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According to some estimates, the prevalence of ADHD has increased up to 30% in the last 20 years.[1]
S variant is associated with the lower transcriptional activity of the promoter when compared to the L variant.[4,7-9,11]

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Gonen, M. Planning for subgroup analysis: a case study of treatmentmarker interaction in metastatic colorectal cancer. Controlled Clinical Trials 2003;24 : 355-363. doi: 10.1016/s0197-2456(03)00006-0.

• Authored Book:

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The Journal of Neurobehavioral Sciences

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Contents

Review Article

Animal Models of Attention Deficit and Hyperactivity Disorder: A Critical Overview and Suggestions

Abstract

Attention deficit and hyperactivity disorder (ADHD) is a neurodevelopmental and neuropsychiatric disorder that appears as a subset of attention deficit and different subspecies in which both occur together and is generally observed in childhood. Pharmacological agents such as atomoxetine and methylphenidate, which are widely used against the disease, appear with different and important side effects. Since the causes of the disease are not clearly understood, many studies are carried out on various animal models in order to both understand the etiology and develop new treatment models. In this review, a holistic approach to ADHD will be presented and advances in animal models, neuroimaging, neurodevelopmental, and neurochemical conditions will be presented using different perspectives. It is very important to understand how different animal models are effective in the development of pharmacological agents. In addition, comparing ADHD with different types of disease can detect similarities and further strengthen the etiological basis. Our major proposal is to draw attention to the further development of animal models related to the importance of the thalamus, which officially sees a filter of perception. Different animal models are needed to do all this because the disease is not fully modeled, except for the symptoms of ADHD. The current review will conclude that none of the currently discussed models meet all the necessary validation criteria, but that newly created genetic models, therapeutic strategies, and the disease mechanism may be radically important points.

Keywords: *Animal models, attention deficit and hyperactivity disorder, neurochemistry, neurodevelopment, neuroimaging, pharmacology*

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Introduction

Attention deficit and hyperactivity disorder (ADHD) is classified as a heterogeneous neurodevelopmental disorder manifested by varying levels of hyperactivity, impulsivity, and inattention in humans. According to some estimates, the prevalence of ADHD has increased up to 30% in the last 20 years.[1] Although ADHD is a common and highly inherited disease, its genetic etiology is not yet fully known. Many studies have shown the genetic predisposition of ADHD but estimate that the heritability of ADHD ranges from 50% to 80% and is not known for sure.[2-6] The 1999 General Surgery Academy report on child mental health notifies "For most children with ADHD, the overall effects of these existing gene abnormalities appear negligible. This shows that these nongenetic factors are also important."[7] As our genes have not changed significantly over a thousand years, these "non-genetic factors" should explain the increased incidence of ADHD. Some of the roles that the environment can play in ADHD can be listed as follows: maternal obesity, maternal smoking, chaotic families, maternal stress during pregnancy, and inconsistent-harsh parenting.[8,9] In addition, nutrition can be classified as an environmental factor and has a critical importance for fetal development. Recent studies show a strong link between nutrition during pregnancy and the risk of having a child with neuropsychiatric diseases such as anxiety, depression, and ADHD.[10]

Patients with ADHD are generally defined in three ADHD subtypes; the first is mostly the inattentive subtype (most commonly seen in girls), the second is the predominantly hyperactive/ impulsive subtype (most commonly in boys),

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and the third is the combined subtype (i.e., includes both inattention and hyperactivity).[11] Especially psychostimulants (such as methylphenidate [MPH], atomoxetine, pemoline, and d-amphetamine) are used in their treatment.[12] There is great interest in developing specific animal models to outline specific forms of ADHD in order to develop specific therapeutic strategies outside of these treatments. ADHD is a neurobehavioral disorder of childhood and is characterized by deterioration in children's behavior. The diagnosis of this disease is based on behavior. Therefore, when validating an ADHD model, it should be based on behavior in the same way. The general characteristics of an ADHD model can be listed as follows: it must be compatible with a theoretical rationale for ADHD (construct validity), predict previously unknown aspects of ADHD behavior, genetics, and neurobiology in clinical settings (predictive validity), and simulate the basic behavioral characteristics of the disease (appearance validity).[13] The prevalence of ADHD is increasing worldwide, and although it is available for drug interventions, definitive treatment has not been found because most of the underlying etiology is still unknown[14] and underlying deficiencies include hyperactivity, attention deficit, and impaired neurocognitive events.[15]

The aim of this review is to overview ADHD animal models to show the new studies of treatment strategies, to draw attention to the lack of animal models used in the development of effective diagnosis and treatment methods for ADHD, and to provide recommendations along with critical deficiencies.

The place of developmental cognitive neuroscience in attention deficit and hyperactivity disorder

The tasks of the frontal lobe are to line up incoming information, associate current experiences with past experiences, monitor behavior, suppress inappropriate reactions and plan for future purposes. These are also called executive functions of the frontal lobe. At the core of executive functions is the ability to initiate, maintain, inhibit attention, and draw attention in another direction. Therefore, a frontal lobe dysfunction can cause disturbances in impulse control, attention, and/or cognitive activities.[16]

How are actions planned by the brain?

The prefrontal cortex (PFC) is the region where attention, perception, perceptual analysis, abstract thinking, and social behaviors are controlled and converted into behaviors; briefly, it organizes the senses from all lobes and converts them into behaviors (works in collaboration with amygdala and thalamus). As shown in Figure 1, through glutamatergic and dopaminergic activity, this information is transferred to each other by providing communication between neurons.[17,18] Primary motor cortex is the region where all calculations and decisions are made before a move is made (stop and think before doing). Then, the synaptic neurons (carrying information) are coming to the premotor cortex, then choosing the appropriate movement (the region of choosing the right move after realizing that it should stop and think). After deciding on the appropriate movement, the transition to the application to the motor motion area is the primary motor area.[19] Managerial functions are motor planning, directing attention, changing cognitive sets, monitoring, and adapting behavior through attention and process memory and are associated with the dopaminergic activity.[17]

