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Polymorphisms of serotonin transporter gene and psychological status in patients with multiple sclerosis

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Keywords
Multiple Sclerosis; Depression; Serotonin Reuptake Transporter Protein; C. Elegans; Genetic Variation

Abstract

Background: Multiple sclerosis (MS) is the most common neuroinflammatory disease in young adults. Anxiety and depression may predispose individuals to MS and flare-ups. Serotonin transmission is modified in some brain regions of patients with MS, and these changes may contribute to their psychiatric abnormalities. We studied the frequencies of common polymorphisms of the serotonin reuptake transporter (SERT) gene in patients with MS according to their psychological status.

Methods: The 5-HTTLPR, rs25531, and STin2VNTR polymorphisms of the SERT gene were genotyped by polymerase chain reaction (PCR)-based methods in 100 patients with MS and 100 healthy controls.

Results: There were no remarkable differences in SERT gene polymorphisms between patients with MS and healthy controls. Unlike the control group, 41% of the patients showed some degree of depression based on Beck Depression Inventory (BDI), but no association was observed between SERT gene polymorphisms after the patients were stratified by depression status.

Conclusion: In addition to SERT gene polymorphisms, modulation of serotonin at the synapses may also be regulated by genetic variations in tryptophan hydroxylase type 2 and serotonin receptors. Further studies with functional brain imaging of the serotonergic system in patients with MS can provide information on the role of serotonin in this disease.

Introduction

Multiple sclerosis (MS) is the most common neuroinflammatory disease that causes

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neurological deficits in young and middle-aged adults.[1,2] Both genetic and environmental factors are seemed to be involved in the etiology of MS. In addition to certain human leukocyte antigen (HLA) alleles, genetic variation of interleukin-2 receptor alpha chain (IL2RA), IL7RA, kinesin family member 1B (KIF1B), H6PD, and tumor necrosis factor receptor superfamily-1 (TNFRSF1) are reported to be associated with MS.[3]

Some patients experience progressive devastating disease, and many others have a relapsing-remitting course that can lead to wide-spectrum chronic disabilities[4] including cognitive deficits[5] and psychiatric problems.[6] Psychiatric disorders as anxiety and depression are common comorbidities among the patients with MS.[7] These comorbidities adversely affect the course of MS.[8] On the other hand, anxiety and depression is commonly believed to predispose individuals to MS or flare-ups of the disease. Although the correlation between MS and these disorders has been found, the pathophysiologic basis for this correlation has not been elucidated. Moreover, the optimal pharmacotherapeutic options for neuropsychiatric comorbidities in patients with MS are debatable, although a significant number of patients need to be treated with psychiatric medication.[9]

Serotonin (5-hydroxytryptamine) plays a pivotal role in the pathophysiology of most neuropsychiatric disorders.[10] Serotonin level itself is controlled by serotonin reuptake transporter (SERT) gene on chromosome 17q11.2, and different polymorphisms affect the transcription activity of this gene, leading to impaired serotonin reuptake. A 44-bp insertion/deletion in the SERT gene promoter region with long (L) and short (S) forms affects gene transcription activity. The S allele is dominant to the L allele, whereas the L allele induces a two- to threefold higher level of SERT gene transcription than the S allele. The L/L genotype is associated with higher levels of SERT gene products than S/S or L/S.[11] There is a single nucleotide polymorphism in the L allele, rs25531 (A to G), and the L_G allele is associated with decreased expression of the SERT gene.[12] STin2VNTR, a 17-bp variable number of repeat in the second intron, is another polymorphic site in the SERT gene that results in alleles carrying 9-, 10-, or 12-repeat units. Transcriptional activity of the SERT gene is also affected by polymorphism at this site, as alleles with 9 or 12 repeats are associated with higher transcriptional activity than the 10-repeat allele.[13]

The changes and roles of this neurotransmitter in MS has been studied. Knocking out the SERT gene in experimental autoimmune encephalomyelitis (EAE), an animal model of MS, had some effect on inflammatory cell infiltration in the central nervous system (CNS).[14] Serotonin transmission has been shown to change in some brain regions including the limbic, paralimbic, and frontal cortex in patients with MS, and this may contribute to psychiatric abnormalities in these patients.[15,16] Specific serotonin reuptake inhibitors decreased the severity of neurological deficits in EAE, and had a neuroimmunomodulatory function.[17] In clinical studies, the beneficial effects of selective serotonin reuptake inhibitors (SSRIs) have been reported as a reduction in relapses and radiological improvements in patients with MS.[18] Relapses induced by stress were decreased by the administration of escitalopram, an SSRI.[19,20] In addition, the high prevalence of neuropsychiatric comorbidities and the suspected role of serotonin and SERT in these diseases highlight the possible involvement of serotonin in the pathogenesis of MS.[20]

To evaluate the effect of serotonin on MS and neuropsychiatric comorbidities, we studied common polymorphisms of the SERT gene in patients with MS according to their psychological status, and compared the findings to those in healthy individuals.

