Ocular, Systemic Manifestations and Efficacy of Treatment of Behcet's Disease Patients at King Hussein Medical Center.

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AbSTRACT

Objectives: To review ocular and systemic manifestations, and efficacy of systemic treatment of Behcet's disease patients at King Hussein Medical Center.

Methods: This retrospective study was conducted at the ophthalmology and rheumatology departments at king Hussein Medical Center. All patients who were diagnosed to have Behcet's disease according to the International Study Group criteria between January 2012 and April 2017 were included in the study. Patients with incomplete Behcet's disease or those who were recently diagnosed to have Behcet's disease (less than 6 months) were excluded from the study. Data regarding demographic features was initially collected then patient's files were reviewed regarding the possession of HLA-B51, systemic manifestations, and complications of the disease. Type of ocular involvement and ocular complications were studied, and the offered treatment options and their efficacy were evaluated.

Results: One hundred and eleven patients were included. The mean age of cases was 30.2 years with male predominance (ratio 5:1). The most common clinical findings was genital ulcers (75.7%) followed by skin lesions (46.8%) and uveitis (32.4%). Arthralgia and arthritis was the most common systemic complication (14.4%). The most common eye involvement was vitritis (58.3%) followed by anterior uveitis (55.6%), retinal vasculitis (30.6%), retinitis (8.3%), pan uveitis (8.3%), and optic neuritis (3.8%). HLA- B51 and pathergy test were positive in 55.9% and 34.2% of cases, respectively. Colchicine and oral Prednisolone were the most used drugs and infliximab was the most effective single drug used in the treatment of Behcet's disease

Conclusion: After oral ulcers, the most common clinical finding found in Behcet's disease patients was genital ulcers. Ocular involvement of Behcet's disease was relatively uncommon and vitritis was the most common manifestation. HLA- B51 was significantly associated with ocular involvement. Infliximab was the most effective drug in controlling the activity of Behcet's disease.

Key words: Behcet's disease, Ocular manifestations, Systemic manifestations.

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Introduction

Behcet's disease (BD) is a multisystem inflammatory chronic relapsing disorder characterized by occlusive vasculitis with unknown etiology.[1] It was only in 1937 when a Turkish dermatologist Hulusi Behcet first described the disease as a triad of recurrent oral aphthous ulcers, genital ulcers, and uveitis.[2] It usually affects people between 20 and 40 years of age with male predominance.[3, 4] There is an obvious geographical variation regarding its prevalence in the world being the highest in

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Turkey (420 cases per 100,000 population) and well documented in other countries of the Middle east and Japan.[5, 6] The diagnosis of BD is mainly clinical based on its multi- systemic manifestations. The most widely used criteria for diagnosis is the one invented by the International Study Group (ISG) in 1990; were to establish the diagnosis of BD the patient must has recurrent oral aphthae in addition to the presence of at least 2 of 4 findings; genital ulcers, ocular involvement, skin involvement, and positive pathergy test.[7] In 2006, the international Criteria for Behcet's Disease (ICBD), based on a scoring system was used in Europe to diagnose patients with BD.[8] This scoring system gives points to each systemic manifestation as follows: genital ulcers 2 points, eye involvement 2 points, and one point for each of the remaining manifestations. Getting 3 or more points needed to establish the diagnosis of BD. The exact etiology for BD is still unknown. However BD was found to be highly prevalent in population with HLA- B5 and its split HLA- B51 possession.[9] Ocular involvement occurs in approximately 70-100% of patients and is associated with a high risk of blindness.[10] Uveitis occurs as bilateral non-granulomatous panuveitis and retinal vasculitis. However, a minority of patients, especially females, may have isolated anterior uveitis. It is reported that uveitis might be the initial manifestation of BD in 10-15% of the patients.[11] The policy in our hospital is to start patients with BD on Colchicine for cutaneous and articular involvement. For ocular involvement, when topical and local therapy are ineffective the patients will be started on Azathioprine or Methotrexate and when those are ineffective Cyclosporine may be added. Finally biologic agents may be used when all previous medication fail. So the choice of treatment depends on the patient's tolerance to the drug and its side effect, the patients life style, the patient's preference (some patients prefer to use weekly dose of Methotrexate than daily dose of Azathioprine) and finally if there is any contraindication for the drug like pregnancy. Also the type of medication may change during follow up for the same reasons.

