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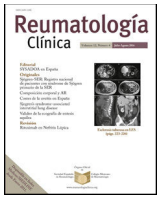

Original article

HLA-B*51:01 in Iranian patients with Behcet uveitis syndrome

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ABSTRACT

Background: Behcet's disease (BD) is a multisystem disorder prevalent along the historic Silk Road, with Behcet's uveitis (BU) representing a significant complication contributing to disability. Various studies have linked different HLA alleles with BD across diverse populations.
Methods: In this study, we investigated the association between HLA-B51:01/x and HLA-B27/x genotypes with Behcet's uveitis in 50 unrelated Iranian patients diagnosed with Behcet's uveitis, comparing them to a control group of 70 healthy individuals. Our analysis aimed to determine the susceptibility conferred by these alleles and assess their clinical relevance.
Results: Our findings indicate a notable susceptibility conferred by the HLA-B51:01/x genotype for Behcet's uveitis ($P = 0.0001$). Conversely, the B27/x genotype did not demonstrate significant associations with Behcet's uveitis. Furthermore, we employed prevalence-corrected positive predictive value (PcPPV) calculations to gauge the clinical utility of testing for these alleles within the Iranian Behcet's uveitis patient population. The PcPPV for B27/x genotype testing was determined to be 0.05%, while the PcPPV for B51:01/x genotype testing in the same population was 0.065%. These results suggest that carriers of the B*51:01 allele, when presenting with clinical symptoms, exhibit a heightened risk for Behcet's uveitis compared to the general population.
Conclusion: Individuals carrying the B51:01 allele, when symptomatic, face an elevated Behcet's uveitis risk. This insight aids in targeted clinical assessments for at-risk populations.

HLA B51 en pacientes iraníes con uveítis en contexto de síndrome de Behçet

Palabras clave:
Uveítis de Behçet
Genes HLA
PCR

RESUMEN

Antecedentes: El síndrome de Behçet es un trastorno multisistémico que prevalece a lo largo de la histórica Ruta de la Seda, y la uveítis de Behçet representa una complicación importante que contribuye a la discapacidad. Varios estudios han relacionado diferentes alelos HLA con BD en diversas poblaciones.
Métodos: En este estudio, investigamos la asociación entre los genotipos HLA-B51:01/x y HLA-B27/x con la uveítis de Behçet en 50 pacientes iraníes no relacionados con diagnóstico de uveítis de Behçet, comparándolos con un grupo de control de 70 individuos sanos. Nuestro análisis tuvo como objetivo determinar la susceptibilidad que confieren estos alelos y evaluar su relevancia clínica.
Resultados: Nuestros hallazgos indican una notable susceptibilidad conferida por el genotipo HLA-B51:01/x para la uveítis de Behçet (p = 0,0001). Por el contrario, el genotipo B27/x no demostró asociaciones significativas con la uveítis de Behçet. Además, empleamos cálculos de valor predictivo positivo (PcPPV) corregido por prevalencia para evaluar la utilidad clínica de las pruebas de estos alelos dentro de la población iraní de pacientes con uveítis de Behçet. Se determinó que el PcPPV para la prueba del genotipo B27/x era del 0,05%, mientras que el PcPPV para la prueba del genotipo B51:01/x en la misma población fue del 0,065%. Estos resultados sugieren que los portadores del alelo B*51:01, cuando presentan síntomas clínicos, presentan un mayor riesgo de padecer uveítis de Behçet en comparación con la población general.

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Conclusión: Las personas portadoras del alelo B51:01, cuando presentan síntomas, enfrentan un riesgo elevado de uveítis de Behçet. Esta información ayuda en evaluaciones clínicas específicas para poblaciones en riesgo.