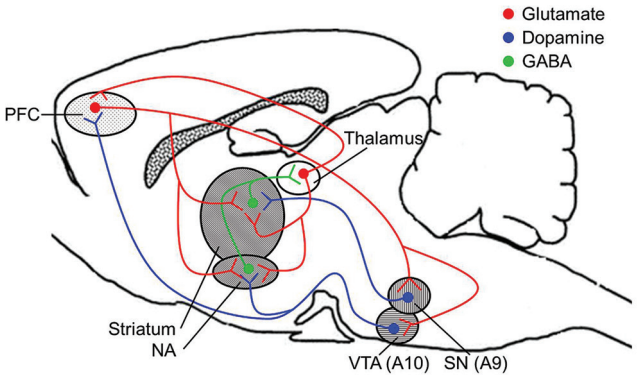

Figure 1: Relationship between dopamine transporter and growth factor. The importance of dopamine transporter in driving cellular activation in the postsynaptic membrane and the importance of working in cooperation with growth factors[18]

The importance of thalamus in attention deficit and hyperactivity disorder animal modeling

There are a number of nuclei in the thalamus, and these nuclei control the information from the surrounding lobes in the postsynaptic connections due to their ganglion feature. They act as an association region in transforming into behavior and reflect the information to the PFC in the conduct of the behavior as a motor. If neurodevelopmental nutrition disorders, especially neurochemical activity disorders with dopaminergic activity, have occurred in the PFC, symptoms that usually occur with ADHD, such as incompatibility in emotional response, inability to inhibit impulses, neglect of the consequences of their behavior, excessive mobility, restlessness and disturbance in attention occurs.[17,20] Anterior cingulate gyrus (ACG) located just above it, helps manage the organization by disabling irrelevant information and enables us to continue our attention. ACG acts as a filter for incoming data, separating and classifying information. Furthermore, ACG is the center of our brain's attention and has a connection with the hippocampus, where our long-term memory resides, through a thick fiber node called the cingulum. Moreover, the thalamus translates the information reflected from all these regions by sending to the motor activity of the behavior into the frontal cortex.[21-23]

Based on these, for the most suitable animal model of ADHD the criteria and recommendation can be made as below:

1. The model must fit a theoretical rationale for ADHD (construct validity): Two principle behavioral processes that are claimed to be major constitutive components in ADHD etiology, prereinforced behavior ought to be demonstrated
2. The model should imitate the fundamental behavioral characteristics (visual validity) of ADHD, impulsivity ought not be present at the beginning and should develop gradually over the long run, continuous attention deficit ought not be observed only when stimuli appeared at wide intervals over time, hyperactivity ought not be observed
3. The model should be neurodevelopmental, a prehereditary model
4. The model ought to anticipate new parts of ADHD conduct, hereditary qualities, and neurobiology (predictive validity).[24]

Although there is a human-like effect in the rodent brain in ADHD, this biochemical balance is different from each other since the thalamus and ACG in the human brain are more developed. In particular, dopaminergic neurons project from the ventral tegmental area and substantia nigra to the prefrontal cortex and then to the dorsal striatum. The filtering center in these projected neurons is the ACG, but in ADHD models, the models may be inadequate because this part is underestimated [Figure 2].[25]

The importance of imaging studies in animal modeling

Anatomical differences were found in people with this diagnosis in imaging studies. Among the detected findings, differences such as PFC, orbitofrontal cortex, basal ganglia, some parts of the corpus callosum, cerebellum shrinkage, and thus decreased functionality were found.[26-30] Total brain volume also decreases, especially in individuals with ADHD.[25,31] Studies are carried out to determine whether this reduced volume is due to the neuronal network, or genetically based or related to brain neurochemistry, and

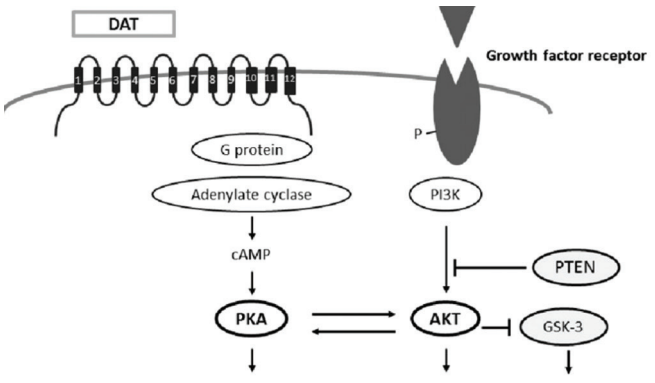

Figure 2: Molecular neurochemistry and anatomy of attention deficit and hyperactivity disorder in rodent brain. Dopaminergic neurons and glutamate neurons connect up to the prefrontal cortex. While both types of neurons have an excitatory effect from the ventral tegmental area and substantia Nigra (SN, A9) to the citriatum, GABA neurons have an inhibitory effect from the thalamus to the citriatum and nucleus accumbus[25]

animal models that are suitable for this research started to be created. Clinical proof focuses to some degree to diminished capacity of the striatum, but it is not well understood how specific genes are expressed differently and do not predispose to ADHD how they shape striatal physiology.[32] The PFC includes the anterior cingulate cortex (ACC), and this area plays major roles in learning (knowledge) and cognition.[32-35] For this reason, PFC hypoactivation and disinhibition (malfunctioning) can cause PFC-related cognition degradation.[36] Medial PFC (mPFC) and ACC are regions associated with preparatory attention in which phasic responses are both inhibitory and stimulating; this suggests that differential afferent regulation in putative PFC pyramidal cells is important for the preparation step. It also receives dopaminergic inputs from the ventral tegmental area, which is necessary for optimal cognitive function in the deep layers found in the rat PFC. Thus, the neurotransmitter dopamine (DA) is a neuromodulator of mPFC function, and it can be concluded that DA receptor transcripts are expressed more densely in the V-VI layers than other superficial or intermediate layers of the mPFC.[37,38]