This study was conducted at King Hussein Medical Center to review all patterns of ocular and systemic manifestations along with systemic treatment options and its efficacy in the management of Behcet's disease among Jordanian patients.

Methods

This retrospective study was conducted at the ophthalmology and rheumatology departments at king Hussein Medical Center. All patients who were diagnosed to have Behcet's disease according to the International Study Group criteria between January 2012 and April 2017 were included in the study. Patients with incomplete Behcet's disease or those who were recently diagnosed to have Behcet's disease (less than 6 months) were excluded from the study. Data regarding demographic features was initially collected then patient's files were reviewed regarding the possession of HLA-B51, systemic manifestations, and complications of the disease. Type of ocular involvement and ocular complications were studied, and the offered treatment options and their efficacy were evaluated. The patient is considered to be under control when the disease is quiet and patient is not taking oral prednisolone exceeding 10 mg daily. The study was approved by the ethical committee of the Royal medical services.

The obtained results were analyzed and compared with that of other studies conducted in nearby countries and worldwide. Probability values of $p<0.05$ were considered significant.

Results

One hundred and eleven patients were included. The mean age of cases was 30.2 years with male predominance (ratio 5:1). Figure 1 represents the distribution of the patients' age groups. The main duration of the disease was 4.7 ± 2.4 years. According to the ISG criteria, oral ulcers must be found in each patient to establish the diagnosis of BD. In this study oral aphthous ulcers were found in all patients and genital ulcers were found in three quadrants of patients, Table I. Other associated systemic complications, which are not part of the ISG

criteria for the diagnosis of BD, are presented in Table II. Ocular involvement was found in 36 patients (32.4%). Ocular involvement was the initial manifestation of the disease in 10% of those patients. Bilateral involvement was noticed in 34 (94.4%) cases. The most common eye involvement was vitritis (58.3%) followed by anterior uveitis (55.6%), retinal vasculitis (30.6%), retinitis (8.3%), pan uveitis (8.3%) and optic neuritis (3.8%). Ocular complications of BD uveitis were in decreasing order of frequency as follows: cataract (50%) followed by posterior synechiae (26.9%), glaucoma (19.2%), retinal vein occlusion (7.7%), optic disc pallor (5.6%), and macular edema (5.6%). Surgical treatment was needed in 8 patients; 5 of them needed cataract surgery, 2 of them needed glaucoma surgery and one patient required pars plan vitrectomy. Behcet's disease was responsible for deterioration of vision to less than 0.1 (6/60) in 48 eyes (68.6%). HLA-B51 was positive in 55.9% of all patients with BD. In addition, HLA- B51 was positive in 69% of patients with ocular involvement compared to only 45% of BD patients with no ocular involvement ($P<0.01$, *t-test*).

There is a variety of medications used to control the activity of BD, number and types of medications depend on the patient's response, compliance and tolerance. Table III summarizes the type of medications used at our patients and their percentages. One of the female patients was pregnant and so a combination of Azathioprine and Oral Prednisolone was used. Frequencies of patients used one or more drugs are illustrated in Figure 2. It was noticed that only 3 female patients out of 22 (13.6%) were using 3 or more medication, while for male patients the number was higher and it was 30 out of 89 (33.7%), $P< 0.03$. The most efficiently used single drug to control BD was Infliximab.

Figure 1. Distribution of the patient's age groups in BD.