Introduction

Behcet's disease (BD) is a rare systemic vasculitis disorder with an unknown etiology. BD can manifest globally but is more frequent in the region along the Silk Road, including Mediterranean, Middle Eastern and Far Eastern countries.[1] This disease has the highest prevalence in Turkey, from 20 to 420, and then in Iran, from 80 to 100 per 100,000 inhabitants.[2] Although any organ can get involved, it is specially characterized by oral and genital ulcers, ocular inflammatory involvement, skin lesions, and vascular involvement.[3] Inflammation of the middle layer of the eye (uveitis) is a major involvement site and an important cause of disability in BD.[4] The most widely used system to classify the eye involvement in uveitis is based on the primary anatomical location of the inflammation, and was originally established by the International Uveitis Study Group (IUSG). It divides uveitis into four anatomical categories: anterior uveitis, intermediate uveitis, posterior uveitis and panuveitis.[5] The Behcet's uveitis (BU) is most commonly characterized by a chronic panuveitis or posterior uveitis with occlusive retinal vasculitis. Without appropriate and timely treatment, Behcet's uveitis is a progressive blinding disease.[6] Although the etiology and pathogenesis of BD is not fully elucidated, it is believed to be triggered by environmental factors in individuals with certain genetic backgrounds. Familial aggregation of BD also supports the involvement of genetic factors in its pathogenesis. No Mendelian inheritance pattern has been described in BD. Several studies have shown that immune abnormalities may underlie the development of BD. It is hypothesized that BD pathogenesis is an aberrant inflammatory response initiated by infectious agents or autoantigens in patients with predisposing genetic factors and both innate and acquired immunity pathways are involved. The immunopathogenesis of Behcet's uveitis concerning maturation markers of dendritic cells, intraocular effector cell profiles, and the cytokine/chemokine environment is different from other autoimmune uveitis.[7]

The HLA (human leukocyte antigen) complex located on a 4 Mbp stretch within chromosome 6P21.3 consists of more than 200 genes.[8] These molecules are divided into three classes. HLA class I molecules are composed of a heavy and light chain. The heavy chain is encoded by the polymorphic HLA locus and the light chain is an invariant protein of β2-microglobulin (β2m).[9] HLA-I molecules are expressed at the cell membrane and play a critical role in the immune response by presenting the loaded peptides to CD8+ T cells and interacting with natural killer (NK) cells. Bearing in mind the role of HLA genes in the inflammatory response of the immune system and the occurrence of these responses in Behcet's disease, these genes are considered candidate genes for BD.[10]

Several studies to date have shown the contribution of specific HLA genes in BD pathogenesis. For example, the BD susceptibility has been proposed to be associated with the HLA class I-B*51 allele.[11] A study conducted in a Turkish population showed that HLA-B51 was significantly increased in BD patients compared to the controls.[12]

In another study conducted in the Korean population, the increase of HLA-B*51 allele in Behcet's patients was confirmed, and furthermore showed that the frequency of HLA-B*51 allele in the patients with symptoms of uveitis was statistically significant.[13] Currently, the strongest risk factor for Behcet's disease, especially with eye symptoms, is the aberrant expression of the HLA-B*51 allele. This gene may contribute to BD pathogenesis by several different mechanisms, involving both adaptive (by the presentation of certain pathogenic peptides to CD8 T cells) and innate (by interacting with natural killer cell receptors and activating intracellular inflammatory pathways associated with heavy chain folding problems and endoplasmic reticulum stress) immune responses.[14] Identification of endoplasmic reticulum aminopeptidase 1 (ERAP1) polymorphisms as a recessively inherited risk factor only in people carrying HLA-B*51 allele manifested the significant role of peptides loaded onto the antigen-binding groove of HLA-B*51.[15] Among more than 250 subtypes of HLA-B*51 identified by protein sequencing, HLA-B*51:01 allele subtype has been most associated with BD in several populations.[16] In this regard, a study was performed in the Greek population in which a significant number of the BD patients were carriers of the B*51:01 allele.[17] Investigation of the linkage between BD and other HLA-B alleles revealed a weak correlation between the HLA-B*27 allele and this condition. One study has shown a significant association between Behcet's uveitis and HLA-B*27 in the Korean populations.[18] This discrepancy could be due to the sensitivity of the methodologies employed, hence a study with valid and modern methods needs to be conducted on the genetic relationship between Behcet's uveitis and HLA gene alleles. In this study, for the first time, with high resolution and at the molecular levels, we have investigated the association of Bechet's uveitis with HLA-B*51:01/x and HLA-B*27/x genotypes, in Iranian population.