DA release can activate G-protein-coupled receptors such as D2-like (D2, D3, and D4) and D1-like (D1 and D5) DA receptors. While the D1-like receptor-mediated pathway enables Gs-type G proteins, which are stimulus (s) and positively bind to adenylate cyclase (AC), to be activated; however, the D2-like receptor-mediated pathway enables inhibitor (i) and G-type G proteins that are negatively bound to AC to be activated. Briefly, activation of the DA receptor-mediated pathway provides regulation of adenosine-cyclic monophosphate (cAMP)-concentration-dependent signaling pathways. In addition, cAMP activates protein kinase A (PKA), which is known to play an important role in neuronal synaptic plasticity.[39,40] One of the basic pathophysiological models of ADHD studied to date is the hypo-dopaminergic hypothesis. In this context, it is well known that too low or too high D1 stimulation levels can impair memory and attention behaviors and lead to diseases.[36,41,42] Imaging studies can also provide us wide information about reaching the most possible result that can be achieved on comparing different animal models in different therapeutic effects. Furthermore, radiolabeling studies have showed that both cocaine and MPH share analogous forms of attachment within the dopaminergic system (e.g., nucleus accumulators, etc.) involved in repeated substance use and euphoria.[43-45]

The importance of animal modeling

The most frequently cited principles of animal models were proposed by McKinney and Bunney[46] about 50 years ago. According to what has been known since 1969, an animal model to be ideally classified should be similar to the disorder to be modeled in terms of etiology,

symptomatology, biochemistry, and treatment.[46] Animal models offer many advantages when studying diseases. A few of them are as follows: For brain-based diseases, they provide the opportunity to work on simpler nervous systems, exhibit easily interpretable behaviors, offer an easily controlled environment, provide genetic homogeneity, and allow various interventions that cannot be performed on humans. On the other hand, in animal models of ADHD, it has appeared as a crucial tool for understanding the contribution of maternal nutrition to prenatal programming, the development of three macronutrients (protein, fats, and carbohydrates), and subsequent neuropsychiatric disorders. Therefore, the importance of exposure periods reflecting the neurodevelopmental stages of human gestation in emphasizing the translational aspects of animal models is very important. Nutritional programming of neurobehavioral disorders constitutes a solid basis of preclinical studies; in addition to neurodevelopmental disorders due to neurodevelopment, synaptogenesis, and synaptic plasticity, changes in risk assessment and response have also been observed.[11] According to the findings from previous studies, several rodent models led to the emergence of ADHD-like symptoms, including DA receptor 4 (D4R)-KO mice, DA transporter (DAT)-knockout (KO) mice, and spontaneous hypertensive rats (SHR). In addition, a hyperactive mouse line was established through phenotypic selection performed over multiple generations, according to a new animal model. Consequently, the relatively simple nervous systems of rodent models enabled the identification of neurobiological changes underlying certain aspects of ADHD behavior. In this way, the formation of animal models is important and needs to be studied further.[47-51]

Pedigree differences in animal models

The results obtained in behavioral pharmacology studies with genetic interventions raised the question whether there may be differences in basal and postintervention responses in models depending on the lineage of animals, and there may also be differences in ADHD models due to lineage. As an example, the most studied ADHD model is the SHR showing inattention, hyperactivity, and impulsivity,[52] but the behaviorally SHR model known to be limited in two significant respects:

1. The animal model was bred for hypertension, so to separate the factors that result from the hyperactivity of hypertension
2. SHR does not have a suitable control type to statistically determine whether phenotypic differences between lines are associated with hyperactivity or other factors.

The control strain Wistar-Kyoto (WKY) rat, commonly used in this direction, shows activity levels below other rats, so it has been proposed and used as a model of depression.[53-56] On the other hand, studies of animal models of three different lineages compared, due to the lack of receptors shed light on the selection of the correct lineage to better treat and understand the disease. For example, comparing the ideal animal models (SHRs) for ADHD subtypes, WKY rats, and behavioral differences between Sprague-Dawley (SD) rats, the SHR model is an ideal animal model for the mixed subtypes of ADHD. Especially glucocorticoid receptor (GR) functions have an important place in ADHD models behavior. On the other hand, further studies are required to determine whether WKY rats can be used as an ideal model for ADHD. The existing GR agonist can effectively correct nonselective attention and spontaneous activity in SHR rodent models.[57]

The Animal Models of Attention Deficit and Hyperactivity Disorder

The most widely used Napoli high and low inducible rat lines have been used on the basis of behavioral arousal (Làt-maze) versus novelty since 1976.[58] The five-preferred series reaction time task (5CSRTT) is also a psychologically used laboratory behavioral test.[59] Poor performers in the five-prefer serial reaction time task and Napoli high excitability rats are more useful models for ADHD compared to other animal models which focus on less important signs of hyperactivity. Furthermore, it may have limited value due to ADHD-like behavior is shown or are manufactured in a way but that does not lead to a clinical diagnosis of ADHD in humans. This behavioral ADHD does not meet the criteria for animal models and is therefore excluded from the current review. These excluded animal models include the Napoli highly excitable rat, the WKY Hyperactive rat, the acallosal mouse, the hyposexual rat, the PCB-exposed rat, the lead-exposed mouse, and the rat reared in social isolation. With these excluded models, new models have started to be created. SHR meets most of the validation criteria and provides good comparison with clinical ADHD cases.

Model of attention deficit and hyperactivity disorder due to dopamine transporter gene deficiency

DAT carrier KO mice are important as one of the few transgenic animal models of developed ADHD disease. It is a model developed according to the suggested role of DA in ADHD. Administering the specific MPH drug to this model reduces hyperactivity and improves learning in both DAT-KO mice and patients with ADHD. This model was also created by combining heterozygous pairs of C57BL/6J strain DAT-KO mice to produce wild type and homozygous DAT-KO animals.[60]

Attention deficit and hyperactivity disorder model due to increased ataxin-7 gene expression

Ataxin-7 (Atxn7) has been proven to be a gene associated with hyperactivity. In a study, mice overexpressing an Atxn7 gene (Atxn7 OE) were created to investigate whether increased expression of Atxn7 in the brain is associated with ADHD-like behavior. When looking at the methods

used, immunofluorescence and quantitative real-time polymerase chain reaction (RT-PCR) methods confirmed the overexpression of the Atxn7 gene and protein in the PFC and striatum (STR) of Atxn7 OE mice, and Atxn7 OE mice showed hyperactivity, but did not show impulsivity. In particular, the ADHD drug atomoxetine (administered intraperitoneally 3 mg/kg) reduced ADHD disease-like behavior and Atxn7 gene expression in the PFC and STR of these modeled mice. These findings show that this drug plays a role in the pathophysiology of Atxn7. It has also been revealed that Atxn7 OE mice can be used as one of the hyperactive-impulsive phenotypes of the ADHD animal model. This study also provides valuable information on the potential genetic basis of ADHD, which is not fully known. As is known, ADHD can mostly be detected behaviorally. The emergence of genetic foundations has an important place in terms of science.[61]