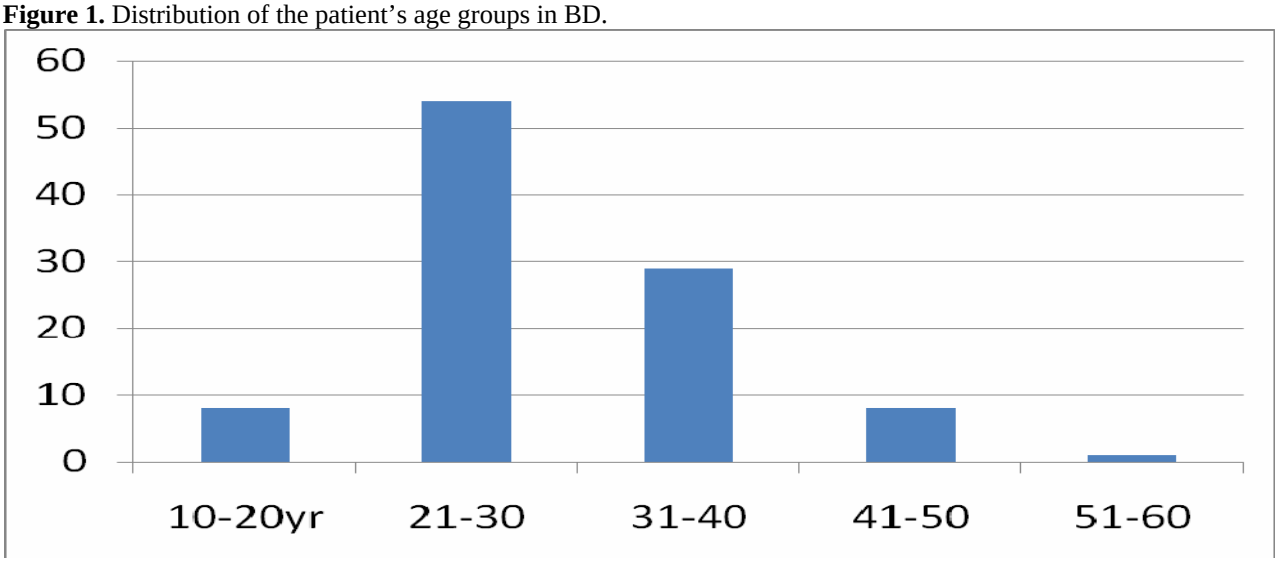


Table I: Frequency of BD manifestations among studied population according to ISG criteria.

Systemic Manifestation	Number Of Patients	Percentage
Oral ulcers	111	100%
Genital ulcers	84	75.7%
Uveitis	36	32.4%
Skin lesions	52	46.8%
Positive pathergy test	38	34.2%

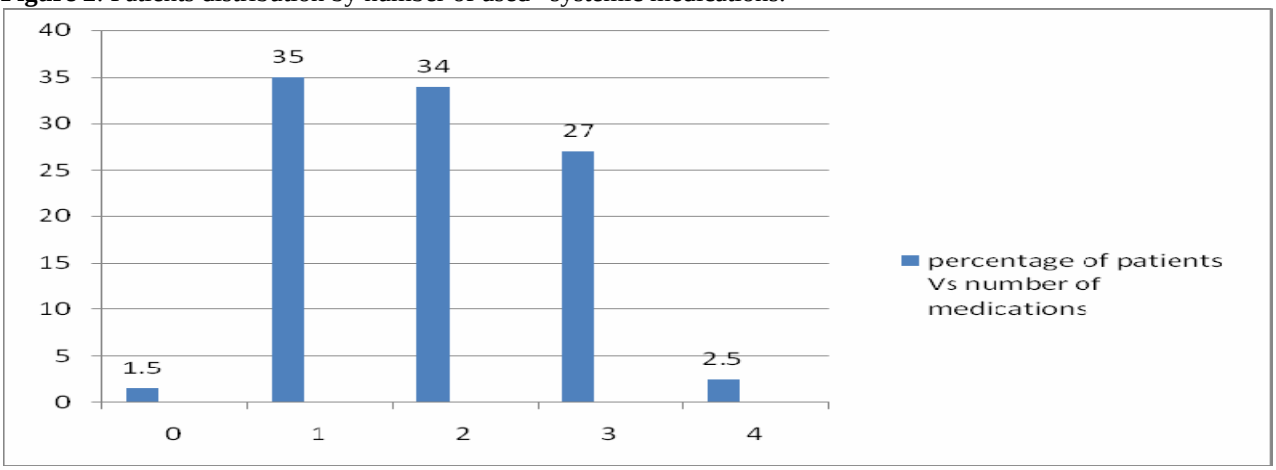
Table II. Frequency of other systemic complications of BD, not part of the ISG criteria**.**

Complication	Number Of Patients	Percentage
Arthralgia and Arthritis	16	14.4%
Deep venous thrombosis	15	13.5%
Neuro-Behçet's	12	10.8%
Gastro-intestinal involvement	5	4.5%
Pulmonary artery aneurysm	5	4.5%
Sagittal sinus thrombosis	4	3.6%
Pulmonary embolism	4	3.6%
Superior vena cava thrombosis	2	1.8%
Cerebral vascular accident (CVA)	2	1.8%
Inferior vena cava thrombosis	1	0.9%

Table III: Frequency of medications used for studied cases.

