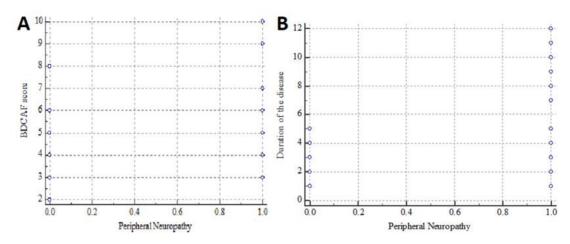


Figure (3): Scatter plot describing the correlation between the occurrence of peripheral neuropathy and A. BDCAF score. B. Duration of the disease

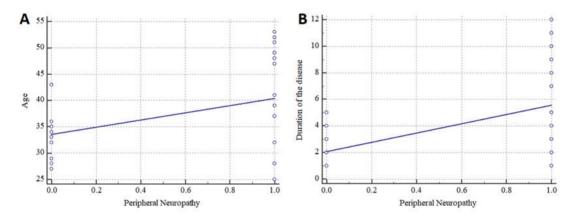


Figure (4): Scatter diagram with regression line illustrated the ability of A. Age and B. duration of the disease in the prediction of peripheral neuropathy

Table (5): Correlations between	n patients'	demographic	characteristics	and PN

Variable	r	P-Value*		
Age	0.605	0.026		
Sex	146	0.44		
Duration	0.565	0.001		
BDCAF Score	0.786	0.035		
Colchicine treatment	106	0.578		
r= Correlation Coefficient, BDCAF= Behcet Disease Current Activity				
Form, * P-Value based on Spearman's rank correlation coefficient				

Variable	β	T-test		
Variable		P-Value		
Age	0.121	0.039		
Duration	0.665	0.021		
BDCAF Score 0.522 0.053				
BDCAF= Behcet Disease Current Activity Form				

#### Table (6): Predictors of peripheral neuropathy

## DISCUSSION

The number of reported patients with neurological insults has been increased. On the contrary, the literature is still doubtful about the true existence of PN along with the possible predictors of such condition among BD patients (Benabdeljlil, 2018 and Caruso & Moretti, 2018). Thereafter, the present study was carried out to retrieve patients at higher risk to develop PN coupled with the optimal electrophysiological studies, which enhance the early detection of even subclinical PN among BD patients.

The evidence revealed in our investigation brings to light that; even though nearly 20% of BD patients experienced clinical manifestations of PN, approximately 50% had PN coupled with demyelinating changes which established electrophysiologically. Thereafter, we supposed to carry out a routine full assessment neurological along with electrophysiological study throughout the follow up period to retrieve BD patients with subclinical PN. Subsequent to that, close follow up protocol should be principally established, for elderly patients, those with long duration of the disease, and patients with high BDCAF score.

The underlying pathogenesis of PN among BD patients includes both humoral and cellular immune-mediated

al., components (Kalra et 2014). Noteworthy, the humoral component is evident based the presence on of immunoglobulins gathered with the deposition of the complement on the myelinated nerve fibers (Al-Araji and Kidd, 2009). Subsequently, the cellular immunity role is supported based on the activation of T-cells succeeded by passing of blood-nerve barrier, and the expression of numerous cytokines (Dutra and Barsottini, 2016). These immunological components play a crucial role in PN development, whereas the manifestations of PN improved considerably among BD patients after receiving immune treatment (Kalra et al., 2014).

Perhaps the significant immunemediated mechanisms, the degradation of nerve axons as an eventual impact of blood vessels damage may be established in order that the activated T-cells are attracted to the nervous system which leads to subsequent nerve ischemia (*Shahien and Bowirrat, 2010*).

study, In our based on the electrophysiological studies, the pattern of sensory nerve affection was noticeably higher than motor nerve affection. These findings were compatible with Hammad et al. (2014) study who stated that, the sensory and motor nerve conduction studies of ulnar, median, and sural nerves showed statistically significant а

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difference, whereas the sensory affection was considerably more than the motor affection. Similar to that, *Akubulat et al.* (2007) reported that sensory nerve affection was predominantly higher than motor affection.

