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DISTRIBUTION OF VITAMIN D RECEPTOR BSMI AND FOKI GENE POLYMORPHISMS IN PATIENTS WITH MULTIPLE SCLEROSIS IN THE SERBIAN POPULATION

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Multiple sclerosis (MS) is a chronic, autoimmune demyelinating disease of the central nervous system. The association of vitamin D deficiency, sun exposure, and higher incidence of multiple sclerosis has been known for long, and a number of studies have confirmed anti-inflammatory and neuroprotective properties of vitamin D. Vitamin D receptor (VDR) is responsible for most of the biological effects of vitamin D, and four VDR single nucleotide polymorphisms (SNPs) have been identified as possible risk factors in several autoimmune diseases. The aim of our study was to determine the prevalence of VDR polymorphisms–BsmI (rs1544410) and FokI (rs2228570) in multiple sclerosis patients within the Serbian population.

A total of 169 participants from southeastern Serbia were enrolled in our study, 80 of whom were diagnosed with multiple sclerosis. The PCR-RFLP method was used for FokI and BsmI VDR polymorphism screening.

There was a statistically significant difference in the distribution of FokI genotypes and alleles between MS patients and control subjects ($p = 0.006$; $p = 0.001$). There was no statistically significant difference in BsmI genotypes and alleles between MS patients and healthy subjects ($p = 0.140$; $p = 0.153$).

Our case-control study showed that the distribution of FokI rs2228570 polymorphism was more prevalent in patients with multiple sclerosis in the Serbian population, while there was no statistically significant difference in the distribution of BsmI rs1544410 polymorphism between patients with multiple sclerosis and controls.

Keywords: SNPs, vitamin D receptor, vitamin D, neuroinflammatory diseases, multiple sclerosis

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INTRODUCTION

Multiple sclerosis (MS) is a chronic progressive autoimmune disease of the central nervous system that results in substantial neurologic deficits and disability. This gradual neurologic damage is the result of demyelination processes and dissemina-tion of gliosis. The clinical course of multiple sclerosis is highly variable and unpredictable (1, 2). The etiology of the disease is multifactorial, with complex interactions between environmental, genetic and epigenetic factors, all playing significant roles in MS etiopathogenesis. The role of vitamin D in multiple sclerosis has been known for long, at least since 1960s, when vitamin D levels and sun exposure (ultraviolet electromagnetic radiation 295-310 nm) were associated with a higher incidence of MS (3). Over the years, several studies have confirmed that vitamin D has an important role in the pathogenesis of MS, but this is still a subject of controversy (4). Active vitamin D from extra-renal tissues has autocrine and paracrine effects in the regulation of autophagy, apoptosis, phagolysosomal fusion, proliferation, differentiation, and chemotaxis of the immune cells.

Effects of vitamin D depend not only on vitamin D levels in plasma, but also on the binding of active vitamin D and its receptors. Vitamin D can bind in extra-renal tissues to the nuclear vitamin D receptor (VDR) and surface receptor protein disulfide isomers family A members 3 (PIDIA3). When calcitriol enters the cells that express VDR, VDR forms a VDR/VDR homodimer or VDR/RXR heterodimer with the retinoic acid receptor–RXR. These then activate vitamin D response elements–VEDREs, which target cell DNA and transcription factors synthesis (5).

Vitamin D and VDR have an important role in both adaptive and innate immunity (6). VDR is known to be strongly expressed in many types of activated immune cells: B cells, T cells, antigen presenting cells (APC), while the expression of VDR is significantly lower in resting B and T cells (7, 8).

Being important as it is, the genotype and polymorphisms of VDR have been extensively studied. The VDR gene is located on 12q13.1 chromosome and is about 100 kb wide, with 9 exons and an extensive promotor region. There are 30 known VDR gene polymorphisms, the main ones being FokI (exon 2), TaqI (exon 9), BsmI, and ApaI (intron region between exons 8 and 9) genotypes (5, 9). VDR gene variants have been identified as possible risk factors for a number of autoimmune diseases, inclu-ding multiple sclerosis, systemic sclerosis, rheumatoid arthritis, systemic lupus erythematosus, and other less common autoimmune diseases (10).

