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Evaluation of 5-HTTLPR Gene Polymorphism and Resilience Components on the Development of Psychopathology in Adolescent Sexual Abuse Cases

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ABSTRACT

Introduction: More than one-fourth adolescents are exposed to unexpected frightening experiences and traumas until adulthood. In this study, we aimed to determine the potential role of serotonin transporter (5-HTT) gene polymorphism regarding resilience factors in the symptom variability of individuals exposed to sexual abuse.

Methods: Adolescents aged 11–17 years, who were admitted to the Marmara University Child Psychiatry Outpatient Clinic Forensic division with sexual abuse experience history, were informed about the research, and volunteers were included in the study. Turkish versions of "Kiddie-Schedule for Affective Disorders and Schizophrenia-Present and Lifetime (K-SADS-PL)" was used to assess the psychopathology and functionality. The evaluation of participants also included self-reports based on "Eysenck Personality Inventory" and "Ways of Coping Inventory" for reflecting the resilience domain.

Results: The sample included 16 girls (88.9%) and 2 boys (11.1%), and the mean (±standard deviation) age was 14.58±1.97 years. Genotyping of the insertion/deletion polymorphism (5-HTTLPR) in the 5-HTT gene's transcriptional control zone was established, and 8 participants (44.4%) were determined to be of the LL genotype, while 7 (38.8%) were LS and 3 (16.6%) were SS carriers. Considering the relationship between coping styles regarding resilience and genetic variants, 87.5% of participants (n=7) exhibiting problem-focused coping style were determined found to carry the LL allele, while 90% (n=9) who exhibited emotion-focused coping styles were the SS-LS allele carriers (p=0.003).

Conclusion: Our findings suggest that 5-HTTLPR gene polymorphism has a significant impact on the formation of coping styles. More studies are needed to determine other factors involved in the complex relationship between 5-HTTLPR gene polymorphism and development of psychopathology.

Keywords: Adolescent, sexual abuse, 5-HTTLPR, polymorphism, resilience

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INTRODUCTION

More than one-fourth of children are exposed to traumas, such as abuse, home- or school-based violence, natural disasters, traffic accidents, medical trauma, war, terrorism, migration, and the loss of a close relative (1). Epidemiological data suggest that exposure to trauma in children is about 25%-45% (2 Younger children have been reported more likely to be victims of sexual abuse, which is three times more common in girls (3,4). Although not many studies have been carried out on the national sample, it is estimated that the frequency of physical abuse in children is 30%-35% and the rate of sexual abuse is 13% in our country (3,5).

There is a known relationship between childhood abuse and childhood or adulthood psychopathology; however, it has also been reported in the literature that a psychiatric disorder does not develop in one of 3 individuals (20%-50%) who have been sexually abused in childhood (2,4,6,7,8). Individual differences play a role in shaping the response to trauma, and this response is purely individual (6,9).

Factors affecting the likelihood of exposure to a traumatic event and influencing the development of symptoms after such an exposure are considered risk and protective factors. Risk factors include family functioning (low socioeconomic level, domestic violence, parental and family relationships, social support, and diseases), individual factors (such as gender, low IQ, and learning difficulties), and social vulnerabilities (social inequalities, society's tolerance toward violence, cultural norms, etc.) (10).

Neurotransmitters responsible for neuronal transmission are also known to play important roles in the generation of an individual stress response (11). Serotonin transporter (5-HTT, SERT), a transmembrane protein, which is responsible for the neuronal reuptake of serotonin released into the synaptic cleft, is a key regulator of serotonergic transmission and has been suggested to have an important role in the etiology of many psychiatric disorders (12,13,14). Two polymorphisms have been reported for the 5-HTT gene: Variable Number of Tandem Repeats polymorphism, which occurs when a 17-bp region repeats 7, 9, 10, or 12 times in the second intron of the gene and the other is a polymorphism defined by the difference between the numbers of repetitive insertions/deletions of a 44-bp guanine, cytosine (GC) rich sequence in the transcription control region of the 5-HTT gene (5-HTT gene-linked polymorphic region [5-HTTLPR]). The long (L) form of

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the allele occurs when the 44-bp sequence is repeated 16 times, whereas the short (S) form occurs when it is repeated 14 times. According to this polymorphism, genotypes are classified as L/L, L/S, and S/S (14).

