

Epidemiology and Genetic Aspects of Behçet's Disease

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ABSTRACT

Behçet's disease (**BD**) is a systemic inflammatory disorder which affects the skin, mucosa, eyes, joints, blood vessels, brain, and gastrointestinal tract. Although BD has been reported from all over the world, it is more common in the geographical regions on the historic Silk Route. However, the highest prevalence of the disease is in Turkey. It mostly affects individuals aged between 20 and 40 years and affects men and women equally. Although its etiopathogenesis has not been well understood, yet, various genetic, environmental and immunological factors are thought to play a role. Although the human leukocyte antigen (**HLA**)-B51 has long been suggested to be the most important genetic predisposing factor in many populations, recent studies have shown that there are additional independent associations at the major histocompatibility complex (**MHC**) Class I genetic loci. Large genome-wide association studies reported association between single nucleotide polymorphism of some genes and BD. Additionally, targeted next generation sequencing has demonstrated non-synonymous variants of IL23R, Toll-like receptor 4 (**TLR4**), nucleotide-binding oligomerization domain-containing protein 2 (**NOD2**), and familial Mediterranean fever gene (**MEVF**) in pathogenesis of BD. This section sheds light on the epidemiology and genetic aspects of BD in the light of the current literature.

Keywords: Behçet's disease, Epidemiology, Genetic

INTRODUCTION

Behçet's disease (**BD**) is a type of vasculitis causing changes in endothelial function by affecting arteries and veins of all sizes. The disease has a very high incidence in countries spanning on the ancient Silk Road from Asia to Mediterranean. It is, therefore, prevalent in Turkey, Japan, Korea, and China [1]. The prevalence of BD has been reported as being between 0.12 and 7.5 per 100.000 individuals in the USA and Europe [2]. The disease was first described in 1937 by Hulusi Behçet as a triple symptom complex, and these symptoms are still being used in the diagnosis of the disease. Hulusi Behçet also reported recurrent aphthous stomatitis, genital ulcers, and uveitis combined with other findings of erythema nodosum, papulopustular lesions, rheumatic pain, hemoptysis and thrombophlebitis [3].

BD is a multi factorial disease and triggering factors such as oral cavity infections and viruses can induce an inflammatory response in genetically susceptible individuals. The examination of inflamed tissues in patients with BD suggests that tendency to thrombosis and mixed cellular perivascular infiltration accompanied by vasculopathy or vasculitis may be the underlying pathological process [4]. BD has been classified as "variable vessel vasculitis" in the 2012 International Chapel Hill Consensus Conference Nomenclature of Vasculitides, as it can affect arteries and veins of all sizes [5]. However, some authors identified the BD among the auto inflammatory disease [4].

The disease has a complex pathogenesis and it has not yet to be understood; however, microbial triggers, environmental factors, endothelial dysfunction, genetic predisposition, and immunological abnormalities have been associated to the disease pathogenesis [6]. Genetic and immune system anomalies have been recently emphasized as being the main factors in the pathogenesis of the disease [7]. Genome-wide association studies (**GWAS**) have revealed a close association between the interleukin (**IL**)-23R-IL12RB2, IL-10, signal transducer and activator of transcription 4 (**STAT-4**), chemokine C-C motif receptor 1 and 3 (**CCR1-CCR3**), killer cell lectin-like receptor K4 (**KLRC4**), endoplasmic reticulum aminopeptidase 1 (**ERAP1**), tumor necrosis alpha-induced protein 3 (**TNFAIP3**), and fucosyltransferase 2 (**FUT2**) loci and BD [8]. In light of current literature data, this section will focus on the epidemiology and genetic aspects of BD.