Materials and methods

Patients and controls

Blood samples from 50 unrelated Iranian patients with Behcet's uveitis from the Uveitis Clinic of Farabi Eye Hospital were collected. It should be noted that due to the very low frequency of Behcet's uveitis in the population, it was not possible to collect more specimens. The diagnosis of BD was based on International Criteria for Behcet Disease and all patient were examined and evaluated by one ophthalmologist expert in the field of uveitis (MZ or NE). In addition to complete eye examination, supplementary paraclinical investigations including fluorescein angiography (FA) and macular optical coherence tomography (OCT) were done. Also, 70 healthy people over 40 years of age who had no history of Behcet's disease and other similar diseases were selected as controls. The age in control group was over 40 years; thus, the chance of future development of BD in this group deemed to be low. These patient and control groups had the same geographical origin. In the patient group, information regarding the anatomic subtype of uveitis (including anterior, intermediate, posterior, panuveitis), family history of BD, family history of other inflammatory eye diseases and history of non-ocular inflammatory diseases were collected. After obtaining consent from the patient, or their legal guardians and control groups, questionnaire forms were prepared and information was collected. This study was authorized by the ethics committee and review board of the Tehran University of Medical Sciences.

Table 1
Primer sequences for B*51:01 and B*27 alleles.

Allele	Sequence (5′–3′)	Size
B*27	GCTACGTGGACGACACGC TCTCGGTCAGTCTGTGCCTT	149bp
B*51:01	TACGCCTACGACGGCAAA CTTCCCGTTCTCCAGGTG	183bp

Statistical analysis

All clinical and genotyping data of the HLA-B*51:01/x, HLA-B*27/x allelic marker genes, were recorded into a database and analyzed with SPSS, version 26 for Windows (Chicago, IL, USA). Fisher's exact test and relative risk were used for comparing the frequencies of studied genotypes between the Behcet patients and control group. Fisher exact tests were utilized for statistical analysis of results, and $P < 0.05$ is presumed to be statistically meaningful. Besides, positive predictive value (PPV) figures, the efficiency of a diagnostic test and represents the likelihood for a person with a positive test of having or developing the disease. In this case-control study, the subsequent formula was employed to characterize prevalence-corrected positive predictive value (PcPPV):

$$\mathrm{PcPPV} = \frac{a}{(a+b)} = \frac{(P_{\mathrm{DT+}} \times P_{\mathrm{D}})}{(P_{\mathrm{DT+}} \times P_{\mathrm{D}})} + [P_{\mathrm{CT+}} \times (1 - P_{\mathrm{D}})]$$

where P_D is the frequency of the disease in the whole population, P_{DT+} is the ratio of patients with a positive test and P_{CT+} is the ratio of control group with a positive test.[19]

HLA allele typing and amino acid polymorphism analyses

About 5 ml of blood was collected from the patient and control group in vials containing EDTA and DNA extraction from whole blood was done in less than a week by a modified salting-out extraction method. Sequence-specific primers (SSP) were applied to characterize HLA-B*51:01 and HLA-B*27 alleles. To determine the B51 allele, at first, this allele was typed together with the B52 allele using SSP method, then the B52 allele was typed alone, the remaining alleles were B51, and the B51 types were the B5101 allele at the resolution levels. Oligo 7 software was used for primer design and gene sequences were obtained from NCBI. Sequence of designed primers is shown in Table 1. PCR-SSP profile for amplification of HLA-B*51:01 and HLA-B*27 was 60 s at 96 °C for denaturation; five cycles of denaturation at 96 °C for 20 s, annealing at 70 °C for 45 s and extension at 72 °C for 25 s; 25 cycles of denaturation at 96 °C for 20 s, annealing at 65 °C for 50 s and extension at 72 °C for 30 s; and 5 cycles of denaturation at 96 °C for 20 s, annealing at 55 °C for 60 s and extension at 72 °C for 120 s.[20] Then the PCR products were electrophoresed on 6% polyacrylamide gels and application of a 50-bp DNA ladder. PCR bands became visible by ethidium bromide staining and the correct size of each specific allele was determined by using the running DNA ladder. Some examples of HLA-B*51:01 and HLA-B*27 locus-specific typing results are manifested in Fig. 1. Also, in order to ensure accurate detection of the B*51:01 allele sequence, the sequence of this allele in one of the patient's samples was determined by Sanger sequencing technique, as shown in Fig. 2.

Results

*The effect of B*51:01/x and B*27/x genotypes on Behcet's uveitis protection or susceptibility*

The results of the distribution of types of uveitis in this study show that 29 patients had posterior uveitis and 21 patients had panuveitis. 93% of posterior uveitis patients and 66% of panuveitis patients had the B*51:01/x genotype (Table 2).