Model of attention deficit and hyperactivity disorder linked to dopamine concentration and receptors

Discovering genes is important in ADHD. Studies in this direction have found several relationships between various monoaminergic genes and polymorphisms in ADHD. These include genes and polymorphisms such as DA D1, D4, and D5 receptor (DRD1, DRD4, and DRD5) genes, DA norepinephrine (NE), a2-adrenoceptor gene, and serotonin transporter (DAT1, SERT1, and NET1).[62,63] In these models, the system was functionally disrupted, and in some animal models, extracellular DA concentrations and upregulated postsynaptic DA D1 receptors (DRD1) decreased while others increased extracellular DA concentrations. DA pathways are suggested for ADHD models. However, DA release of DA stimulation is impaired in these models, which is associated with impaired DA delivery. The aspects of its behavior in ADHD models may be due to the imbalance between decreased dopaminergic and increased noradrenergic regulation of neural circuits involving PFC. The aspects of its behavior in ADHD models may be due to the imbalance between decreased dopaminergic and increased noradrenergic regulation of neural circuits involving PFC. There is evidence that psychostimulants can reduce motor activity by increasing serotonin levels, which increases the importance of these drugs in ADHD. Besides explaining the neurobiology of ADHD and its relationship with genes, these animal models can also be used to test new drugs that can be used to alleviate ADHD symptoms. These include new psychosocial additions to be found. One of the approaches that can be applied to model the symptoms of ADHD in experimental animals is to damage the dopaminergic pathways using 6-OH-DA in developing rats. The pathophysiological mechanism of ADHD is not fully known, as previously mentioned. In particular, the role of synaptic transmission systems is not fully understood. However, due to the downregulation of DA D1-like receptor pathways of GABAergic interneurons in ACC, the results obtained with the SHR animal model in the studies performed show that; dopaminergic activity stands out when looking at the differences in DA modulation of GABAergic transmission recorded from V layer pyramidal cells compared to WKY rats in the control of SHR animal models. In WKY rats, both miniature and spontaneous inhibitors increase the frequency of postsynaptic currents (for example, mIPSCs and sIPSCs, respectively), although this failure to work in SHRs brings along the inadequacy of the model. Similarly, the neuronal network amplitude of amplified IPSCs (eIPSCs) increased by DA in WKY rats comparing to SHRs. DA also increased the amplitude of unitary IPSCs (uIPSCs) that were larger than SHR patterns in WKY rats. Based on the observations made in the study, it can be concluded that D1-like receptor pathways hold promise in ADHD as potential regulators mediating these modulating effects.[64] In another study, atomoxetine's therapeutic effects on motor activity were studied. The expression of the DA D2 receptor with atomoxetine and the effects on ADHD was investigated. Young male SHR was used. As a result, it was observed that daily atomoxetine at a dose of 1 mg/kg continuously improved the motor activity. Thus, it was found that treatment with atomoxetine significantly (in a dose-dependent manner) decreased DA D2 expression in the hypothalamus of the PFC, striatum, and SHRs. In other words, hyperactivity in young SHRs can be improved by treating with the drug atomoxetine via DA D2 receptors, which is important for ADHD disease.[65] On the other hand, not only DA receptors but also other receptor mechanisms are important in ADHD modeling and many mechanisms depend on the receptors.

Sprague- Dawley acute dopamine depletion model in rats

McDougall *et al*.[66] used a protocol in 2005, 2 h apart rodents from the tyrosine hydroxylase inhibitor α-methyl-DL-p-tyrosine (AMPT) group get two intraperitoneal injections of AMPT (25 mg/kg each). After, locomotor activity was detected for 30 min to validate the animal models which placed in open-field boxes to monitor.

Due to the effects of TAT-DATNT, animals were placed in open field boxes for 15 min after induction of DA depletion. The animals were then given an intracranial injection of 40 nmol of TAT or TATT-DATNT. The rodents were returned to the open field rooms for 60-min recording session. As a result, the TAT-DATNT peptide improved spontaneous and locomotor behavior in SHR rats.[66,67]

The model of primary cortical astrocyte culture

In the DAT mutant and knock-out models in which astrocytes are cultured, the findings of neurogenesis, the importance of the GABAergic system on the nutrition of the region and neuronal networks, and the relationship between glial GABA and cortical tonic inhibition with the disease have clearly been revealed.[68]

Naples high volatility model

The Naples high volatility (NHE) model is a different model used to demonstrate ADHD. These rodents have a balanced cortical and an upgraded limbic cycle in their cerebrums. NHE rats show the distinctive roles of the dorsal (lower coding of repetitive stimulus-reward relationships to a habit) and ventral (increased value is given to true primary reward) striatum. As a result, this model has emerged as a model that can be used for gambling disease in ADHD and revealed that the dynamics in the reward system can be associated with reduced attention to pathological gambling.[69]

Model of attention deficit and hyperactivity disorder in constitutive adhesion G protein-coupled receptor L3 knockout mice

Adhesion G protein-coupled receptor L3 (LPHN3 and ADGR L3) has been associated with ADHD in several ways. In a study, the characteristics (impulsivity, gait, locomotive activity, recognition memory, sociability and visuospatial, anxiety-like behavior, and aggression) were investigated in mice with ADGRL3 deficiency in many behavioral areas related to ADHD. As a result, the combination of behavioral and transcriptomic findings has been confirmed to be an experimental animal model of ADHD in constitutive ADGRL3 KO mice. According to the data obtained, changes in gene expression in the DA system provide information to support the interspecies link between ADGRL3 inactivation and the abnormal function of the DA system. It also supports and justifies studies in ADGRL3 transgenic animals to reveal significant and biologically relevant gene expression changes in the PFC and striatum. In addition, future transgenic animal models created using more different techniques as CRISPR-Cas9 will lead to the generation of variants as ADGRL3 associated with disease. In this case, it is thought that specific noncoding polymorphisms in this gene can provide more detailed information about how the ADHD model can emerge.[70]