In the brain tissue, active vitamin D functions as a neurosteroid that regulates the genomic expression of dozens of brain proteins and also has important positive non-genomic functions in the brain (11). These proteins have an important role in brain development, neuronal connectivity, and neuronal transmission. It also influences brain tissue plasticity by regulating the synthesis of debrin, growthassoci-ated protein 43, macrotubule-associated protein-2 (MAP) and molecular transport of creatine kinase b, kinesine, Rho A, and dynactine (12, 13). Vitamin D also has neuroprotective properties by reducing pro-inflammatory cytokine production from microglia, nitric oxide production, and oxidative stress. Additionally, VDR has been found in the cortex, amygdala, thalamus, and hippocampus (14) and is expressed in both neuronal and glial cells (15). Low serum levels of vitamin D have been demonstrated in a number of neurodegenerative and neuroinflammatory diseases, although direct causality has not been confirmed (13).

The function of VDR gene could be modified significantly by the presence of these single nucleotide polymorphisms (SNPs). Therefore, the aim of this study was to examine the relationship between susceptibility to MS and the genotype and frequency of VDR polymorphisms BsmI (rs1544410) and FokI (rs2228570) in the Serbian population. To the best of our knowledge, this was the first research to investigate the effects of BsmI and FokI VDR polymorphisms in patients with multiple sclerosis in the Serbian population.

METHODS

A total of 169 participants from southeastern Serbia were enrolled in our study. Of these, 80 examinees were patients from the Clinic of Neurology, University Clinical Center Niš, diagnosed with relapsing-remitting multiple sclerosis (RRMS), according to the McDonald's recommended criteria for multiple sclerosis (16, 17), and clinical course (18). The patients with multiple sclerosis were diagnosed in accordance with the clinical, morphological, and immunological criteria. The mean age of the participants was 38.69 ± 9.95 years (24 males and 56 females). In the control group, there were 89 randomly selected healthy individuals, with mean age 46.81 ± 16.78 years (42 males and 47 females). The exclusion criteria were: the presence of previous autoimmune diseases, HIV infection, hepatitis B, hepatitis C, tuberculosis, and acute infections. Informed

consent was obtained from all the participants in our study. Signed informed consent was obtained from the study participants. The study was approved by the Ethics Committee of the Faculty of Medicine of the University of Niš, No: 12-6647-2/7.

The whole blood samples were obtained from all subjects from the cubital vein and ethylenediaminetetraacetic acid (EDTA) was used as an anticoagulant. DNA was isolated from 200 µl whole blood samples using the QIAamp DNA Blood Mini Kit (Quiagen GmbH, Hilden, Germany) and stored at -20 0C.

The polymerase chain reaction restriction fragment length polymorphism (PCR-RFLP) method was used for the screening of VDR genes–FokI and BsmI. PCR products were generated in the volume of 25 µl using the KAPA2G Fast HotStart Ready Mix (Kapa Biosystems Inc., Wilmington, MA, USA), 50 ng/µl DNA and 10 µM of each primer. The PCR conditions were as follows: initial denaturation for 2 min at 95 0C, followed by 35 cycles of denaturation for 15 s at 95 0C, annealing for 15 s at 60 0C, extension for 15 s at 72 0C, and final extension for 30 s at 72 0C. Restriction digestion was carried out by using the FastDigest restriction enzymes (Fermentas GmbH, St. Leon-Rot, Germany), FokI for 5 min at 37 0C, BsmI for 5 min at 65 0C. The products of restriction digestion were analyzed by 8% vertical polyacrylamide gel electrophoresis for FokI and 6% for BsmI.