Medication	Number of patients	percentage
Colchicine	83	74.8%
Oral Prednisolone	69	62.2%
Azathioprine	37	33.3%
Infliximab	17	15.3%
Cyclophosphamide	6	5.4%
Cyclosporine	4	3.6%
Methotrexate	2	1.8%
Salazopyrin	1	0.9%

Figure 2: Patients distribution by number of used systemic medications.



Discussion

BD is a well-known disease in the Middle East. Its prevalence showed wide geographical variation in the world being highest in Turkey. Geographical variation also present among Middle East countries; it was found to be as high as 170 per 100,000 people in Iraq compared to 68, 2.1, and 20 per 100,000 people in Iran, Kuwait and Saudi Arabia respectively.[12, 13] This variation is not only attributed to the geographical factors but also to the used criteria and method of the study for the diagnosis of BD as well. The prevalence of BD among Jordanian population is not well explored but it is strongly believed that Jordan like other countries of Middle East has a relatively high prevalence. The mean age of the patients included in this study was 32.3 years

which was comparable to other studies with some insignificant variations.[13] Most of the patients (91%) were below the age 40 years. Therefore efforts should be made to early control the activity of the disease because it affects the young age groups with associated morbidity and mortality. The disease was more frequent in males with a ratio of 5:1. Most of the studies also found the disease to be more prevalent among males but with variable ratios.[14] In Saudi Arabia the ratio was also high, 3.4:1.[15] In a previous study conducted in 2004 by Mustafa TA, BD in Jordan was found to be much more frequent in males with a ratio 6.7:1.[16] The most common findings that are part of ISG criteria after oral aphthous ulcers were genital ulcers (75.7%) followed by skin lesion particularly erythema nodosum (46.8%), positive pathergy test (34.2%) and uveitis (32.4%). These results were similar in order to that found in other international studies but with variability in frequency.[14] However, the order and the frequencies of those manifestations were completely different in a study conducted 7 years ago by Smadi *et al*. where the most common finding was skin lesions (92%), unlike most other studies performed worldwide where genital ulcer were the most common.[15, 17] This might be explained by the fact that dermatological assessment was performed by a dermatologist at the dermatology department where the patients underwent detailed skin examination. Like other studies arthralgia and arthritis was the most common systemic complication of BD (14.4%).[14] Other serious complications like deep venous thrombosis was also frequent (13.5%). The rest of complications were much close to that found in other studies.[15]

In our study ocular involvement was noticed in 32.4% of BD patients. Smadi *et al* reported a frequency of 32%.[17] This is considered a relatively low frequency when compared to other countries. For example ocular involvement was reported to be (55%), (69%), (35%), (51%) and (55%) in Iran, Japan, China, Korea and Germany, respectively.[17] This suggests that a geographical variation may exist regarding BD manifestations particularly the ocular ones and Jordan may be one of the countries with low frequency of ocular involvement. The most common eye involvement was vitritis (58.3%) followed by anterior uveitis (55.6%). The most common eye complication of BD was cataract. These data were mostly consistent with data from a study conducted by Abu-Ameerh *et al*. to explore the ocular manifestations of BD where they reported that vitritis followed by anterior uveitis were the most common forms of eye involvement and cataract was the most common complication.[18] Visual acuity of less than 6/60 was noticed in forty- eight eyes (68.6%). This reflects the adverse effect of BD and its burden on the life style of the patients. HLA- B51 was positive in 55.9% of all patients with BD. There is a wide variation regarding the frequency of HLA- B51 in the world; it was found to be as low as 23% in USA to as high as 78.9% in Serbia.[19,14] However , HLA B51 was positive in 69% of patients with ocular involvement compared to only 45% of BD patients without ocular involvement ($p<0.01$). This suggests that HLA -B51 may play an important role in eye involvement among patients with BD. Use of anti-inflammatory, immune-suppressive, and cytotoxic agents is mandatory in the successful treatment of BD. Colchicine was the most frequent drug used in treatment of BD (74,8%). However, it should be mentioned that this drug is effective for cutaneous and articular involvement of BD but not for the ocular involvement.[20] Oral prednisolone was used in 62% of patients and more than 80% of those patients were using a dose of more than 10 mg daily. This means that about 50% of BD patients failed to achieve reasonable control of the disease. Because the main aim of therapy is to reach a point where the disease is well controlled without the use of systemic steroid or a daily dose not exceeding 10 mg. Seventeen patients were using Infliximab and all of them were well controlled and not on systemic steroids exceeding 10 mg daily. That means Infliximab was very effective in treatment of BD. This should encourage us to extend the use of such biologic agents in the treatment of BD. The use of two or less medications was found in

70.5% of BD patients. To control BD, three or more drugs were used more frequent for males than females. This statistically significant difference (*P <0.03*) indicates that the disease was more severe and more aggressive in males patients. Although the sample size was relatively small, this study showed variable presentation of Behcet disease in different communities including Jordan and there is a need to modify the treatment options presented to the BD patients in Jordan and to extend the use of biologic agents which will decrease the morbidity and mortality of the disease.

