Cross-sectional Study

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Prevalence, types, and characteristics of headache in Behcets disease without involvement of the central nervous system in the Syrian population: a case-cohort study

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Introduction: Oral ulcers, genital ulcers, and uveitis represent the typical trial of Behcet's disease (BD). It is well common on the Old Silk Road. The mucocutaneous lesions are the hallmark of BD, but neurological involvement is one of the severe symptoms. Headaches may be an early sign of BD neurological involvement. This study aims to investigate the headache prevalence and its types, and characteristics in a Syrian sample of BD patients.

Methods: BD patients were clinically interviewed and examined to collect their information, symptoms, and signs. the International Study Group for Behcet's Disease diagnosis criteria was used to confirm the BD diagnosis. The International Classification of headaches was used when classifying the headaches.

Results: One hundred twenty participants were included in the study. half of them were BD patients and the control group was also 60 participants. Among Syrian BD patients, 36.7% suffer from primary headaches and 36.7% suffer from secondary headaches. These findings were not significantly different between the BD patients and the healthy population. Our results showed that there was no statistically significant difference between the two groups.

Conclusion: Headache should not be considered a predictor for neurological involvement among BD patients. Additional attention to BD patients or the specific treatment for headaches is not required and does not differ from the general population.

Keywords: Behcet's disease, primary headache, secondary headache

Introduction

Bechet's disease (BD) was first described by Hulusi Behcet in 1937, who identified the trial of symptoms: oral ulcers, genital ulcers, and uveitis[1]. BD tends to affect younger ages between 20 and 40 years of age and less frequently in children[2], with a significant prevalence among the people from the Mediterranean, Middle East and Far East. It has been named "silk road disease" for this reason[3]. Both genders can be affected by BD; male dominance is found in Arab populations, whereas female dominance is evident in China, Korea, and Northern European Countries[4]. No data about the prevalence and characteristics of BD are available in Syria.

The mucocutaneous lesions are the hallmark of BD, but the most severe symptoms are uveitis, large vessels, and neurological involvement[5]. 5–10% of BD patients have central nervous involvement, most of which is parenchymal involvement. The prevalence of headaches in BD varies, as some researchers considered it a prominent complaint of many patients, rather than a neurological symptom[6–8]. Some patients complain about occasional, mild headache, while others reportedly experience daily disabling severe headache.

HIGHLIGHTS

- The aim of this research is to investigate the headache prevalence and its types, and characteristics in a Syrian sample of Bechet's disease (BD) patients compared to non-BD patients.
- Headaches may be an early sign of BD neurological involvement. Among 60 Syrian BSD patients, 36.7% suffer from primary headaches and 36.7% suffer from secondary headaches. These findings were not significantly different between the BD patients and the healthy population.
- Additional attention to BD patients or the specific treatment for headaches is not required and does not differ from the general population.

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There are theories concerning headache's higher prevalence in BD patients. It's classified as a primary headache such as tension-type headaches, and migraines, and a secondary type of headache such as uveitis and retinitis. In addition to specific types of headache in patients with BD, which is not classified as primary and secondary and are called "non-structural headaches[3]".

Many researches have previously investigated the characteristics and specific treatments of headache in BD; however, the pertinent studies have thus yielded conflicting results[6,7,9,10]. The percentage of headache was 35%and 65%, respectively[6,7]. Considering this disparity and the location of Syria on the Silk Road, we aim of this research is to investigate the headache prevalence and its types, and characteristics in a Syrian sample of BD patients.

Materials and methods

Study design and sample size

A case-control study was conducted in the Rheumatology Department of Damascus Hospital, from February 2019 to June 2020 on 120 participants, 60 BD patients, and 60 healthy control.

The sample size, when calculated using the website (openepni.com), was at least 55, with a confidence interval of 95%, in each group.

This study was approved by the ethics committee of Damascus University. All patients were fully informed and agreed to the concept and aim of this study.

We confirm that all methods employed in this study were carried out by the relevant guidelines and regulations.

Study population

The total number of participants was 120, 60 BD patients and 60 healthy people.

The control patients were matched in age, sex, and socio-economic characteristics. This control group participants were referred to the hospital and were selected from patients in urology and orthopaedic clinics, without previous medical history or receiving any treatment. We asked many participants if they ever had headaches, and if yes, they were enroled in our study.

Inclusion criteria

BD patients older than 18 years old who were diagnosed depending on the BD classification criteria of the International Study Group[7].

Exclusion criteria

Pregnant women and women with gave birth within the last 6 months, patients with other connective tissue diseases, or other auto-immune diseases, central nervous trauma and/or diseases, a history of papilledema, psychological stress and/or disorders, liver disorders, renal diseases, malignancy and any other disorders that can cause headaches, were also excluded.

