Letter to the Editor

No Family Clustering in Behçet's Syndrome

Mehmet Engin Tezcan. Family Clustering in BS

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To the Editor,

Behçet's syndrome (BS) has various clinical expressions. That's why we called the disease as syndrome. BS patients have been sub-classified to various clusters based on clinical expressions(1). The question *"Why different types of clusters in BS take place?"* is not certainly known.
Like most of the diseases in BS, both genetic and environmental factors have roles in the pathogenesis of the disease. But we do not know the weight of the factors during the emergence of the disease. Therefore, I conducted a basic study that depends on a simple questionnaire for examining the hypothesis *" BS patients in the same family generally accumulate in the similar clinical cluster"* . It was previously evaluated in a large cohort (2). But, I wanted to reassess the hypothesis in my BS cohort.
Although, BS patients have heterogeneous clinical expressions and BS has no universal diagnosis criteria, for standardising the study group, I used International Study Group Criteria for Behçet Disease (ISBD) criteria(3). So, all patients in the study fulfilled the ISBD criteria. Also, I clinically sub-classified the patients to one of the BS cluster. These clusters were mucocutenous, vascular, acne-arthritis-enthesis and eye diseases as described previously (1). Additionally, for clinical purposes, I also classified patients to neurologic, intestinal and undetermined clusters. This study was approved by the Local Research Ethics Committee and carried out in compliance with the Helsinki Declaration.
Eighty-five patients and their relatives have given consent to be a study participant. Firstly, I re-evaluated the family history of the patients for BS. Then, I asked patients the question: *"Do you have any first or second degree relatives with one of the BS related symptoms including oral and genital ulcers,eye disease, cerebral events, skin lesions, vascular thrombosis, haemoptysis or pulmonary symptoms?"* Lastly, I interviewed with the relatives of my patients that replied the latter question in the affirmative or already diagnosed as BS. Herein, I checked their symptoms for both fulfilling ISBD criteria and sub-classified participants fulfilling ISBD criteria to one of the above-mentioned BS clusters.
The patients were classified most frequently to mucocutenaous cluster and then eye cluster. Furthermore, 22 (25.9%) of the patients had first or second degree relatives with BS. Herein, enthesis-arthritis-acne cluster had highest frequency of family history. But, there was no apparent accumulation of similar findings in index BS cases and their close relatives (Table).Moreover, Karaca et all. previously showed that only papullopustuler and arthritis cluster may also clusters in families(2).
According to result of these studies, there was no finding that supports my first hypothesis "*BS patients in the same family generally accumulate in the similar clinical cluster"*. Still genetic may have major role in the emerging of the BS, such as it is accepted as a member of a group of diseases called MHC-I –opathy (4). Furthermore, epigenetically, DNA methylation in several gene loci relates to BS. But like most of the diseases, genetic background (e.g. Alterations in MHC-I related genes) is not enough for the expression of full-blown disease. Herein, I have a second hypothesis that, even in the similar genetic background, multiple and separate hits of environmental or non-genetic factors may take role in the pathogenesis. Herein, envorimental factors may

also alter DNA methylation. In BS, signs of the disease get out one by one in time during ensuing relapses. For example, in vascular cluster, different type of vascular involvements usually manifest at each successive relapse(5). In these circumstances, different environmental factors may be the cause of separate relapses and further new-onset findings. Therefore, multiple hit of non-genetic factors may determine the characteristics of full-blown disease.

References

1. Tunc R, Keyman E, Melikoglu M, Fresko I, Yazici H. Target organ associations in Turkish patients with Behcet's disease: a cross sectional study by exploratory factor analysis. J Rheumatol. 2002 Nov;29(11):2393-6. PubMed PMID: 12415598.
2. Karaca M, Hatemi G, Sut N, Yazici H. The papulopustular lesion/arthritis cluster of Behcet's syndrome also clusters in families. Rheumatology (Oxford). 2012 Jun;51(6):1053-60. PubMed PMID: 22286924.
3. Criteria for diagnosis of Behcet's disease. International Study Group for Behcet's Disease. Lancet. 1990 May 5;335(8697):1078-80. PubMed PMID: 1970380.
4. McGonagle D, Aydin SZ, Gul A, Mahr A, Direskeneli H. 'MHC-I-opathy'-unified concept for spondyloarthritis and Behcet disease. Nature reviews Rheumatology. 2015 Dec;11(12):731-40. PubMed PMID: 26526644.
5. Yazici H, Seyahi E. Behcet syndrome: the vascular cluster. Turkish journal of medical sciences. 2016 Nov 17;46(5):1277-80. PubMed PMID: 27966293.

Table. Features of the clusters' family history	
Mucocutenaous Cluster	**n=27**
*Family history for BS n(%)**	10/27(37.0)
Mucocutenaous	5(50.0)
Eye	3(20.0)
Vascular	2(20.0)
Eye Cluster	**n=18**
*Family history for BS n(%)**	1/18(5.6)
Undetermined	1(100.0)
Enthesis-arthritis-acne Cluster	**n=18**
*Family history for BS n(%)**	8/18(44.4)
Mucocutenaous	3(37.5)
Enthesis-arthritis-acne	3(37.5)
Neuro-Behçet	1(12.5)
Undetermined	1(12.5)
Vascular Cluster	**n=12**
*Family history for BS n(%)**	2/12(16.7)
Mucocutenaous	1(50.0)
Eye	1(50.0)
Neuro-Behçet Cluster	**n=3**
*Family history for BS n(%)**	0/3(0.0)
Intestinal Cluster	**n=1**
*Family history for BS n(%)**	0/1(0.0)
Undetermined Cluster	**n=6**
*Family history for BS n(%)**	1/6(16.7)
Eye	1(100)
BS: Behçet's syndrome * First or second degree relatives	