Materials and Methods

One hundred patients from southwestern Iran with proven MS based on the McDonald criteria[21] were included in this study. A total of 100 unrelated sex- and age-matched healthy individuals from the same geographical region were included as the control group. The study protocol was approved by our University Ethics Committee.

After each participant had provided his/her informed consent in writing, all participants were asked to complete Beck Depression Inventory (BDI-II) to evaluate their depression status. The total score on this questionnaire (which consists of 21 multiple-choice items) was calculated by adding the scores for each answer, which ranged from 0 to 3. Based on the commonly accepted cut-off scores for grading the severity of depression, 1-15 points was considered as no depression, 16-31 as mild depression, 32-47 as moderate depression, and 48-63 as severe depression.[22]

Then, blood samples were obtained from patients and controls for genetic analysis. Genomic

DNA was extracted from blood samples with the QiaAmp DNA Mini Kit (Qiagen, Valencia, CA, USA). To distinguish the L (419 bp) and the S (376 bp) variants of 5-HTTLPR, genotyping was done by polymerase chain reaction (PCR) based on a previously described method.[23] To detect the A/G single nucleotide polymorphism in the L allele, PCR products were digested with MspI (Vivantis Technologies, Selangor, Malaysia) according to the manufacturer's recommended procedure.[23,24] Genotyping of STin2 VNTR, the 17-bp repeat element in the second intron, was done by PCR to identify alleles STin2.7 (214 bp), STin2.9 (248 bp), STin2.10 (265 bp), and STin2.12 (299 bp).[25]

Allele and haplotype frequencies as well as deviations from the Hardy-Weinberg equilibrium were determined with Arlequin version 3.01 software. Genotypes and genotype combinations were calculated by direct counting. Gene frequencies were compared between patients and controls with the chi-squared or Fisher's exact tests using Epi Info software (version 6, CDC, Atlanta, GA, USA), and $P < 0.05$ was considered statistically significant.

Results

Genetic analysis of the SERT gene was done for 5-HTTLPR, rs35521, and STin2VNTR with PCR-based methods in 100 patients with MS (87 women and 13 men, mean age of onset 31.3 ± 8.5 years) and 100 healthy controls. According to their clinical course, at the time of study 91% of the patients had relapsing-remitting, 8% had secondary progressive, and 1% had primary progressive MS.

The results of SERT gene analysis are shown in table 1. The frequencies of alleles, genotypes, genotype combinations, and haplotypes did not differ significantly between patients with MS and healthy controls.

Table 1. Serotonin transporter gene polymorphisms in patients with multiple sclerosis (MS) in comparison to healthy control

Serotonin transporter gene			Depression scores (BDI-II) in patients with MS [n (%)]				All patients with MS (n = 100)	Healthy controls (n = 100)	P
			Mild depression (n = 26)	Moderate depression (n = 15)	No depression (n = 52)	Undefined (n = 7)			
Alleles [n (%)]	5-HTTLPR	L_A	25 (48.1)	12 (40.0)	53 (51.0)	7 (50.0)	97 (48.5)	102 (51.0)	0.34
		L_G	0 (0)	2 (6.7)	0 (0)	0 (0)	2 (1.0)	0 (0)	
		S	27 (51.9)	16 (53.3)	51 (49.0)	7 (50.0)	101 (50.5)	98 (49.0)	
	STin2VNTR	10	15 (28.8)	10 (33.3)	35 (33.7)	4 (28.6)	64 (32.0)	72 (36.0)	0.39
		12	37 (71.2)	20 (66.7)	69 (66.3)	10 (71.4)	136 (68.0)	128 (64.0)	
Genotypes [n (%)]	5-HTTLPR	L_A/L_A	6	3	15	2	26	26	0.67
		L_G/L_G	0 (0)	1 (3.3)	0 (0)	0 (0)	1	0	
		L_A/S	13 (25.0)	6 (20.0)	23 (22.1)	3 (21.4)	45	50	
		S/S	7 (13.5)	5 (16.7)	14 (13.5)	2 (14.3)	28	24	
	STin2VNTR	10/10	0	2	5	1	8	13	0.51
		10/12	15	6	25	2	48	46	
		12/12	11	7	22	4	44	41	
Genotype combinations	L_A/L_A, 10/10		0	2	4	1	7	12	0.11
	L_A/L_A, 10/12		5	1	10	1	17	10	
	L_A/L_A, 12/12		1	0	1	0	2	4	
	L_G/L_G, 12/12		0	1	0	0	1	0	
	L_A/S, 10/10		0	0	0	0	0	1	
	L_A/S, 10/12		9	5	12	1	27	25	
	L_G/L_G, 12/12		4	1	11	2	18	24	
	S/S, 10/10		0	0	1	0	1	0	
	S/S, 10/12		1	0	3	0	4	11	
	S/S, 12/12		6	5	10	2	23	13	
Haplotypes	L_A-10		0.26	0.33	0.28	0.29	0.28	0.28	NS
	L_A-12		0.22	0.07	0.23	0.14	0.20	0.23	
	L_G-12		0.00	0.07	0.00	0.00	0.01	0.00	
	S-10		0.03	0.00	0.06	0.00	0.04	0.08	
	S-12		0.49	0.53	0.43	0.57	0.47	0.41	

MS: Multiple sclerosis; BDI-II: Beck Depression Inventory-II; NS: Not significant

All individuals in the control group were psychologically normal based on their BDI-II score, whereas 26% of patients with MS had mild depression, 15% had moderate depression, 52% were not depressed, and 7% did not complete the inventory correctly. No associations were observed between SERT gene polymorphisms after the patients were stratified for depression status.