Other genetic factors

Other genes that are effective in ADHD etiology are in the serotonergic system: Adrenergic receptor genes such as tryptophan hydroxylase gene, dopa decarboxylase gene, alpha 1C (ADRA 1C), and alpha 2C (ADRA 2C), are the step of a third stimulus in serotonin synthesis. In addition, not only genetics but also receptor and enzyme activity encoded by genes are important. Furthermore, DA neurochemistry is very important in ADHD neurophysiology, and there are five DA receptors. The enzyme that catalyzes the D3 receptor is DA B Hydroxylase, tyrosine hydroxylase for the D4 receptor, catechol-O-methyl-transferase for the D5 receptor, and monoamine oxidase catalyzes the DAT gene, and its receptors. In addition, a relationship was found between the 5-HTT (serotonin transporter) gene and ADHD.[71,72] It has been shown that the A1 allele of the DA D2 receptor gene (DRD2) known to be located on chromosome 8 (on the long arm) may be important in ADHD. The A1 allele was detected in 46.2% of patients with ADHD, and it was stated that this gene plays a role in ADHD as a modifier rather than an etiological factor. While the D2 receptor is also observed in the striatum, it is found in moderate amounts in the hippocampus, amygdala, and thalamus. It is known that the D2 receptor is at a low level in the PFC.[73] In individuals with ADHD, it has been reported that single-photon emission computed tomography is associated with DA-carrying receptors.[74-76] An even lower than normal level of DA in humans causes various neurodegenerative disorders and ADHD.[77] When it is at a higher level than normal, it causes other disorders due to abnormal functioning brain functions, and the DRD2 gene, one of the five receptors of DA, has the effect of the Taq A1 Allele (rs1800497 polymorphism).[78] All of these genes constitute the epigenetic mechanisms of ADHD because these receptors provide mRNA stabilization and form the neurodevelopmental basis in the PFC. The production of new neurons from the mother's womb to adulthood and the epigenetic mechanisms that are integrated with dopaminergic activity are tried to be elucidated by various imaging and physiological examinations and animals are made through these models. When looking at the neuron cell, the protein and gene expressions required for the formation and development of neuronal networks can also be maintained with the help of neurochemistry by the work of these receptors and genes, and histone modifications are also required to be studied at the molecular level. The conclusion that can be drawn from this is that more animal studies are needed for ADHD on genetic factors.

Potential Therapeutics in Attention Deficit and Hyperactivity Disorder Treatment

Since ADHD is defined as a neurocognitive disease with behavioral symptoms as inattention, hyperactivity, impulsivity, and working memory defects, the neurocognitive approach in animal models makes a very important contribution to the development of treatment modulation. The most common mechanism of treatment known for this disease includes stimulant drugs (e.g., MPH and atomoxetine), and the mechanism is blocking the DAT and increases synaptic DA.[79,80] While these pharmacological agents are beneficial in this disease, they cause a variety of side effects, including risks for future substance use disorders in ADHD patients. For this reason, studies with various active substances were carried out in animal models to create new treatment options.

In a study, it was used an interfering peptide (TAT-DATNT) to cleave a protein complex composed of the interaction between DAT and the DA D2 receptor (D2R). Locomotor behavior was found to be increased in SD rats. It has been found that the degradation of D2R-DAT increases

the level of extracellular DA, especially when *in vivo* high-performance liquid chromatography and microdialysis are used. More importantly, the TAT-DATNT peptide significantly reduced hyperactivity and improved spontaneous transition behavior in the SHR model in a common ADHD animal model. A different way of regulating the activity (i.e., other than direct inhibition by a DAT inhibitor) of dopaminergic neurotransmission and DAT and a potential target site for the future development of ADHD treatments are presented in this study.[67] Given DA dysregulation and the effect of DAT on ADHD, better results can be demonstrated by comparing whether the D2R-DAT protein complex is a suitable treatment target for ADHD in different animal models. Consequently, this study investigated whether the TAT-DATNT peptide would have any beneficial effect on ADHD-like symptoms (i.e., impaired working memory and hyperactivity) in the widely used rat model of D2R-DAT disorder, ADHD SHR, and positive results were found. Likewise, studies with different proteins can be said to be promising. In another study, the SHR ADHD rat model was used and morphological changes were tried to be found during *in vitro* development of frontal cortical neurons in comparison with the control group WKY rats and the effects of adenosine A2A (A2AR and A1R), A1, and caffeine receptors signals were investigated. Cortical neurons cultured from WKY rat and SHR treated with caffeine or A1R and A2AR agonists or antagonists after analyzed by immunostaining for tau proteins (microtubule-associated protein) and protein 2.

Furthermore, the involvement of PI3K, not PKA signaling, was evaluated in this study. Importantly, frontal cortical neurons have been isolated for the first time from the ADHD model, which has been shown to cause impairments in differentiation and growth. It increases the potential of caffeine and A2AR receptors as an adjuvant for the treatment of ADHD, showing that A2AR and caffeine can act as a neuronal level capable of maintaining the growth of ADHD neurons.[81] Agents that can be used to increase the effects of different drugs that can be produced for ADHD in the future have been revealed. Furthermore, in another study, male SHRs (4 weeks old) and normal control WKY rats were used to find expression profiles of lncRNAs in the hippocampus from an ADHD model using SHRs, and rat brains were subjected to some testing. Microarray analysis technology was used to determine the expression profiles of lncRNAs and mRNAs in SHRs and WKY rats; then, the differentially expressed lncRNAs were verified by RT-PCR. Gene Ontology (GO) and pathway analysis (for expressed mRNAs or nearby genes) was used to determine the possible functions of lncRNAs in ADHD disease. In results, a total of 267 differentially expressed 311 mRNAs and lncRNAs (123 downregulated and 144 upregulated) were identified in SHRs compared to WKY rats. RT-PCR analysis was used on selected 15 lncRNAs and was confirmed. GO and Kyoto Encyclopedia of Genes and Genome pathway analyzes have shown that irregular lncRNAs in the brain play a role in neuronal function and maintenance, as well as development processes. The close relationship between differentially expressed lncRNAs and mRNAs was revealed by co-expression network analysis. In addition, the expression analysis system of disordered lncRNAs, downstream genes, and the organization of memory and learning showed that lncRNA NONRATT0006598.2 is associated with the Baiap2 gene, which may be involved in ADHD progression. The findings have the potential to contribute significantly to the advance of ADHD disease and to find possible therapeutic targets for lncRNAs and mRNAs and ADHD treatment.[82] LncRNAs (transcripts with not translated into protein and their lengths exceeding 200 nucleotides) and protein-encoding mRNAs could have a potential therapeutic effect for future ADHD therapy. In another study, the effect of catalpols (ingredient of Rehmanniae radix preparata, a Chinese medicinal herb) behavior and neurodevelopment on the ADHD SHR animal model were investigated. SHR was divided into some groups such as the SHR group, catalpol group (daily 50 mg/kg), MPH group (daily 2 mg/kg), and WKY rat group. With the findings obtained from this study, it was revealed that catalpol can effectively improve hyperactive and impulsive behavior and that catapol in ADHD can improve spatial learning and memory in SHR, which is a widely recognized animal model.[83] Hence, the Chinese traditional herb was found to be an effective therapeutic for AHDH. Studies have been conducted except for bioactive compounds found as therapeutic agents that can be used in ADHD treatment.