EPIDEMIOLOGY

Prevalence of Behçet's Disease

The differences among the geographical regions associated with clinical manifestations of BD continue to be a surprising aspect for researchers. Many studies are published on the clinical features of the disease in some regions or in certain ethnic groups [9]. BD is known to be rarely observed in Sub-Saharan Africa. In a study conducted in Nigeria, only 15 people were found to have been diagnosed with BD at the Lagos State University Teaching Hospital, between 2007 and 2011; nine patients were male while six patients were female, and 80% of patients were reported

to have ocular involvement [10]. On the other hand, Khabbazi et al. [11] detected 166 cases of BD in the Azeri population living in Iran. In this study, the female-to-male ratio was found to be 1.7/1, the age at onset of the disease was 25.8 ± 8.9 , while 7.1% of the patients were reported to develop blindness. In another randomized, field based prevalence study conducted in Iran, the prevalence of BD was found to be 10/100.000 [12].

Turkey is said to be the country with the highest prevalence of BD. The prevalence of disease in Istanbul was 421/100,000. Furthermore, the prevalence of disease to vary between 20 and 370 per 100.000 in Turkey [9]. In a recent study, the prevalence of BD was reported to be 17/100.000 in the Central Anatolian province of Kayseri [13].

The prevalence of BD is known to have gradually decreased from South to North. Although the prevalence of the disease in two previous studies conducted in Italy was reported as 3.8 per 100.000 in Northern Italy; it was found to be 15.9 / 100.000 in Potenza located in the South [14,15]. In these studies, authors also draw attention to the prevalence of the BD of Italian-origin and non-Italian origin for populations living in this area. The prevalence of BD in the Italian-origin population was found to be 3.5 / 100.000; whereas in the non-Italian-origin group, the BD prevalence was 8.5/100.000 [14,15].

The regional variability in disease expression is one of the well-known epidemiological properties of BD. In addition to genetic factors, environmental factors can also affect the frequency of the disease and of individual symptoms [16]. The relationship between the geographic distribution of HLA-B51 and the prevalence of BD has been well-established. The frequency of HLA-B51 in the normal population of the Silk Route region and in patients with BD was reported to be 20 to 25% and 50 to 80%, respectively. However, in the Northern Europe and USA, the frequency in the normal population and in patients with BD was found to be 2 to 8% and 15%, respectively [17]. The incidence of BD in the Japanese immigrants living in the USA or in Hawaii, and in the Turkish immigrants living in Germany is reported to be low [16]. In a study conducted in Berlin, the risk of developing BD in Turkish immigrants (77.3%/100.000) was found to be higher than among Germans (1.47%/100.000) and non-Germans (excluding Turks) (26.6%/100.000); however, the rate was reported to be lower than the risk of disease development reported in Turkey [18].

Gastrointestinal involvement of BD is much more common in Japan and Korea compared to Turkey. In Turkey, gastrointestinal involvement is between 1.4% and 3%; whereas it rises up to 15% in Korea and 58% in Japan. Positivity of the skin pathergy test (**SPT**) for BD varies according to geographical regions, and this test is considered to be highly sensitive and specific in Turkey, the Middle Eastern countries and Japan [16]. Ideguchi et al. [19] reported that SPT positivity was approximately 50% in Japan. In their multi-centered study conducted in Turkey, Alpsoy et al. [20] demonstrated that SPT positivity 37.8%. In the study conducted by Davatchi et al. [21] in Iran found SPT positivity was found to be 52.5% in BD patients. On the other hand, Togashi et al. [22]

reported that SPT positivity in BD was 90%, in a study in which they proposed the use of a new technique to perform SPT. In this study, SPT was performed with a skin prick test with neat and filter-sterilized saliva on the forearm skin.

Age and Behçet's Disease

Although the age onset of BD differs between countries, the disease is known to begin in the third decade of life in most countries. The mean age at onset of the disease in Turkey is 25.6, Ireland 20.8, Italy 25, Portugal 25.7, Germany and Lebanon 26, Iran and Egypt 26.2, France 27.6, Tunisia 28.7, Greece and Korea 29, Saudi Arabia 29.3, Iraq 29.4, Jordan 30.1, Israel 30.7, America 31, Switzerland 33, India 33.1, China 33.8, Japan 35.7, and in Brazil is 40. The incidence of the disease individuals over 50 years of age is however on a decrease. The prevalence of BD in children is reported to be about 2%, a rate which is reported to have increased in recent years [23]. Although rare, the disease has also been reported during the neonatal period [24].