In case of exposure to stressful life events, individuals with single or double-copy of short allele 5-HTT promoter gene polymorphism are reported more likely to present with depressive symptoms and be diagnosed with depressive disorder compared to homozygous long-allele carriers; this relationship is also valid for suicide attempts (15,16). The occurrence of psychiatric disorders in individuals with S alleles may be due to decreased expression of 5-HTT in neurons, with reduced transcriptional activity of the gene (14). Temperament characteristics, such as anxiety, high "neuroticism," and "harm avoidance," were found to be more common in the carriers of 1 or 2 copies of the S allele compared to homozygote L. This situation not only increases the risk of anxiety reactions, but also negatively affects the ability to cope with stress (17). The term "resilient individuals" is applied to individuals without impaired functioning owing to their ability to adapt to difficult situations that may be destructive for others (18). The coping styles refer to the behavioral and cognitive responses of individuals to stressful situations and suggest the possibility that the individuals with long-allele 5-HTT promoter gene polymorphism present with higher resilience components.

Although exposure to traumatic events significantly increases the risk of long term psychopathology, there is no absolute causal relationship between them as the functionality of many individuals with traumatic experiences remains unaffected and they report no psychopathological symptoms. In this study, we hypothesized that among the adolescents exposed to sexual abuse, individuals with S alleles would display lower resilience to trauma exposure compared to homozygous long-allele carriers. We also aimed to investigate the possible effects of 5-HTT gene polymorphism on psychiatric symptoms and coping characteristics.

METHODS

The study sample included 18 adolescents aged 11-17 years (and their parents), who were admitted to the Forensic Clinic of Marmara University Child and Adolescent Psychiatry Department, with a history of exposure to sexual abuse. Volunteering participants provided written informed consent. The ethical approval was obtained from the ethics committee of Marmara University Medical Faculty (protocol number 09.20122060, dated 01.11.2012). Exclusion criteria were as follows: verbal and performance IQ scores of 70 and below, the presence of chronic and serious medical illness or seizure-like neurological impairment, psychosis, autism spectrum disorder, and technically inappropriate conditions concerning the collection, relocation and the genetic analysis of samples, and the suspect of contamination.

Clinical Assessment

To assess psychopathology and functionality, semi-structured interviews with children and their families were conducted by child and adolescent psychiatrists using of the Turkish versions of "Kiddie-Schedule for Affective Disorders and Schizophrenia-Present and Lifetime (K-SADS-PL)" (19). The presence of Pervasive Developmental Disorder and Mental Retardation were assessed using a Diagnostic and Statistical Manual of mental disorders (DSM)-IV-based clinical interview and Wechsler Intelligence Scale for Children-Revised Version (WISC-R), as these diagnoses are not screened through K-SADS-PL.

The adolescents participated in the study were requested to complete the Eysenck Personality Inventory (20). The scale consists of 24 items and 4 subscales, which are outwardness (6 items), neuroticism (6 items), psychotism (6 items), and lie (6 items). The lie subscale is a control scale serving to check the validity of the whole test. The score for each personality attribute ranges from 0 to 6 (21). The inventory has also been used instudies for the adolescent populations (22). In a study, the Cronbach Alpha internal consistency coefficient was reported as r=0.81 (23). In addition, participants were requested to complete Ways of Coping Inventory, a 30-item and 4-point Likert-type scale, developed to examine cognitive and behavioral ways of coping with stressful situations (24). In this scale, 5 subscales are located in 2 dimensions: Problem-Focused Coping (PFC; safe approach, optimistic approach, and social support) and Emotion-Focused Coping (EFC; helpless approach and submissive approach) (25).