Table 1. *Primer sequences for rs2228570 and rs1544410*

FokI (rs2228570) primer sequences	
Forward primer	AGC TGG CCC TGG CAC TGA CTC TGC TCT
Reverse primer	ATG GAA ACA CCT TGC TTC TTC TCC CTC
BsmI (rs1544410) primer sequences	
Forward primer	GGA CCT GTG GCA ACC AAG ACT
Reverse primer	GCC CGC AAG AAA CCT CAA ATA

The polyacrylamide gels were then stained with ethidium bromide and visualized under UV light. The primer sequences used for rs2228570 and rs1544410 are given in Table 1.

The FokI polymorphism rs2228570 have three genotypes: ff, fF, and FF. Homozygous genotype ff was detected by the presence of two fragments sized 196 bp and 69 bp, while the presence of the C allele was characterized by only one fragment sized 265 bp. The heterozygous genotype Ff was characterized by the presence of all three fragments, 265 bp, 196 bp, and 69 bp.

The BsmI polymorphism rs1544410 had three genotypes: bb, Bb, and BB. Homozygous genotype was detected by the presence of two fragments sized 654 bp and 76 bp, while the presence of A allele was characterized by only one fragment sized 730 bp. The heterozygous genotype Bb was characterized by the presence of all three fragments: 730 bp, 654 bp, and 69 bp.

The statistical analysis was done using the Chi-square test ($\chi 2$) to determine statistical differences between the studied groups. Genotype and allele frequencies were compared to the values predicted by the Hardy-Weinberg equilibrium using the Chi-square ($\chi 2$) test. Statistical analysis was considered significant at $p < 0.05$. The SPSS software package (SPSS Inc. Chicago, IL, USA) version 15 was used for statistical data processing.

RESULTS

There were 80 MS patients and 89 healthy subjects of both sexes enrolled in our study. The distribution of genotypes for FokI and BsmI are displayed in Table 2, and the distribution of FokI and BsmI alleles are displayed in Table 3. All genotype frequencies were in accordance with Hardy-Weinberg equilibrium in controls and in patients with MS.

Table 2. *Distribution of FokI and BsmI genotypes between MS patients and healthy controls*

Polymorphism	Genotype	MS	Control
	FF	39 (48.75%)	62 (69.66%)
FokI	Ff	28 (35%)	25 (28.09%)
	ff	13 (16.25%)	2 (2.25%)
	BB	22 (27.5%)	34 (38.2%)
BsmI	Bb	38 (47.5%)	37 (41.57%)
	bb	20 (25%)	18 (20.23%)

*FokI $p \leq 0.006$; BsmI $p \leq 0.140$

Table 3. *Distribution of FokI and BsmI alleles between MS patients and healthy controls*

Polymorphism	Alleles	MS	Control
FokI	F	106 (66.25%)	149 (83.71%)
	f	54 (33.75%)	29 (16.29%)
BsmI	B	78 (48.75%)	73 (41.01%)
	b	82 (51.25%)	105 (58.99%)

*FokI $p \leq 0.001$; BsmI $p \leq 0.153$

There was a statistically significant difference in the distribution of FokI genotypes and alleles between MS patients and control group examinees (p = 0.006; p = 0.001). There was no statistically significant difference in the distribution of BsmI genotypes and alleles between MS patients and healthy subjects (p = 0.140; p = 0.153) (Tables 2 and 3).

DISCUSSION

The etiology of autoimmune diseases is usually multifactorial and depends on the complex interaction between environmental factors and genetic predisposition. Multiple sclerosis is characterized by chronic autoimmune response which causes neuroinflammation, post-inflammatory gliosis, and neurodegeneration in CNS lymphocytic infiltrates. Proinflammatory effects of CD8+ and CD4+ T cell response predominate at demyelination lesion site, where the myelin and axonal destruction occur (19). Since vitamin D mediates differentiation, regulates proliferation, modulates and affects cytokine production in immune cells (20), it is thought to be one of the main predisposing factors in a number of autoimmune diseases, including multiple sclerosis (21). Low serum levels of vitamin D are associated with both severity and high relapse incidence in MS (22, 23). Furthermore, high levels of vitamin D have been found in patients with RRMS without relapses, but with a similar EDSS score. Although the role of vitamin D in the pathogenesis of MS has been thoroughly studied in the last 20 years, its actual contribution has not been fully understood.

