DIFFERENCES IN BEHÇET’S DISEASE PHENOTYPE ACCORDING TO SEX: HYPOTHESES AND RESEARCH PERSPECTIVES

Received: September 29, 2022
Accepted: November 6, 2022

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Abstract
Behçet’s disease (BD) is a multisystem vasculitis affecting both arteries and veins. Although the disease affects both sexes equally, males and females may express different phenotypes. The exact association between sex-related factors and BD phenotype is not clear, while many factors, such as genetic factors, hormones, and environmental and epigenetic factors may be the underlying factors of sex-related differences. This article summarizes the current literature focusing on the underlying factors determining differences in BD phenotype according to sex.

Keywords: Behçet’s disease, Sex, Female, Male, Hypothesis

How to cite: Sönmez HE, Batu ED. Differences in Behçet’s disease phenotype according to sex: hypotheses and research perspectives. Cent Asian J Med Hypotheses Ethics 2022:3(3):154-159. https://doi.org/10.47316/cajmhe.2022.3.3.01

INTRODUCTION
Behçet’s disease (BD) is a systemic vasculitis that affects numerous organ systems by involving all sizes of arteries and veins [1]. The main signs of the disease are recurrent oral and genital aphthous lesions, while a variety of gastrointestinal, ophthalmic, neurologic, cardiovascular, and musculoskeletal manifestations may be seen [2]. Although the disease does not favor one sex over another [3], the phenotype of the disease may differ according to sex [4, 5] (Figure 1). For instance, mucocutaneous manifestations except erythema nodosum are more common in females [6-9] while uveitis and neurologic involvement are more frequent among males [9, 10]. Although clinical studies showed differences between males and females with BD, the underlying factors determining differences according to sex remain unknown. Herein, we will discuss the potential scientific hypotheses on the effect of sex in the course of BD [11].

Current knowledge on the effect of sex in the course of Behçet’s disease
Behçet’s disease is a variable vessel vasculitis mainly affecting people in the second or the third decade. The disease shows a marked geographic distribution along the “Silk Route,” with the highest prevalence rates in the Middle and the Far East [12]. The phenotype of the disease may differ according to ethnic origin. For instance, gastrointestinal involvement is more common in the Far East, while it is rare in the Middle East and...
Turkey. As well as ethnic differences the disease course may vary with female or male sex. Men usually have a more severe disease course than women, while the severity of the disease declines over time [12, 13]. Females more frequently have oral ulcers, which exacerbate with menstruation. Similar to oral ulcers, other mucocutaneous manifestations such as genital ulcers, necrotic folliculitis, acneiform lesions, and erythema nodosum are also more frequent in females [14, 15]. Arthritis and arthralgia are reported to be more common in females [16, 17], while some studies indicate similar frequency in both sexes [14]. On the other hand, ocular, neurologic and vascular involvements are significantly more common in male BD patients [14, 18, 19]. Furthermore, males with BH are also prone to have a more severe course with a higher mortality rate [13]. A study from France including 817 BD patients found that mortality was associated with the male sex, younger disease onset age (15–25 years), arterial involvement, and frequent flares [20].

Besides sex chromosomes, there are some strong associations between particular genetic locus and diseases. The presence of human leucocyte antigen (HLA)-B51 is a risk factor for BD [24]. A recent meta-analysis showed that HLA-B51/B5 was more prevalent in males and was associated with higher rates of genital ulcers, ophthalmic and cutaneous symptoms, and a lower rate of gastrointestinal involvement [25]. However, the presence of HLA-B51/B5 is insufficient to explain the differences between men and women in BD. Furthermore, there are HLA-B51/B5 negative cases, as well. Studies focusing on sex-specific genetic effects in BD are limited. Most recently, Jo et al. [26] evaluated 1216 female and 1762 male patients with BD to demonstrate the sex-specific genetic effects in disease pathogenesis. In the aforementioned study, genetic analysis revealed that the male sex was associated with a higher genetic risk for BD. The most significant sex-specific genetic differences were located in the HLA class I region. The HLA-B/MICA (rs116799036), HLA-C (rs12525170), and KLRC4 (rs2617170) locus showed higher genetic risk for BD in males, while IFNGR1 (rs4896243) loci were associated with higher disease risk for BD in females. Previous studies confirmed an association between BD and variants located in the HLA-B/MICA locus [27, 28]. Although not clear, the locations of these variants may play a role in the pathophysiology of BD by disrupting antigen binding or presentation. The primary function of KLRC4 is not known, but it is associated with cytotoxic activity in γδ T cells and natural killer cells that may also contribute to the pathophysiology of BD [29]. Previously, variants in IFNGR1 were reported as possible genetic risk factors for recurrent oral ulcers [30]. Oral ulcers are more common in females with BD. These findings suggested that genetic factors might influence disease presentation and lead to phenotypic differences between males and females. However, these findings must be validated in different ethnic groups and larger patient groups.