On the other hand, it turned out that a physical acoustic noise with the effect of external exposure can create a different effect that can treat this disease. This study was conducted on the SHR model of ADHD investigated how acoustic noise affects brain activity. Neuronal immunohistochemical staining and markers of plasticity, ΔFosB, and Ca2/calmodulin-dependent protein kinase II of Wistar rats (n = 24) and SHR (n = 16) were evaluated after the exposure to repeated ambient silence or acoustic noise. Furthermore, SHR (n = 6) was repeatedly treated with MPH. As a result, it showed that the applied acoustic noise shifts a decreased neuronal activity in the core accumulator, tuberomammillary nucleus, and dorsolateral PFC in SHR to normal activity levels in mated rats. This result can explain why noise is selectively beneficial in ADHD.[84] In this way, studies carried in animal models of ADHD, and the positive results obtained seem to have potential therapeutic properties in the future. These results should be supported by further studies and phase studies should be started.

Pharmacological Effects and Animal Models

There are many medications used to treat ADHD. These drugs are known to affect different mechanisms and the use of these drugs in different ways has been tested in experimental animals. Current drugs used for the treatment

of this disease function mostly by regulating brain DA and/or NE levels. For example, MPH, the most effective and frequently prescribed drug for ADHD, functions as a psychostimulant that stimulates DA release in the central nervous system and inhibits its reuptake, thus enhancing the temporal and spatial presence of DA at postsynaptic receptors. On the other hand, as a nonstimulant drug, atomoxetine is also widely used in ADHD and different neural diseases with its NE reuptake inhibitor function. The reduction of ADHD symptoms by atomoxetine could possibly be associated with levels of NE and DA in the PFC, as well as its effects on cognition and arousal in attention. These mechanisms may be mediated by activation of NE a-2 and/or DA D1 receptors.[34,85-89] In addition, recently, it can be said that both atomoxetine and MPH cause an increase in cortical histamine release in rats, and it was observed that MPH was more effective when these two substances were compared in this study.[84] One study found that atomoxetine supports the hypothesis that it can evolve cognitive function. The drug atomoxetine (NE reuptake inhibitor) was involved in histamine release, and it is found that it can be used for the treatment of cognitive deficits associated with neuropsychiatric disorders and ADHD.[90] There are also reports in contrast to MPH given at low doses and at high doses. SHR cannot offer the same therapeutic effects on hyperactivity behavior in rats.

Therefore, similar observations were made in SHR rats at a high dose (comparing with the other) of TAT-DATNT (4.0 nmol) by trying different dose effects, on hyperactivity a U-shaped dose-response curve was seen in SHR, but when given much higher than this dose, MPH, on the contrary, it increases excessive dopaminergic neurotransmission and fulfills the stimulating effects observed in SHR rats.[67,91,92] Although WKY rats reported higher levels of DAT in the striatum of SHR rats at 2 weeks of age compared to WKY rats when compared to a control strain for SHR rats,[93] there was no significant difference in overall D2R or DAT levels between SHR and WKY rats. TAT-DATNT administered in the same dose and had no effect on locomotor activity in WKY rats. Unlike it had dopaminergic effect on the SD rat strain. On the other hand, TAT-DATNT has been found to be dose-dependent and likewise, the effects of MPH on WKY rats are dose dependent.[94,95] On the other hand, L-threo-dihydroxyphenylserine (L-DOPS) for ADHD is a NE prodrug that increases brain NE and DA levels. A study aimed to measure the effects of this drug on ADHD-like behaviors in rats and its effects on PFC and DA neurons in the ventral tegmental region. Therefore, behavioral tests and electrophysiological tests were applied on rats. In addition to the L-DOPS drug, the peripheral amino acid decarboxylase inhibitor benserazide (BZ) also participated in the experiments in this study. In conclusion, in behavioral tests, BZ + L-DOPS improved the hyperactivity, impulsive action, and inattention of adolescent SHRs (SHR/NCrl) (well-validated animal model of combined ADHD type). BZ + L-DOPS also resulted in impulsive selection and reduction of impulsive action in Wistar rats, but did not improve inattention of Wistar Kyoto rats (WKY/NCrl) (predominantly inattentive type proposed model). It was emphasized that the L-DOPS drug has effects on PFC and DA neurons and BZ + L-DOPS can be an alternative treatment for ADHD.[96] According to positive results from the studies, it is important to understand how the drugs are effective and how they show effects with combined therapies. Therefore, more studies should be conducted, and new treatment strategies for ADHD should be investigated.