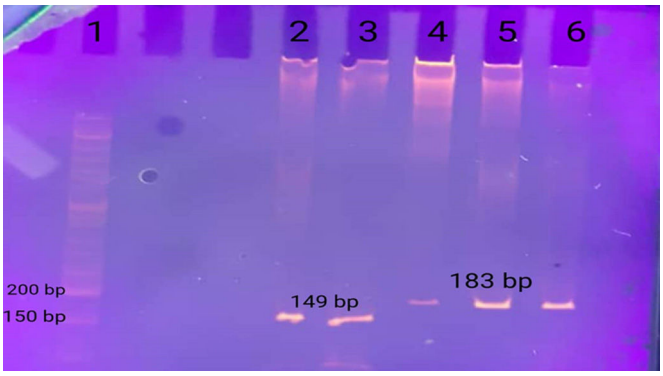

Fig. 1. Examples of B*51:01 and B*27 locus-specific typing results. DNA ladder (Orange Ruler 50bp DNA Ladder, CinnaGen, Iran); (1) positive patient and (2) positive control (3) for B*27 allele; positive patient, (4) positive control (5, 6) for B*51:01 allele.

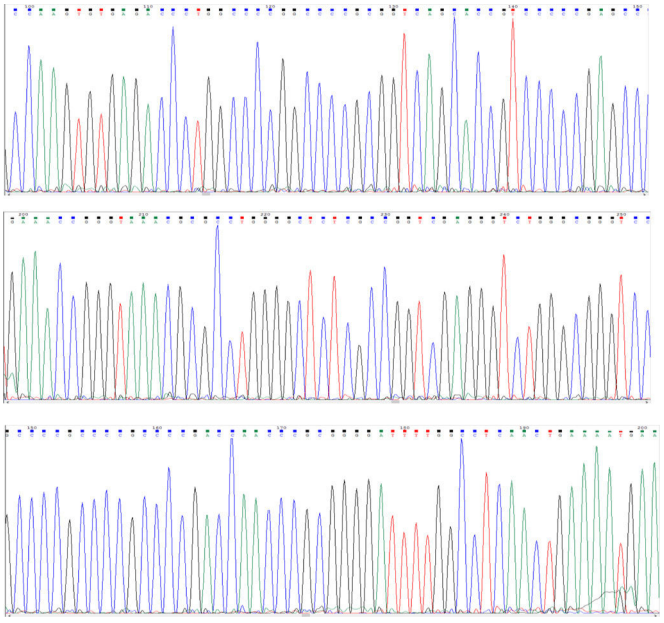

Fig. 2. Sequence of HLA-B*51:01 allele.

Moreover, the results of gender distribution show that men constitute 86% and women constitute 14% of Behcet's uveitis patients in the study. 74% of Behcet's uveitis patients in this study are in the age range of 20–40 years. Also, the average age of the patients was 38.

The distribution of B*51:01/x and B*27/x genotype frequencies in the total patients and healthy controls is summarized in Table 2. As compared with controls, statistical analysis of the B*27/x genotype demonstrates that there is no significant association between this genotype and total Behcet's uveitis in Iranian patients ($P = 1$, RR = 1.4) in contrast to B*27/x, the results showed that the frequency of B*51:01/x genotype was significantly higher in total Behcet's uveitis patients ($P = 0.0001$, RR = 1.76) when compared to the controls.

*Clinical importance of testing for the B*51:01/x and B*27/x genotypes*

In case-control studies, relative risk (RR or OR) is generally utilized to predict the risk of specific alleles and genotypes. Since

Table 2
The distribution of the B*51:01 allele in different types of Behcet's uveitis.

Types uveitis	Patients (fr) $N = 50$	Alleles	Patients (fr)
Posterior	29 (58%)	Posterior (B5101+)	27 (93%)
		Posterior (B5101−)	2 (7%)
Panuveitis	21 (42%)	Panuveitis (B5101+)	14 (66%)
		Panuveitis (B5101−)	7 (34%)

this method does not consider the prevalence of the disease in the general population, it does not provide a true risk assessment. On the other hand, prevalence-corrected positive predictive values (PcPPV) predict the absolute risk based on the prevalence of the disease in the general population. The PcPPV of testing for B*51:01/x and B*27/x genotypes were measured for Behcet's uveitis. The prevalence of Behcet's uveitis for estimating the predictive values was taken as 0.04% based on the studies in the Iranian population.[21]

The PcPPV of testing for the HLA-B*27/x genotype, which indicated no significant association with Behcet's uveitis, was 0.05% for total Behcet's uveitis patients (Table 3). This demonstrates that individuals who are carrying the HLA-B*27/x genotype have a 0.05% absolute risk to develop Behcet's uveitis. HLA-B*51:01/x genotype with a probability of 0.065% had high PcPPV value for the development of Behcet's uveitis. This high PcPPV value indicates that in the presence of clinical symptoms, carriers of this allele have a high risk for developing Behcet's uveitis compared to the normal population (0.04%) (Table 3).