VDR is required for most of the vitamin D biological effects, and the efficiency of VDR transactivation depends on its correct molecular structure (24). The main four SNPs that have been thoroughly studied and have strong potential to affect the efficiency of VDR are FokI (rs2228570), ApaI (rs7975232), BsmI (rs1544410), and TaqI (rs731236).

FokI polymorphism (T/C) is responsible for the production of two isoforms of different sizes (424 amino acids length for f allele and 427 amino acid length for F allele), with different activities (25). Etten et al. have demonstrated that FokI polymorphism affects transcriptional activity and level of cytokine synthesis by immune cells (26). Higher transcriptional activity by F isoform was also previously reported (27). Other polymorphisms do not have an effect on VDR structure, but can affect the stability, functioning, and translational activity of VDR mRNA (28), although this finding was later disputed (29).

In our study, we found statistically significant differences in the frequencies of VDR FokI genotypes and alleles between healthy control subjects and patients with MS, which was also reported for the Turkish population (30). In the case-control studies which included FokI genotype, there were no positive associations found in the Iranian (31), Kuwait (32), Czech (33), and Sicilian (34) population. Here, we did not find statistically significant differences in distribution between frequencies of BsmI genotypes and alleles in healthy controls and patients with MS. To the best of our knowledge, there have been studies which investigated BsmI polymorphisms in different populations, but the results vary significantly between populations. In the case-control studies which included BsmI genotype, there was not any positive association detected in the Sicilian (34) and northwestern Greek (35) population. Positive associations were found in the Iranian (31), Kuwait (32), Mexican (36), Slovak (37), and Czech (33) population.

Several meta-analyses have been done in order to explain further the effects of these VDR polymorphisms in the pathogenesis of MS. In a meta-analysis performed by Garcia-Martin et al., there was no association between the control and MS group for FokI and BsmI polymorphisms (38). However, in two more recent meta-analysis, done by Zhang et al. and Tizaoui et al., the association between control group and MS group was confirmed (39, 40). In three meta-analyses, no association was found for BsmI polymorphism between control and MS group (39–41). It has been hypothesized that these conflicting results are probably the result of the complex interaction of other triggers, genetic and environmental factors, which can be different in different populations. Another possible cause of these inconsistent results is perhaps the poor design of conducted studies, including small sample size, clinical heterogeneity, and unknown vitamin D status.

Due to the ethnic, racial, and territorial distribution of vitamin D receptor polymorphisms, the obtained results show that the distribution of VDR polymorphisms differs between patients with multiple sclerosis and healthy subjects on the territory of the Republic of Serbia. In addition, it must also be taken as a limit that the demonstrated statistically significant presence of polymorphism for FokI vitamin D receptor in patients suffering from multiple sclerosis is only a part that can potentially be the cause of the disease, due to its multifactorial origin.

In conclusion, our case-control study showed that the distribution of FokI rs2228570 polymorphism was more prevalent in patients with multiple sclerosis in the Serbian population. In addition, we did not find any statistically significant difference between the MS group and controls regarding the BsmI rs1544410 in the Serbian population.
These results should be considered preliminary since VDR polymorphisms alone are not enough to cause disease. Additional research of other genetic factors that mediate immunological response in neuroinflammatory diseases is needed to further validate the importance of genetic factors in the pathogenesis of multiple sclerosis.

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Competing Interest

Authors declare no relevant conflicts of interest.

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