The Importance of Animal Modeling in Other Diseases That May Occur with Attention Deficit and Hyperactivity Disorder

ADHD is a disease that can be seen together in different diseases. First, it can be seen with different mental and cognitive disorders (difficult to learn, abnormal social behavior, anxiety, and depression), but on the other hand, it has been found that it may also be associated with other diseases.[97] Most of the mechanisms and causes of the different disorders in the presence of this disease are unknown. Studies have been conducted to determine these and further studies are needed. ADHD was frequently reported in children with allergic rhinitis in screenings.[98-100] A study was conducted by Suzuki *et al*.[101] after the classical model of 6 hydroxydopamine (6-OHDA) of Heffner and Seiden[102] was created.[101,102] They found that the 6-OHDA treatment treated the rats and the rat group treated with 6-OHDA had more than 6-fold higher locomotor hyperactivity on a postnasal day 46 compared with controls. They reported that they showed an increase. In this study, the impairment of hyperactivity was also observed in rats with 6-OHDA lesions.[100] In addition, it has been suggested that rats with 6-OHDA lesions have difficulty coping with sleep induction, suggesting difficulty in sleep induction in ADHD, in line with the previous reports.[103] With the application of publication therapies for ADHD in animal models, information is also obtained on whether they will cause other diseases in the future. Despite the clinical efficacy of pharmacological therapeutics, concerns remain about probable drug use and the risks, so more studies should conduct to eliminate these concerns.[104-106] It was investigated whether the function of glutamatergic α-amino-3-hydroxy-5-methyl-4-isoxaz olepropionic acid receptors (AMPARs) and expression change in ADHD SHR models; AMPAR-mediated synaptic transmission was observed in hippocampal excitatory synapses on hippocampal slices in SHR models. Immunogold labeling densities of AMPAR subunits GluA2/3 and GluA1 were measured. They showed that this reduced AMPAR-mediated synaptic transmission in stratum and stratum radiatum origins (in CA3-CA1 pyramidal cell

synapses) on SHRs compared to control rats. In result is shown, in part, that learning changes in individuals with ADHD in AMPAR dysfunction, which probably involves molecular changes in the hippocampus, and this is an important detail. Napoli high volatility (NHE) model is an animal model utilized in displaying ADHD using. These rodents have a balanced cortical and an upgraded limbic cycle in their cerebrums. ADHD and its accompanying pathological gambling include similar deficiencies of prefrontal-striatal dialogue. In one study, experiments were conducted to reveal whether NHE rats (NRB compared to normal randomly bred rats) are a useful model for the gambling vulnerability that exists in ADHD. Results obtained in NHE rats show the distinctive roles of the dorsal (lower coding of repetitive stimulus-reward relationships with a habit) and ventral (increased value to true primary reward) striatum. As a result, it has been revealed that the dynamics in the reward system can be associated with decreased attention versus pathological gambling.[69,107]

Also, Fragile X syndrome (FXS) is caused by a mutation in the X-linked gene FMR1. FMR1 encodes the fragile X mental retardation protein, an RNA binding protein that regulates protein synthesis. In FXS syndrome commonly ADHD and ADHD-related symptoms are seen. In a study of α2-agonists clonidine and clonidine witch normally used in ADHD, was tested on FXS. FMR1 KO mice (emerges as inherited form of mental retardation) were used. Findings found that clonidine is a stimulus to combine with behavioral therapies based on positive reinforcement and changes procedural behavior.[108] With different diseases, ADHD can occur and as seen in this previous study some properties that have good effects on ADHD can help recovery in other diseases.

Investigating the causes of these different disorders and deficiencies with studies conducted is an important factor in finding new treatment options. When recent studies are examined, the effects of disorders such as allergic rhinitis, AMPAR dysfunction, FXS, and pathological gambling in animal models have been examined. In this way, new treatment opportunities can be improved both for the other diseases and ADHD. For example, based on the appearance of AMPAR dysfunction, different targeted treatment models can be created for the treatment of ADHD.

Behavioral Analysis and Tests in Attention Deficit and Hyperactivity Disorder Animal Modeling

It is very important to apply behavioral tests as a complement to the experimental method in studies aimed at elucidating treatment or disease mechanism for brain diseases. The reason for this is that the brain is a part that reflects all our operational activities that make up us, unlike diseases, in other body parts, and we have the chance to analyze this reflection with the best behavior patterns. There are many tests and observations in terms of behavioral interpretation for ADHD. In order to question the accuracy of the modeling, they also offer the opportunity to comment on the clinical comparison with the patient and on the questions of whether it can treat the disease symptomatically or how it can design it to completely eradicate the disease. These tests, in the general framework of ADHD, can be measured in the animal, together with brain imaging and electroencephalography (EEG), in behavioral tests, it is possible to observe which brain region the animal has impulsivity, hyperactivity, sociality, anxiety, memory and attention disorders.[109] The passage of DA and NE, which affects PFC function, is impaired in ADHD patients. Primary drugs used in ADHD treatment increase NE and DA delivery. Existing psychostimulants (e.g., pemoline, MPH, and d-amphetamine) which is used to target dopaminergic systems, and pharmacological treatments, and these are mostly used.[110,111] The behavioral effects of these drugs on experimental animals can also be examined by various methods. Experimental animals are kept in cages with a camera system for behavioral analysis of drugs given to the model because the effect of the drug on the locomotor activity and the type and count of the movements in stereotype activity and the relationship between the disease and the drug is behaviorally clarified.[112] Behavior ethogram consists of the following types of behaviors: Upbringing (head lift raised on hind legs), sniffing upside down (nose contacting the ground), widespread movement (it can be measured with the periodicity of the transition of the home cage), face washing (forward from ears to nose and mouth), back-moving (forelimbs), grooming (cleaning itself paws or mouth), rotation (hanging from the front legs with the mouse and drawing rapid close circles on the top bars of the cage), immobility (no visible movement of the animal), stick grip (hanging from the front of the cage from the grid on the cage), circling (following a circular path at cage floor), and digging (using front legs and move the sawdust).[113] In one study, an analysis on the sum of all behavioral stereotypes observed for a measure of stereotype expressed by each strain of mice injected with d-Amphetamine and the serotoninergic agonist 2,5-dimethoxy-4-iodoamphetamine in relation to ADHD, specifically breeding and up-down, it has been reported that sniffing is common. It has also been observed that the serotonergic drug shows catatonia in animals differently. An ideal and reliable animal model should show all the symptoms present in ADHD patients in animal models and respond similarly to the same pharmacological interventions. Currently, none of the existing animal models of ADHD develop specifically to model the neurodevelopmental changes that occur in behavior initiation and progression, nor do they model various aspects of behavioral and executive functional symptoms.[114-116]