Genotype distributions at both loci showed no deviation from the expected Hardy-Weinberg values in patients and controls.

Discussion

Serotonin is a monoamine neurotransmitter synthesized by tryptophan hydroxylase type 2 (TPH2) in serotonergic neurons of the CNS, where it regulates neurological processes such as anxiety, mood, appetite, sleep, cognition, learning, and memory.[26] SERT is an integral membrane protein that regulates serotonin levels in the synaptic cleft after neuronal stimulation. It terminates the action of serotonin by rapid reuptake of released serotonin from the synaptic cleft into the presynaptic neuron. Serotonin transporter belongs to the Na^+/Cl^- dependent group of neurotransmitter transporters. Serotonin reuptake into neurons occurs through cotransport with Na^+ and Cl^- and countertransport with K^+.[27]

We found no remarkable differences in SERT gene polymorphisms between patients with MS and healthy controls. Unlike the control group, 41% of the patients had some degree of depression based on their BDI-II score. Because this questionnaire relies on psychological status during the previous 2 weeks, we are unable to extend these results to other situations. Furthermore, we cannot determine from our results whether depression is a predisposing factor for susceptibility to MS, or is an effect of the disease. MS is a chronic crippling disease which may affect the patient's whole life. Patients may not be able to do their work, may lose their job, and may have economic problems. Negative expectations about the vague future of their disease and fears that their disease will worsen are likely to contribute to anxiety and depression.

Although the L variant has been associated with higher levels of SERT gene products and higher reuptake activity, S allele carriers were reported to be more susceptible to depression.[28,29] Contrary to the recent report by Saul, et al. who found an association between depression severity in patients with MS with one or two copies of the 5-HTTLPR S allele,[30] the frequency of S allele carriers in the present study did not differ significantly between patients with MS who reported feeling depressed and those with normal psychological status (53% vs. 51%). Moreover, the frequency of S allele carriers was lower in patients (31%) than in the control group (47%).

In addition to SERT gene polymorphisms, the modulation of serotonin at the synapses can be regulated by genetic variations in TPH2 and serotonin receptors.[31] Cofactors such as tetrahydrobiopterin and folic acid are essential for tryptophan hydroxylase activity. This enzyme is also highly sensitive to reactive oxygen species, and chronic inflammation following infection or trauma may damage this enzyme.[32] Furthermore, natural or chemical serotonin antagonists in foods or dietary supplements can block the effects of serotonin.

In addition, adequate levels of Na^+ and Cl^- in the extraneuronal space and K^+ in presynaptic neurons are necessary for optimum SERT functioning,[27] and altered ion levels in injured neurons may lead to dysregulation of SERT activity in the CNS of patients with MS.[33]

The incidence and prevalence of MS have shown an alarming rise worldwide in recent years.[34] Although both genetic and environmental factors are thought to be important in the development and exacerbation of MS,[35] genes are more stable and genetic changes occur slowly, whereas environmental factors can change relatively quickly. The increased prevalence of MS is thus probably related to changes in environmental factors such as infection, diet, air and water pollution, radiation, and stress.[36] Although studies designed to identify new target genes with genome-wide associations would be helpful, epigenetic studies might be more useful. Epigenetic changes in the interactions with environmental factors may alter the expression pattern of certain genes, which may in turn lead to the induction of MS.[37]

This preliminary study focused on functional polymorphisms of the SERT gene in patients with MS who had different levels of anxiety and depression according to their BDI-II score, in order to shed light on the role of the serotonin-regulating system in mood disorders. This report is the first of its kind, and there are some limitations. To decrease the limitations of the current work, further studies with functional brain imaging of the serotonergic system in patients with MS can better elucidate the role of

serotonin in this disease.[27] This method would clarify the role of SERT in depressed or anxious patients with MS, and provide information of use to determine the optimum pharmacological therapy with antidepressants in these patients. This would be an ultimate goal in these researches at future.[38]

Conclusion

In addition to SERT gene polymorphisms, modulation of serotonin at the synapses may also be regulated by genetic variations in tryptophan hydroxylase type 2 and serotonin receptors. Further studies with functional brain imaging of the serotonergic system in patients with MS can provide information on the role of serotonin in this disease.

Conflict of Interests

The authors declare no conflict of interest in this study.

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