It has long been acknowledged that BD, which starts at an early age, is very severe and most frequently demonstrates major organ involvement [9]. However, this view is not consistent with a recent cohort study conducted in Tunisia. In the aforementioned study, Hamzaoui et al. [25] divided the patients into two groups, as those starting before the age of 20 years and those starting after the age of 40 years, and they demonstrated that there was no significant difference between these two groups in terms of severe organ involvement, except for vena cava thrombosis. However, the authors did not report any difference between the two groups with regards to disease severity. In addition, although men with BD have only mucocutaneous involvement in the first years of their illness, the risk of developing major organ involvement is known in those with early-onset of the disease [9].

Gender and Behçet's Disease

BD can also affect both genders. The incidence of BD is reported to be higher in women in some countries; whereas in some countries it is found to be higher in men. The male/female ratio in Scotland is reported to be 0.36, in America 0.38, Spain 0.5, Korea 0.63, Israel 0.64, Brazil 0.69, Japan 0.98, Portugal 1, Turkey 1.03, Iran 1.19, France 1.32, China 1.34, Germany and Greece 1.4, Italy 2.4, Tunisia 2.7, Russia 3.7, and in Kuwait 4.9 [26].

Gender is one of the major prognostic factors of BD. It has been suggested that the disease has a more severe course in males, with more frequent organ involvement and a higher mortality rate [9]. In a meta-analysis, there were differences in the course of the disease with regards to gender; male gender was associated with ocular involvement, papulopustular lesions, superficial and deep venous thrombosis, whereas the female gender was associated with genital ulcer and joint involvement [27].

Epidemiology of Behçet's Uveitis

BD is the most important cause of uveitis in countries with high prevalence of disease. Hatemi et al. [9] reported that the ratio of developing uveitis associated with BD, to the total number of uveitis cases correlated with the prevalence of BD in that country. The ratio of BD-related uveitis to all cases of uveitis in Turkey was found to be 32.2%, and 10.5 to 12.4% in Iran, in Lebanon 12.8%, Saudi Arabia 8.4% and Japan 8.8%, United Kingdom 2.7%, Italy 2.9%, Germany 2% and in the United States 0.2% [9].

GENETIC FACTORS

Familial Aggregation

Observation of familial aggregation in BD supports the role of genetic factors in the pathogenesis of the disease. BD usually develops sporadically; however, familial aggregation and prevalence in siblings and parents of the patients has been shown to be high. Familial aggregation in BD shows variation among populations. Familial aggregation has been reported to be high particularly in Turkish (18.2%), Korean (15.4%) and Jewish (13.2%) populations; but low in Chinese (2.6%), Japanese (2.2%) and various European populations (0-4.5%). Furthermore, BD associated with familial aggregation was reported to be stronger in BD beginning at an early age than in those beginning during adulthood [8].

MHC Region

The MHC / Human Leukocyte Antigen (HLA) complex is the most polymorphic genetic region with important biological functions (i.e., immune response, development). The human MHC is the most potent region of genomic autoimmune diseases [7].

HLA-B51

The strong relationship between HLA-B51 and BD was first described in the Japanese population. This strong relationship was later demonstrated in different populations. HLA-B5101 and HLA-5108, which are two alleles of HLA-51, have been particularly attributed. HLA-B51 is the genetic factor most strongly associated with BD [7]. In a meta-analysis study involving 4800 BD patients and 16289 controls, the pooled OR of HLA B51/B5 carriers were shown to develop BD compared to non-carriers (OR=5.78 95 % CI (5.00-6.67)) [28]. Two large GWAS have recently been conducted on this subject [29,30]. In a study conducted in Turkey including 1215 BD patients and 1278 healthy controls; in the BD patients, HLA-B51 association was found to be 59% and 29.3% in the control group; a strong relationship was demonstrated between HLA-B51 and BD [29].