Conclusion

The second most common finding found in BD patients after oral ulcers was genital ulcers. Ocular involvement of BD was relatively uncommon and vitritis was the most common manifestation. HLA- B51 was significantly associated with ocular involvement. Infliximab was the most effective single drug in controlling the activity of BD.

References

1. **Paovic J, Paovic P, Sredovic V.** Behçet's Disease, Systemic and Ocular Manifestations. *BioMed Research International*. 2013;2013:7.

2. **Aysin K.** Clinical and Pathological Manifestations with Differential Diagnosis in Behcet's Disease. Pathology Research International. 2012;1-9.

3. **Yurdakul S**, **Yazici H**. "Behçet's syndrome" Best Practice and Research: *Clinical Rheumatology*, 2008 (22); 793–809.

4**. Savey L, Resche-Rigon M, Wechsler B, *et al*.** Ethnicity and association with disease manifestations and mortality in Behçet's disease. *Orphanet J Rare Dis*. 2014; 9: 42.

5. **Kenneth T**, **Florannce C, Murat I, *et al***. Epidemiology and Clinical Characteristics of Behçet's Disease in the US: A Population-Based Study. *Arthritis Rheum*. 2009; 61(5): 600–604.

6. **Aladdin M, Thomas M, Gunnar S, *et al***. Incidence, prevalence and clinical characteristics of Behçet's disease in southern Sweden. *Rheumatology* 2012; 1-7.

7. **Hayashi T, Mizoki N**. Ocular Manifestations in Behçet's Disease. JMAJ. 2006;49(78):260-268.

8. **Davatchi F**. Diagnosis/Classification Criteria for Behcet's Disease. *Pathology Research International* 2012, 5 pages

9. **Rohatgi J, Singal A**. Ocular Manifestations of Behcetís Disease in Indian Patients. Indian J *Ophthalmol* .2003;51:309-13.

10. **Nicholas J.** , Uveitis: 2nd edition, *JP medical publisher*, 2013

11. **Tugal-Tutkun I.** Behçet's Uveitis. *Middle East Afr J Ophthalmol*. 2009 Oct-Dec; 16(4): 219–224.

12. **Palizgir M, Mahmoudi M, Qorbani M, *et al***. Prevalence and Clinical Investigation of the Behcet's Disease in Middle East and North Africa: A Systematic Review and Meta-Analysis. *Iranian Red Crescent Medical Journal In press* (2017).

13. **Davatchi F. Shahram F. Chams-Davatchi C. *et al***. Behcet's disease: from east to west. *Clinical Rheumatology* 2010;29(8) : 823–833.

14. **Paovic J, Paovic P, Sredovic V**. Behcet's Disease: Systemic and Ocular Manifestations. *BioMed Research International*. 2013:1-7.

15. **Al-Dalaan AN, Al Balaa SR, El Ramahi K**. Behçet's disease in Saudi Arabia. J *Rheumatol*. 1994;21(4):658-61.

16. **Mustafa TA, Hadid AA**. Clinial Pattern of Behcet's disease in Jordan. *Qatar Medical Journal* 2004; 12(2):124-128.

17.**Smadi R, Sarhan A, Masha'leh M**, Systemic and Mucocutaneous Manifestations of Behcet's Disease: An Analysis of 107 Cases. *Journal of the Royal Medical Services* 2010;17(2):19-22.

18. **Abu Ameerah MA**, **Mohammed SF, Mohammad MT, et al**. Ocular manifestations of Behçet's disease in Jordanian patients. *Saudi Journal of Ophthalmology*. 2013;27(4): 247–251.

19. **Ucar D, Dalal M, Fox A, *et al***. Behçet's Disease in the United States: Ocular and Systemic Manifestations. Invest. *Ophthalmol.* 2014;55(13):5304.

20. **Nair JR, Moots RJ**. Behcet's disease. *Clin Med (London)* 2017;17(1): 71-77.