Genetic Analysis

Ten milliliters of blood sample was collected in ethylenediaminetetraacetic acid (EDTA) tubes from 18 volunteers participating in the study. DNA was isolated from the whole blood using the DNA isolation kit (High Pure PCR Template Preparation kit, Roche Diagnostics, Germany).The insertion/deletion polymorphism (5-HTTLPR) in the transcriptional control region of the 5-HTT gene was determined using polymerase chain reaction (PCR) with F 5'-GGCGTTGCCGCTCTGAATGC-3 'and R 5'-GAGGGACTGAGCTGGACAA CCAC-3' primers (Klauck and ark, 1997). PCR was performed with 20-100 ng of DNA, 100 µM deoxynucleaotides (dNTPs), 20 pmol of primer (each of F and R), 1.0 mM magnesium chloride ($MgCl_2$), 20 mMTris-HCl pH 8,6, 50 mM KCl, and 1 U Taq polymerase (MBI Fermentas) and the volume was adjusted to 50 µL using distilled water. The PCR conditions were as follows: cycle 1 first denaturation at 95.5°C for 3 min followed by 35 cycles, 1 min denaturation at 95.5°C, 1 min primer annealing at 60°C (annealing), 1 min synthesis at 72°C (extension), and the last cycle was performed at 72°C for 7 min at the final synthesis step. After electrophoresis at 100 volts on a 2% agarose gel containing 0.5 µg/mL ethidium bromide using a gel imaging system (VilberLourmat), the 484 bp product was evaluated as S, while the 528 bp product was evaluated as L form of PCR products. Alleles of XL, XXL, and LJ were not detected. According to this, genotypes were determined as L/L, L/S, and S/S. For both polymorphisms, electrophoresis was performed using a DNA sequencer (100 bp DNA Ladder, MBI Fermentas) in addition to the samples, while the allele was determined during the genotyping process (26).

Statistical Evaluation

The Statistical Package for Social Sciences (SPSS) 20 (IBM Corp.; Armonk, NY, USA) program was used for statistical analysis and $p<0.05$ was considered statistically significant. Descriptive statistics of the continuous variables included in the study were shown as mean, median, standard deviation, minimum and maximum values, descriptive statistics of frequency, and percentage of categorical variables. The normal distribution relevance of continuous variables was tested using the Shapiro-Wilk test. The Mann-Whitney U test was used for 2-group comparisons of continuous variables without normal distribution, and the Kruskal-Wallis test was used for 3 and more group comparisons. Fisher's exact chi-square test was used for group comparisons of categorical variables.

RESULTS

The 18-participant-case group consisted of 16 females (88.9%) and 2 males (11.1%). The average age at the time of application (in years) was 14.58±1.97 years. Based on self-reports, 44,4% of cases defined themselves as "bad," and 55,6% "moderate" socioeconomic level. No case was identified as "high" socioeconomic level. The psychopathologies determined during the semi-structured clinical interviews with K-SADS-PL are shown in Table 1.

Table 1. Psychopathologies determined during assessments

		n	%
Post-traumatic stress disorder	NA	10	55.5
	A	8	44.4
Depressive disorder	NA	6	33.4
	A	12	66.7
Anxiety disorders	NA	5	17.8
	Separation anxiety disorder	3	16.7
	Social Phobia	5	27.8
	Generalized anxiety disorder	5	27.8
Obsessive compulsive Disorder	NA	15	83.3
	A	3	16.7
Tic disorders	NA	16	88.9
	A	2	11.1
Disruptive behavior disorders	NA	9	50.0
	Attention deficit and hyperactivity disorder	6	33.3
	Conduct disorder	1	5.6
	Oppositional defiant disorder	2	11.1
Alcohol/cigarette/ substance use	Yok	11	68.8
	Cigarette	5	31.2
	Alcohol	2	11.1
	Substance	-	

Genetic Distribution: Genotypes according to "polymorphism" or "allelic variant" defined by different numbers of insertions/deletion repeats of a 44 bp GC rich sequence in the transcriptional control region of the 5-HTT gene (5-HTTLPR) were evaluated as L/L, L/S, and S/S. Allelic variants of the sample are shown in Table 2.