Other MHC class I genes

Although the relationship of other MHC class I types and other HLA B types with BD has been demonstrated, the strong linkage disequilibrium (LD) in the MHC region and the inadequate sample size poses a difficulty in showing other HLA associations [8]. Ombrello et al. [31] in their

study in Turkey evaluated the relationship of HLA class type I with BD and the control group and found that the HLA-B51, -B15, -B27 regions were associated with the risk of developing BD; whereas the HLA-A03 and -B49 regions are associated with a protective role against disease.

The MHC Class I gene-related gene (**MICA**) gene is often thought to be one of the candidates genes for predisposition towards for BD [32]. In the meta-analysis conducted by Lee et al. [33] it was found that the MICA-transmembrane (**TM**) A6 allele was associated with a predisposition to disease development among European and Asian populations, whereas MICA*0009 was associated with only the European population. In another meta-analysis of the MICA A6 allele, it was observed that the MICA A6 allele was more frequently observed in BD than in the control group when comparison was made between 752 BD patients and 1175 controls [34].

HLA and clinical manifestations of behçet's disease

Studies suggesting the association between MHC class I alleles and the specific clinical manifestations of the disease have been conducted [8]. Maldini et al. [35] in their meta-analysis reported a moderate correlation between HLA-B51, -B5 and the male gender, high prevalence of eye involvement, skin involvement, genital ulcers, and low prevalence of gastrointestinal involvement. Another study reported that there is a relationship between HLA-B51 and early-onset uveitis in BD patients, and high prevalence of the development of posterior uveitis with HLA-A26 [36]. On the other hand, Kaburaki et al. [37] reported in their study that HLA-A2601 was associated with eye involvement in BD independently of HLA-B5101, and that HLA-A2601 might be a possible predictor of poor visual prognosis in Japan.

Non-MHC Complex Genes

GWAS revealed that there were significant association between IL-23R-IL12RB2, IL-10, STAT-4, CCR1-CCR3, KLRC4, ERAP1, TNFAIP3, and FUT2 loci and BD. In addition, targeted next generation sequencing method has demonstrated the rare non-synonymous variants of IL23R, TLR4, NOD2, and MEFV in BD [32]. In Iran, GWAS of 973 BD patients and 828 controls were conducted and it was demonstrated that MHC, IL10, IL23R-IL12RB2, CCR1, KLRC4, IL12A-AS1, STAT4, and ERAP1 were disease susceptibility loci [38]. In a study investigating the role of nitric oxide synthase gene polymorphisms (**NOS2 and NOS3**) in BD, it was demonstrated that there was a decreased frequency of the NOS3/rs1799983 GG genotype and an increased frequency of NOS3/rs1799983 GT genotype in patients with BD [39]. Jiang et al. [40] have suggested that the GG genotype of the rs17375018 variant in the IL-23R gene increases pro-inflammatory cytokine responses. A meta-analysis including 2538 BD patients and 2792 healthy controls and investigating the prevalence of MEFV mutations in BD revealed that the M694V and M6801 regions were associated with BD; and that E148Q has not however associated with BD [41].

CONCLUSIONS

BD is a disease with an area of interest for many departments due to the fact that it is a multi systemic vasculitis. Disconnections between departments with an interest in the disease may be associated with the presence of variability in epidemiological data. Obtaining more valuable epidemiological data can be possible through more effective communication between departments. The disease has a complex pathogenesis; however, genetic predisposition (mainly HLA-dependent), activation of adaptive and innate immunity by various pathogens and subsequent interaction between T lymphocytes (mainly Th1 and Th17) are the main elements in the pathogenesis. The advances in the fields of genetics have significantly contributed to our understanding of pathogenesis; however, genetics of the disease still remains a mystery. As a result, further genetic studies would contribute to shedding light to disease pathogenesis and the development of new target-related treatment measures.

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