Discussion

Behçet's disease is a chronic, recurrent multisystem inflammatory disorder characterized by genital and oral ulcers, skin lesions, arthritis, and involvement of the vascular, neurological, and gastrointestinal systems, as well as inflammation of the middle layer of the eye, known as uveitis. Behcet's uveitis is one of the important complications of BD, which can even lead to complete blindness.[22] Uveitis can be classified as anterior, intermediate, posterior, or panuveitis based on the location of the inflammation. Anterior uveitis affects the front part of the eye, intermediate uveitis impacts the vitreous and peripheral retina, posterior uveitis involves the choroid and retina, and panuveitis affects all layers of the uveal tract.[5] The etiology of BD is unclear, however Microbial stimuli, environmental factors, endothelial dysfunction, genetic predisposition and immunological disorders is involved in pathogenesis of this disorder. Several evidences suggest that specific genetic backgrounds along with environmental factors play a role in BD development.[23]

In this study, we have examined the association of two HLA alleles with Behçet's uveitis, focusing on anterior and panuveitis, which are both common in Behçet's syndrome. Several studies have shown that immune abnormalities may underlie the development of BD. It is hypothesized that the pathogenesis of BD begins with an inflammatory response against infectious agents or autoantigens in genetically predisposed patients and is sustained by innate and acquired immunity.[24] Moreover, a set of immune mediators such as the products of HLA type I gene complex perform a great role in the inflammatory cascade. However, studies to date have not been able to demonstrate a clear role for specific HLA genes in an inflammation induced BD pathogenesis.[25]

In this study, the role of B*51:01/x and B*27/x genotypes in Iranian patients with Behcet's uveitis has been investigated. We chose to compare Behcet's uveitis patients with a healthy population rather than Behcet's patients without uveitis, as the latter group may develop uveitis in the future, complicating the study. This approach also allowed us to investigate whether uveitis in Behcet's patients has an autoimmune basis similar to Behcet's disease. Genetic studies suggest that diseases such as Behcet's uveitis and inclusion spondylitis, share the same HLA-B27 risk factor, which is likely involved in ocular immune regulation.[26] In addition, B27 causes the accumulation of fibrin and the inflammatory cells and expansion of the hypopyon in the anterior chamber of the eye.[27] Despite these indications, the findings of this study demonstrates that B*27/x genotype is not linked to Behcet's uveitis. In line with our findings, in a serological study in Iran, the authors could not show any significant association between the B*27/x genotype and Behcet's uveitis.[28] But these findings are contrary to previous study in 98 patients with Behcet's uveitis of the Korean population, which confirmed the predisposing role of the B*27/x genotype in Behcet's uveitis.[18] This discrepancy may be attributed to the demographic and genetic differences between the two populations. Also, our findings indicate a highly significant difference in HLA-B*51:01/x genotype frequencies between Behcet's uveitis patients and controls ($P = 0.0001$), highlighting its strong susceptibility in the Iranian population and its association with more severe forms of uveitis, particularly panuveitis, leading to a poorer visual prognosis. Several studies to date have shown the contribution of HLA-B*51:01/x genotype in Behcet's uveitis pathogenesis. In one study conducted in the Korean population, the increased involvement of HLA-B*51 allele in Behcet's patients was confirmed. Also, in the same study it was found that the frequency of HLA-B*51 in the patients with symptoms of uveitis was statistically significant.[13]

The results of gender distribution show that men constitute 86% and women constitute 14% of Behcet's uveitis patients in the study. Therefore, the frequency of this condition in the Iranian male population was about 6 times higher than that of the females.