Methods

Age, sex, previous medical and surgical records, and medications were asked and collected for all participants. The headache characteristics and duration between headache occurrences were collected and registered to all participants. BD duration was also collected only for BD patients. The headache characteristics according to the International Classification of Headache Disorders[3] and the time between headache occurrence and diagnosis of BD.

The patients were interviewed by a rheumatologist , and each patient was individually interviewed and examined.

Headaches related to BD were classified as structural if they started 6 months before the onset of BD or after the disease onset which did not meet the criteria of the International Headaches Society (IHS) for primary headaches. Any other types of headaches were sent to a specialist for additional investigation, except for patients with reliable medical records. Patients with a confirmed diagnosis of neuro-bechet disease by magnetic resonance imaging and cerebral spinal fluid analysis were excluded. The most severe and characterized headache was considered if a patient had complained of more than one type of headache. All patients and control had undergone physical examination including a full neurological examination by the same examiner. All patients and control had fundoscopy because, in patients with papilledema, vision is usually not affected initially.

Study tools

International Study Group for BD diagnosis criteria[11]. These criteria defined BD as recurrent oral ulceration plus two of the following manifestations: genital ulcers, ocular lesions, dermatological manifestations, and a positive pathergy test.

The International Classification of Headaches[12] which defined primary headaches include tension-type headaches, migraines with/without aura, and cluster headaches. Secondary headaches include ocular-related headaches confirmed by an ophthalmologist, infectious or sinusitis headaches, and structural headache which is neither primary nor secondary.

Our study is compliant with The STROCSS 2021 checklist Guideline[13], and this work is submitted on the research registry dashboard.

Data analysis

IBM Statistical Package for the Social Sciences (SPSS) software for Windows version 28.0 was used to statically analyze the data. In this analysis, $\alpha = 0.05$ and $\beta = 0.1$. Also, 11% difference in headache prevalence between the two groups was considered. P value less than 0.05 was considered significant. We used student's t test for comparison of quantitative data and χ^2 test for comparison of qualitative data.

Results

Demographic data

One hundred twenty participants were included in the study. Half of them were BD patients (18 females and 42 males) and the control group was also 60 participants (20 females and 40 males). The age of the participants was between 28 and 41. The total mean of the participants age was 33.84 ($\pm$ 3.31). The mean age of BD patients was 33.48 ($\pm$ 3.28), compared to a control group of 34.20 ($\pm$ 3.33). The mean systolic blood pressure was significantly different between the case and control groups (125.1 vs. 121.7 mmHg; $P = 0.007$), but within normal limits, as none of our patients or controls previously had hypertension. There were

Table 1

Demographic descriptive statistics of the sample

	BD patients ($n=60$)	Control ($n=60$)	Total ($n=120$)	P
Sex, n (%)				0.695
F	18 (30.0)	20 (33.3)	38 (31.7)	
M	42 (70.0)	40 (66.7)	82 (68.3)	
Age, years, n (%)				0.269
28–34	37 (61.7)	31 (51.7)	68 (56.7)	
35–41	23 (38.3)	29 (48.3)	52 (43.3)	
Systolic blood pressure, mmHg	125.1	121.7		0.007

BD, Behcet's disease; F, female; M, male.

not any significant differences in sex and age groups between the case and control group (Table 1).

The symptoms of BD patients

The most common symptoms were the three main BD symptoms: 100% oral aphthous, 60% genital ulcer, and 55% ocular manifestations. However, the prevalence of other symptoms was 50% arthralgia and arthritis, 40% erythema nodosum and vascular manifestations. Pseudo-folliculitis and gastrointestinal manifestations were less frequently reported by our BD patients (30% and 11%, respectively) (Table 2).

The prevalence and characteristics of the headache between the two groups

The total prevalence of different types of headaches was 36.7% and 21.7% in the case and control groups, respectively.

There was not a significant difference between primary headaches between patients with BD and healthy people. The prevalence of primary headaches is higher in patients with BD (36.7%), compared to healthy people (21.7%), and the most common cause of primary headache was tension headache among the participants (Table 3).

Moreover, Secondary headaches had a same prevalence of 36.7% in case group and anterior uveitis was the most common cause of the secondary headaches with 28.3% (Table 4).

Table 2

Frequency of the symptoms in BD patients

Symptoms	N (%)
Oral aphtus	60 (100.0)
Genital ulcer	36 (60.0)
Ocular manifestations	33 (55.0)
Arthralgia and arthritis	30 (50.0)
Erythema nodosum	24 (40.0)
Vascular manifestations	24 (40.0)
Pseudo-folliculitis	18 (30.0)
Gastrointestinal manifestations	7 (11.7)

BD, Behcet's disease.