The diagnoses identified in the allelic variant groups are shown in Table 3. Statistically significant differences were not detected.

Personality Traits: According to Eysenck Personality Inventory evaluations, 72.2% (n=13) of the sample showed neuroticism, 22.2% (n=4) showed outwardness, and 5.5% (n=1) were evaluated in the psychotic group. Furthermore, 38.5% (n=5) of the participants of the neuroticism group were LL allelic variants, while 61.5% (n=8) were SS or LS variant carriers (p=0.23).

Coping Styles: Ways of Coping Inventory was developed to examine cognitive and behavioral coping styles in response to stressful situations, including PFC (safe approach, optimistic approach, and social support) and EFC (helpless approach and submissive approach). Overall, 44.4% (n=8) of the sample was using problem-focused and 55.6% (n=10) was using emotion-focused stress-coping styles. There was no statistically significant difference between the stress-coping styles and psychopathologies.

By examining the genetic variants according to the coping styles exhibited by the sample, it was determined that 90% of the SS-LS carriers exhibited EFC styles, while 87.5% of the LL carriers exhibited PFC styles. This correlation was statistically significant (p=0.003) and shown in Table 4.

Table 2. 5-HTTLPR genetic distribution

	n (%)
LL	8 (44.4)
SS	3 (16.6)
LS	7 (38.8)

Table 3. Genetic condition and psychopathology

		Genetic		p
		LL (%)	SS-LS (%)	
Post-traumatic stress disorder	NA/Under the threshold	6 (60)	4 (40)	0.188
	A	2 (25)	6 (75)	
Depressive disorder	NA/Under the Threshold	4 (66.7)	2 (33.3)	0.321
	A	4 (33.3)	8 (66.7)	
Anxiety disorders	NA	4 (80)	1 (20)	0.118
	A	4 (30.8)	9 (69.2)	

Table 4. Genetic conditions and coping styles

		Genetic		p
		LL (%)	SS-LS (%)	
Coping styles	Problem-focused	7 (87.5)	1 (12.5)	0.003*
	Emotion-focused	1 (10)	9 (90)	

DISCUSSION

The insertion/deletion polymorphism (5-HTTLPR) in the transcriptional control region of the 5-HTT gene being genotyped for 18 participants; 44.4% of cases were determined as LL, 38.8% as LS, and 16.6% as SS genotypes. In a genotyping study conducted in our country, these rates were determined as 29.8% L/L, 38.8% L/S, and 31.4% S/S (14). It is suggested that genetic predisposition increases the risk of developing major depression in response to stressful life events. Similarly, studies have shown that carrying the S allele may be considered a risk factor for the development of post-traumatic stress disorder after trauma exposure (27,28). In addition, individuals carrying 1 or 2 copies of the short S allele were found to exhibit temperaments, such as anxiety, neuroticism, and harm avoidance more frequently compared to L homozygotes (26). Accordingly, besides the negative effects of anxiety, stress-coping capacity may also be negatively affected.

Considering the study sample, the most commonly observed conditions following abuse were found to be anxiety disorders, depressive disorders, and disruptive behavior disorders. It is stated in the literature that 20%-50% of victims of the abuse may remain symptom free, whereas psychopathological conditions, such as anxiety disorders, depression, post-traumatic stress disorder, substance-use disorders, borderline personality disorder, and suicidal behavior may develop in later periods (29,30).

Many studies have reported that in the presence of childhood neglect or abuse, S allele carriers are more frequently diagnosed with major depression when exposed with later traumatic life events, such as job loss or divorce (15,28,31). In a meta-analysis study, it was found that stressful life events pose a risk for depression, but serotonin gene polymorphism does not increase this risk further (32). Similarly, in our study, no statistically

significant difference was found between the genetic variants in terms of the risk of developing psychiatric disorders.