In case–control studies, odds ratios or relative risks can be used to measure the risks, but real-lifetime risk or absolute risk cannot be estimated. The test efficiency for specific allele or genotype can be assessed by way of PcPPV formula. To calculate the absolute risk by PcPPV in any population, the lifetime prevalence of the disorder in the target population is required; the Behcet's uveitis prevalence in Iranian population is 0.04%. The PcPPV of testing for B*27/x genotype, that presented no significant association with Behcet's uveitis was 0.05% for all BU patients. This indicates that individuals who are carrying the B*27/x genotype show 0.05% absolute risk to develop Behcet's uveitis which is not much different from the normal population. The highest PcPPV was presented for B*51:01/x genotype in BU disorder and that was 0.065% for Iranian peoples. Such a high PcPPV value means that in the presence of clinical symptoms, as compared to the general population (0.04%), carriers of this allele have a high risk for developing BU. These results, therefore, strengthen the susceptibility role of B*51:01/x genotype in the development of Behcet's uveitis in the Iranian population.

Differences in racial backgrounds and the diverse nature of BD can partially explain the observed discrepancies between our results and data collected from other regions of the world. According to several studies, it can be concluded that the continuous and progressive aberrant inflammatory response caused by the activation of HLA genes can be effective in the pathogenesis of Behcet's disease.

It has been suggested that changed peptide binding groove in HLA-B*51 impacts on biology of cells and immune function.[29] Indeed, polymorphisms of HLA-B*51 at positions 67, 97, 116

Table 3
The distribution of B*51:01/x and B*27/x genotype frequencies in total BU patients and controls.

All BU patients		Controls	All BU vs. controls		
			Pv	PcPPV%	RR (95%Cl)
Genotypes	N = 50 (fr)	N = 70 (fr)			
B*51:01/x	41 (82%)	34 (48%)	0.0001	0.065%	1.76
B*27/x	2 (4%)	2 (2%)	1	0.05%	1.4

Pv, *P* value of the Fisher's exact test; RR, relative risks; 95%CL, 95%confidence limits of RR; *N*, number of patients; PcPPV, prevalence-corrected positive predictive value; NS, not significant.

and152 influence on the development of BD. These four residues determine the shapes and sizes antigen binding groove of HLA-B molecule.[30]

On the other hand, as mentioned, aberrant interactions of the improperly structured HLA-B*51 with NK cells could also be an attractive explanation for the occurrence of the disease process.[31] Studies have shown that HLA-B*51 interacts through its Bw4 epitope with the inhibitory killer immunoglobulin-like receptor (KIR), KIR3DL, located on NK cells.[32] The improper interactions between the abnormal HLA-B*51 and the NK cells can result in alterations in NK cell activity and induction of the pathogenesis of BD in two possible ways; 1. NK cells without appropriate performance of inhibitory KIR may fail to distinguish self-MHC and induce autologous tissue damage; 2. Drawbacks in the NK cell repertoire may cause persistent viral infections which leads to a chronic inflammatory response in BD.[33] An enhanced understanding of the association between HLA-B*51 and BD may lead to proper therapeutic approaches.

Conclusion

In summary, our findings indicate that the B*27/x genotype has no significant association with Behcet's uveitis, while, B*51:01/x genotype imposes strong susceptibility for Behcet's uveitis. We also have suggested that the role of B*51:01 in the pathogenesis of Behcet's uveitis is probably due to the presence of improper amino acids in its antigen binding groove and the abnormal interactions of such variations of this allele with NK cells. Additional studies are required to display the accurate role of HLA genes and their potential association with other influential factors in pathogenesis of Behcet's uveitis.

Ethics approval

Approval was granted by the ethics committee and the review board of Tehran University of Medical Sciences [49530].

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Authors' contributions

Zahra Hoseini: Conceptualization, Methodology, Formal analysis, Writing – original draft, Visualization. Fatemeh Rezaei Rad: Writing – review & editing, Software, Form analysis. Mohammad Zarei: Conceptualization, Methodology, Software, Form analysis, Resources, Writing. Nazanin Ebrahimiadib: Writing – review & editing. Zahra Salimian Rizi: Writing – review & editing. Mahdi Zamani: Conceptualization, Methodology, Resources, Investigation, Writing – review &editing, Supervision, Project administration, Funding acquisition.

Research involving human participants and informed consent

Questionnaire forms were prepared for each patient and control individuals. Before being included in the study, informed consent was taken from all the patients, or their legal guardians and control subjects.

Conflict of interest

The authors have no conflicts of interest, relevant to the content of this article to declare.

Availability of data and material

Not applicable.

Code availability

Not applicable.

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