The relation between disease duration, and the onset of the headache

In fifty percent (50%) of patients, the headache onset was found to be years after the onset of the disease. On the contrary, 20% of the patients recalled having headaches years before the diagnosis of Bechet disease was confirmed.

Consumption of medications, and family history

BD treatment

The prevalence of headaches in BD patients was not significantly different between prednisolone-received patients at a dose of 7.5 mg/kg daily and those who did not consume prednisolone ($P=0.10$), although the prevalence of headache was about 2 times higher in patients receiving 7.5 mg/kg daily and more.

Headache medication

Additionally, 12 out of 60 patients with BD needed treatment for their primary headache symptoms, whereas only 6 in the healthy group needed treatment. However, there was no statistically significant difference between the case and control group. Also, while comparing the family history between patients with BD and healthy people the P value was $=0.42$, therefore, there was no significant difference between the two groups. However, it was significantly higher in participants complaining of headaches in both groups (Table 5).

Discussion

BD is a multiorgan disease, it affects the younger population especially patients in their second to fourth decades, but it can present at any age[3,4,6]. This increased prevalence in the Old Silk Road and family aggregation strongly suggest the genetic factor in inducing the disease, and the carriers of HLA-B51/B5 are at higher risk of developing BD compared to non-carriers[14]. This confirms with our results; the total mean is 33.84 (± 3.31), and our country Syria is located on a Silk Road.

The dominant gender in our study is male which also confirms the fact that men are dominant among BD patients in the Arab population[4]. Most of the clinical symptoms of BD are believed to be due to auto-inflammatory vasculitis, it is well known that BD can involve arteries and veins of all sizes and shapes[5]. Those vasculitis lesions of BD are without necrotizing vasculitis or giant cell formation[11]. Additionally, BD patients lack specific auto-immune antibodies like the ones seen in other auto-immune disorders like rheumatoid arthritis or systematic lupus erythematous[5].

The frequent early manifestations of neurological involvement in BD are headache, fever, disorientation, poor balance or stroke, pyramidal signs, behavioural changes, and sphincter disturbance[9,15]. This direct neurological involvement can lead to secondary headaches, but primary headache syndromes (such as migraine and tension headache) affect 50% of patients with BD and are responsible for 70% of all headaches in BD[12]. However, headaches in BD patients might be an indication of the neurological involvement of BD, but most of those headaches are benign[9]. Sometimes BD could be misdiagnosed as aseptic meningitis, multiple sclerosis, or primary neoplasm[9]. On the other hand, some studies indicated that although headache is so

Table 3

Comparing between BD patients and control in primary

	BD patients ($n=60$), n (%)	Control ($n=60$), n (%)	Total ($n=120$), n (%)	P
Primary headache	22 (36.7)	13 (21.7)	35 (29.2)	0.07
Tension headache	11 (18.3)	6 (10.0)	17 (14.2)	0.19
Migraine without aura	6 (10.0)	4 (6.7)	10 (8.3)	0.50
Migraine with aura	3 (5.0)	3 (5.0)	6 (5.0)	0.66
Cluster headache	2 (3.3)	0	2 (1.7)	0.49

BD, Behcet's disease.

high among BD patients, they do not consider this as a neurological involvement sign but only a major complaint of many patients[16,17].

The characteristics of primary headaches such as migraine, tension-type and cluster headaches, and secondary headaches related to ocular involvement, and non-structural headaches have been a field of interest in many studies. Meanwhile, the rarity and specific geographical distribution of BD have resulted in studies with small sample sizes, and all reached challenging disparities results[6,7,9,10].

We found a higher prevalence of headaches in BD patients like Borhani *et al*.[7] Volpinari *et al*.[18], and Kale *et al*.[10] the study, but less than the percentage found in some other studies, like Kidd *et al*.[12], Monastero *et al*.[19], and Turkish Headache Epidemiology Study Group[20] Saip *et al*.[21]. These differences may be due to the ethnicity variables.

Tension-type headaches and uveitis-related headaches were more frequent among patients with BD than the control group, according to a study by Vinokur *et al*.[22], and this was similar to our findings.

However, uveitis had a significantly positive correlation with the frequency of headaches in BD patients[12,19]. It differs from another study[10] which found that the most extra parenchymal involvement was venous thrombosis, seizure disorder, and psychiatric problems/depression or anxiety. Also, Vinokur *et al*.[22], in their results, found that the most common cause of secondary headache was venous thrombosis. The frequency of non-structural headaches was one-third of that reported in the study carried out in Turkey[20] and we have only recorded two patients suffering from this type of headache in our study and may be the larger sample size of the Turkish study had played a role.