Personality traits and stress-coping styles are important determinants of the risk for trauma exposure as well as psychopathological symptoms that may occur after trauma (33). In our study sample examined in terms of personality characteristics, 13 of the participants exhibited neuroticism (61.5% are SS-LS group), 4 extroversion (75% are LL group), and 1 (100% is SS) psychotic features. According to the stress-coping styles examined, 44.4% (n = 8) of the sample was found to use problem-focused, whereas 55.6% (n=10) used EFC styles. However, there was no significant relationship between the stress-coping styles and the risk of developing psychopathology, which was probably due to type 2 error.

Regarding the relationship between serotonin gene polymorphism variants and coping styles examined in 18 participants of our study, 87.5% of cases with PFC styles were found to carry LL alleles, whereas 90% of those with EFC styles were found to be SS-LS allele carriers; this relationship was statistically significant. Despite the intense interest in the genetic basis of mental disorders, few studies have addressed the relationship between coping styles and inherited factors. Genetic traits are thought to play a role in determining how susceptible an individual is to environmental stressors and which particular coping style he/she is more prone to use. For instance, in a large sample twin study, it has been reported that coping styles, such as "turning to others" and "problem solving" are largely related to genetic factors (34). In another twin study that investigated the effects of genetic and environmental factors on coping styles, problem solving, turning to others, and avoidance strategies were found to be moderately related to hereditary factors (35). Finally, in a study conducted on monozygotic and dizygotic twins, the relationship of 19 specific coping styles with genetic and environmental factors was examined; 14 of these were reported to be related solely to hereditary characteristics, independent of environmental factors (36).

Although genetically determined to some degree, coping styles may be improved through psychosocial support and therapeutic interventions. Approaches based on the identification of maladaptive strategies and improvement of stress-coping skills on individuals exposed to traumatic life event, may contribute to the prevention of mental disorders in the long term.

Despite numerous reports indicating that being a SS-LS carrier increases the risk of developing psychopathology, the causality of this relationship is not sufficiently clarified. The findings of our study suggest that 5-HTTLPR gene polymorphism has an important effect on shaping one's stress-coping styles. Further research is needed to clarify the different aspects of the relationship between the 5-HTTLPR gene polymorphism and the risk of developing psychopathology.

Limitations

The sample consisted of adolescents between the ages of 11 and 17 years, who were referred for evaluation of sexual abuse and agreed to participate in the study. The sample size was insufficient for many statistical analyses as the nature of the traumatic experience and the difficulties associated with judicial processes limited voluntary participation in the study. In addition, a healthy control group for comparison was lacking.

As the psychopathology screening instrument K-SADS-PL was developed according to the diagnostic criteria of DSM-III-R or DSM-IV-TR, our study did not address the changes in the Trauma and Stress-Related Disorders section in DSM-V.

Variables, such as the nature of the abuse and its duration, the time taken from the exposure to trauma to the admittance, etc., were not standardized between subjects. There is also an uncertainty regarding whether the risk factors in the family affected the exposure to trauma, the development of psychopathology after the trauma, or both.

Future research on larger samples may provide a more detailed picture of the factors that play a role in preventing both the exposure to the abuse and the development of subsequent psychopathology. Thus, individual treatment requirements based on the genotype-phenotype relationship may be identified.

Investigations assessing the risk of the development of severe and destructive symptoms in children exposed to abuse through genetic factors may provide the opportunity for closer follow-up of risk cases and intensify treatment interventions. Efforts to elucidate the factors that influence coping styles and the shaping of resilience can also render possible prevention of children from being victims of abuse by helping them acquire the necessary skills. Due to the insufficiency of actual data, more research is needed in both areas.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Marmara University School of Medicine (Date: 01.11.2012, No: 09.20120160)

Informed Consent: The informed consent form, prepared by the author, was provided before the research from volunteer participants.

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