Scientific Hypotheses and Their Limitations
Sex-related clinical differences have been a matter of interest in many diseases. For instance, autoimmune diseases predominantly affect women, while men are prone to express a more severe course during infectious diseases [21, 22]. Genetic differences between men and women may account for differences in sex-related disease prevalence, manifestations, and response to treatment. Genetic sex differences begin at conception when an embryo bearing either XX or XY chromosomes is formed as a result of the union of an ovum and a sperm cell containing an X or a Y chromosome. The genes on the Y chromosome exhibit functional differences from their homologs on the X chromosome. Furthermore, there are no homologs of some genes on the X chromosome, such as SRY. Men only carry one X chromosome, including maternal imprints, while women have two X chromosomes from both parents. However, the effect of sex chromosomes on BD is not evaluated yet. Previous studies showed that about 10% of microRNAs (miRNAs) are localized on the X chromosome. miRNAs are non-protein coding RNAs that play a role in post-transcriptional process and immune response. The response to environmental triggers differs between males and females by different expressions of sex-specific miRNAs [21, 23]. However, there are no studies on this topic in BD patients.
Many other factors, such as hormones, epigenetic and environmental factors, may impact the course of the disease. After puberty, the emergence of the hormonal effect also plays a vital role in disease occurrence [22]. Worsening of disease during pregnancy was reported in Korean patients with BD [31], while conflicting results showing no clinical exacerbation had also been reported [32]. A study from Canada showed that women with BD had a higher risk for postpartum venous thromboembolism and preterm labor [33]. Activated neutrophils play an important role in BD pathogenesis, and increased neutrophil oxidative burst response was shown in males with BD that might be linked to testosterone effect on neutrophils [34]. Therefore, hormonal differences between males and females may also contribute to the disease phenotype. Further studies are needed to evaluate the hormonal effect on the disease course. Additionally, the clinical disparities between patients with prepubertal onset cannot be explained solely by hormonal variations.

The effect of BD on reproduction was not evaluated comprehensively. Testicular and epididymal involvement may be seen in BD. The prevalence of epididymo-orchitis varies, ranging from 0.6% to 31% [35]. HLA-B51/B5 positivity is more common in males and is associated with a higher prevalence of epididymo-orchitis [25]. Although not clear, epididymo-orchitis is suggested to be part of vasculitis. Recurrent epididymo-orchitis may result in infertility [36]. There is only one study evaluating reproduction in women with BD. This study showed similar ovarian reserve and anti-mullerian hormone (AMH) levels in BD patients and healthy subjects [37]. Thus, BD primarily affects individuals in fertile periods; it is pretty important to follow up these patients in terms of reproduction and fertilization. However, the studies focusing on this issue are limited.

The differences in the phenotype of BD between males and females probably depend on different genetic and epigenetic factors modifying the immune system. The complex nature of BD makes it challenging to specify these factors.

**Further research designs to test the effect of female or male sex in the course of Behçet’s disease and its ethical implications**

The role of sex-related factors in BD pathogenesis is complex. Although clinical studies reveal significant differences in phenotype, the current literature is not sufficient to explain the exact association. Many factors, such as sex chromosomes, genetic variants, hormones, may cause the disease to manifest differently between the sexes. Furthermore, it is known that environmental factors and epigenetic factors affect the disease course. The complex pathogenesis of the disease does not allow researchers to design animal models. Therefore, genetic studies with a multinational design including all ethnic groups may provide clinicians to understand disease pathogenesis. Since the studies will be carried out directly on humans, many ethical dilemmas arise in such studies. Before genetic studies, informed consent should be taken. Several factors should be clarified in informed consent, such as transferring the genetic material (if required), storing biological samples, and analyzing and reporting results. Furthermore, patients should be informed that they may still opt out at any time. Moreover, the influence of hormonal and environmental factors should be also tested.

**CONCLUSION**

In this overview, we discussed the effect of female and male sex on BD. Researchers may consider the relevance of further studies on the association between sex-related differences and disease presentation.

**References**


РАЗЛИЧИЯ ФЕНОТИПА БОЛЕЗНИ БЕХЧЕТА В ЗАВИСИМОСТИ ОТ ПОЛА: ГИПОТЕЗЫ И ПЕРСПЕКТИВЫ ИССЛЕДОВАНИЙ

Резюме
Болезнь Бехчета (ББ) представляет собой мультисистемный васкулит, поражающий как артерии, так и вены. Хотя заболевание одинаково поражает оба пола, у мужчин и женщин могут проявляться разные фенотипы. Точная связь между факторами, связанными с полом, и фенотипом ББ не ясна, в то время как многие факторы, такие как генетические факторы, гормоны, факторы окружающей среды и эпигенетические факторы, могут быть основным фактором половых различий. В этой статье обобщаются данные литературных источников, посвященных основным факторам, определяющим различия в ББ в зависимости от пола.

Ключевые слова: болезнь Бехчета, пол, самка, самец, гипотеза.

Для цитирования: Сенмез Х.Э., Бату Э.Д. Различия фенотипа болезни Бехчета в зависимости от пола: гипотезы и перспективы исследований. Центральноазиатский журнал медицинских гипотез и этики 2022:3(3):154-159. https://doi.org/10.47316/cajmhe.2022.3.3.01