Previous studies reported a link between blood pressure and headache[23]. In our study, the mean systolic blood pressure was significantly higher in patients with BD. This might be due to the consumption of prednisolone or atherogenic pathologies of BD. We did not compare patients with BD to the control group who had normal systolic blood pressure to make sure that the difference in blood pressure does not cause dissimilarity in the prevalence of headaches among the case and control groups.

Some opinions suggest that steroids may be used in a dose of more than 30 mg/day for 15 days in the treatment of BD-related headaches[24,25]. The prevalence of headaches was not significantly different between prednisolone-received patients and those who did not consume prednisolone, so the hypothesis that prednisolone reduces the prevalence of headaches in BD[10] was not confirmed in our study. Therefore, the doses of prednisolone used for the treatment of BD (7.5–15 mg/daily) exert a weak effect on headaches[10]. Otherwise, it is well known that headache is a less common side effect of cyclophosphamide treatment, which may be due to the elevation of blood pressure which could happen during the infusion of cyclophosphamide. No data were found about the prevalence of headaches during cyclophosphamide infusion[26,27]. The rate of using the treatment for headaches in our study was higher in both groups compared to the previous studies[25,26,28]. The facility of buying analgesics in Syria may explain these differences. Moreover, in our study, the presence of a family history of headaches was not significantly different between both groups, which is in concordance with some studies[28,29].

The strengths of the current study were the use of validated diagnostic criteria for headaches, and it was revealed for the first time in our country.

Limitations

To be noted, in this study, we found no specific pattern for intensity, characteristics, or localization of headaches in BD patients. Even if it is the first research that studies the symptoms of headache among Syrian Behcet disease patients, but it is major limitation is the small patient sample size, the enrolment of the study in one referral centre, and the inability to perform MRI and HLAB 27 to all patients. The rarity of the disease and its underdiagnosis in Syria may be the factors that induced a small sample size and were obstacles in the study. However, our findings indicated that headache in Syrian BD patients was not significantly different from the healthy population.

Table 4

The secondary headache in BD patients

	N (%)
Secondary headache	22 (36.7)
Anterior uveitis	17 (28.3)
Posterior uveitis	8 (13.3)
Macular oedema	2 (3.3)

BD, Behcet's disease.

Table 5

Comparing between BD patients and control in treatment, and family history

	BD patients ($n=60$), n (%)	Control ($n=60$), n (%)	Total ($n=120$), n (%)	P
Treatment	12 (20.3)	6 (10.0)	18 (15.1)	0.20
Family history	10 (16.7)	6 (10.0)	16 (13.3)	0.42

BD, Behcet's disease.

Conclusion

Headaches may be an early sign of BD neurological involvement. Headache, especially tension-type headache, is more frequent in BD patients. neuro-Behcets (NBD) must be meticulously investigated in patients with BD who presented with headache. However, further higher sample size or multicenter researches are highly recommended for a better understanding of neurological symptoms especially headaches among Syrian BD patients.

Ethical approval

This study was approved by the Ethical Committee of the Faculty of Medicine, Syrian Private University(QS;32109,2019). We confirm that all methods employed in this study were carried out in accordance with the relevant guidelines and regulations. We have adhered to ethical standards and followed the appropriate procedures to ensure the integrity and validity of our research.

Consent

Written informed consent was obtained from the patients for this research publication. A copy of the written consent is available for review by the editor-in-chief of this journal upon request.

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Not applicable.

Author contribution

All the authors contributed to the study concept and design. K.R., N.R. and M.K.: clinically approached the patients. K R., N.R. and H.D. retrospectively checked the results. H.D. conducted the statistical analysis K.R. N.R. and G.H. drafted the manuscript. M.D. revised the manuscript for scientific accuracy. All the authors revised the final draft of the manuscript and approved it for publication.

Conflicts of interest disclosure

The authors deny any conflicts of interest in regard to the current study.

Research registration unique identifying number (UIN)

1. Name of the registry: Maysoun Kudsi.
2. Unique Identifying number or regiistration ID: research registry9449.
3. Hyperlink to your specific registration (must be publicly accessible and will be checked): https://www.researchregistry.com/browse-theregistry#home/registrationdetails/64e8aa45f4acf50029ff470c/.

Guarantor

Maysoun Kudsi.

Availability of data and material

The datasets, that was used and analyzed during the current study, are available from the corresponding author on reasonable request.

Provenance and peer review

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