Of note, the most affected nerve in current study was sural nerve, whereby approximately half of the included patients showed electrophysiological evidence of affection. This is because the PN among BD patients is a distal polyneuropathy, whereby the lower extremities are predominantly affected, specially the nerves of the lower limbs (Birol et al., 2004). In accordance with our results, Hammad et al. (2014) notified that sural nerve affection was the most frequently involved nerve (50%) among BD patients.

In our study, the higher age of the patients along with higher BDCAF Score and long duration of symptoms were more susceptible to experience PN. In this respect, *Hammad et al. (2014)* showed a statically positive correlation between sural and peroneal nerve neuropathy and the duration of the disease.

Although the evidence showed in the current investigation, this study had some limitations apart from the small sample size, lack of randomization, and the short follow-up period which constringed the capability to detect the long term PN consequences among BD patients. To limitations, overcome these further randomized clinical trials with а considerable sample size along with longterm follow up protocol should be implemented to tackle the obstacles of the current study.

# CONCLUSION

Peripheral neuropathy is a considerable complication of BD, whereby health care providers should employ a routine follow up protocol for early detection of the subclinical PN. Additionally, more concern should be given for elderly patients with high BDCAF score and a long duration of symptoms.

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خلفية البحث: مرض بهست هو مرض مزمن مجهول السبب ، حيث تتأثر العديد من الأعضاء الداخلية كنتيجة لعملية التهابات الأوعية الدموية بناءً على الدر اسات الوظيفية العصبية ، قد يكون لدى 20-40٪ من مرضى بهست إضطراباً عصبيًا صامتًا مع وجود مظاهر سريرية خفيفة للغاية أو عدم وجودها تماماً.

هدف البحث: تم تنفيذ الدراسة الحالية لتقييم مرضى بهست سريريا و من الناحية الفسيولوجية لتقييم مدى انتشار، الاعتلال العصبي الطرفى الظاهر وغير الظاهر، مع تحديد الأسباب التي قد تؤدى إلى وجودة.

المرضى وطرق البحث: شارك فى البحث ثلاثون من لمرضى الذين يعانون من مرض بهست والذين تم تشخيصهم بنائاً على المعايير الدولية لمرض بهجت فى الدراسة الحالية والذين يترددون على اقسام الاعصاب والروماتيزم والمناعه . تم تقديم جميع المرضى للتقييم السريري جنبا إلى جنب مع دراسات التوصيل العصبي الكهربية التى تشمل التوصيل العصبي الكهربى للاعصاب الحركية والحسيه بالاضافة الى قياس مدى تاثر الاعصاب الطرفيه باستخدام معيار مجموع نقاط الاعتلال العصبي.

النت انج: تضمنت هذه الدراسة 30 مشاركا من الذين استوفوا معايير الاشتمال في الدراسة. كمان هناك 22 ذكور و 8 إناث بمتوسط عمر 37.9 ± 8.31 سنة. بناءً على الدراسة. كمان هناك 22 ذكور و 8 إناث بمتوسط عمر 37.9 ± 8.31 سنة. بناءً على على الدراسات الفيسيولوجيا الكهربية ، فإن 16 مريضاً (53.3٪) لديهم دليا على على اعتراك الأعصاب الطرفية حيث كان التاثر في الاعصاب الحسية الحركية (23.3٪) ، والحركية (6.6٪) ، و الحسية (23.3٪). وكسان العصاب الطرفى الحساب الم

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الأكثر تضررا هو العصب الربلي (46.6 ٪) ، الشطوى (43.3 ٪) ثم الزندي (20 ٪).وقد أظهر نموذج الانحدار وحيد المتغير أن عمر المرضى ومدة المرض منبئين مستقلين للاعتلال العصبي الطرفي.

الإستنتاج: إعتلال الأعصاب الطرفية يعد أحد المضاعفات الكبرى لمرضى بهست ولذلك ينبغي لمقدمي الرعاية الصحية استخدام بروتوكول متابعة روتيني للكشف المبكر عن هذا الإعتلال لتجنب المشكلة المحتملة له.