Among the ADHD animal models, the most commonly used ADHD model is defined SHR, but instead the most

classic neurodevelopmental model of ADHD, which is now more preferred by lesional brain systems and it is acquired by neonatal injection of 6-OHDA. This animal model is mostly used to study heavy symptoms of hyperactivity. Despite the existence of this model, the data in the literature on impulsive behavior or attention deficits remain uncertain and studies in this area need to be increased. Regarding the 6-OHDA Mouse Model, ADHD is known to imitate hyperactivity, which is characterized by impulsive behaviors in neurochemical pathology, with visual validity in the PFC. In the model that was lesioned with 6-OHDA in the PFC, neuron loss was also shown due to the Golgi organelles of the pyramidal neurons of the ACG, which are effective in communication between the prefrontal and the cells. The relationship between impaired filtering of information that needs attention, and its relationship is also an important finding for ADHD.[109] A better comprehension on mechanisms neurochemically in ADHD is the key to more beneficial treatments and their improvement. On the other hand, behavioral analyzes are also performed in animal models valid for the same purpose. In addition to this mouse model, sham mice (lesion in the striatum) were added, and impulsivity, hyperactivity, sociality, anxiety, memory, and attention impairment were tested and compared in these animal models. The principal component analysis that is set upon 20 factors restrained in different behavioral tests was conducted to compare all experimental groups and draw conclusions. These tests are MPH, Impulsivity, and Attention Tests (5CSRTT), respectively. As a result, impulsivity decreased and attention increased in all groups given MPH, but this change was observed less in the lesion in the striatum.[109] The 5CSRTT is a behavioral test used to evaluate motor impulsivity and visual attention in laboratory psychological research in animal models. 5CSRTT has its own impulsivity, individual attention, and reaction times. Preclinical studies conducted with 5CSRTT have enabled very useful and effective studies in ADHD diagnosis, medication, and behavioral examination (Bari, 2010; Cocker et al., 2014; Robinson & Emma, 2011[130]; Lusting, 2012 [131]; Zeeb & Fiona, 2014).[117-119]

Disruption of the five-option serial reaction time task in a mouse model created by 22q11.2 microdeletion: Growth with amphetamine

Individuals who have 22q11.2 deletion syndrome (22q11.2DS) carry a major risk for facing neurodevelopmental disorders such as ADHD and schizophrenia. These diseases are associated with general attention deficit. Effect analysis was investigated depending on the continuous performance test of modafinil and amphetamine in experimental animals with this deletion and also in the wild type model. On the other hand, modafinil knows to have more important effects on hypocretin/orexin, serotonin, glutamate, acetylcholine, and histamine functions, which shows how it affects brain activities, especially cognitively, depending on the various neurochemical activity of the brain.[120] In this test, drug discrimination is a striking element in the system because this gives us information that will enable us to relate to the reward system. On the other hand, a focused visual attention assessment was not performed in 22q11.2DS rodent models. The mice with 22q11.2 deletion carriers evaluated that clinically significant deterioration on the ability to distinguish target stimuli from nontarget stimuli (signal detection sensitivity) and the correct response rate (hit rate) (based on 5CSRTT results). Another important result is that this model provides us with various advantages in hippocampal communication with PFC and that we can establish deeper relationships between different neurochemical findings and attention. According to the results of the experiment, the selection of amphetamine instead of modafinil was more effective in deletion mice, and while amphetamine increased the responses, modafinil decreased this response.[121] Acoustic startle reflex (prepulse inhibition [PPI]) was measured in patients diagnosed with ADHD depending on MPH use. MPH has been shown to increase the pre-warning startle reflex, and it shows us that the application of tests to examine sensorimotor disorder is as important as other behavioral tests.[122] In addition, the effects of ADHD medications on this reflex on animals are shown.[123]

Careful cluster switching task: Measuring and making sense of cognitive flexibility of mice

Cognitive impairment provides the representation of the main characteristics of many neuropsychiatric and neurodevelopmental disorders, including posttraumatic stress disorder, depression, autism spectrum disorder, schizophrenia, both prepared in animal models and the disease itself, including circuit dysfunction within the human brain, particularly within the PFC. In the ADHD animal model, the cognitive impairment protocol created enables the evaluation of animal models in this respect and contributes to scientists in better modeling of the disease.[112,124]

Conclusion and Suggestions

In the latest studies, ADHD animal models are being developed through interventions with gene and gene agents. Considering the increasing practicality and widespread use of the applications, it is predicted that the studies will gradually increase in this direction, but it is expected that models with higher etiological and structural validity will be produced with these methods. Although the findings obtained with previous models and clinical studies in humans have an important role in the development of genetic models, it should be discussed how correct it is to rely only on this basis. Neurophysiological and neuropsychological studies also support that ADHD may be due to dysfunction of the frontal structures and the areas they are associated with. Findings supporting this view include executive dysfunctions, quantitative EEG, EEG

and the electrical activity of the frontal region with evoked potentials, detection of decreased blood flow in the frontal and striatal regions with functional imaging methods. In light of this information, animal models can be created based not only on pathological, physiological etiology and symptoms such as behavioral and cognitive but also on the basis of imaging results, by affecting the neuronal networks in the brain of the experimental animal with ADHD with chemical drugs.

In the future, it may be possible to reach the most accurate model home therapist to be developed, especially by a rigorous meta-analysis of studies conducted with different animal breeds, different doses, and different types of drugs, and of course combining them with experimental methods such as brain imaging and brain neurochemistry examination. Genetic-based modeling may put ADHD beyond being a consequence of this gene change. Therefore, this could be used in the future as a genetic marker rather than a disease. Different strains should be investigated in a holistic manner with gene meta-analyzes that can be used as biomarkers. Then, different pharmacological treatments can be developed by examining their neuroscientific and neural cell networks.

Naturally, using the right animal model will be a key point, and precise statements about ADHD can be used when all the right choices are in place. In the light of all this, putting the neuroanatomy of the brain on a good basis and combining it with the neurochemistry mechanism related to ADHD will bring along models that can form not only therapeutic strategies but also the best strategies in the future. It can be used in various pharmacological agents in ADHD-related regions of the brain and develop multiple neuronal networks that inhibit dopaminergic activity. The conclusion that needs to be drawn from the review is to observe that comparing similar ancestry with different ADHD and different ancestry with the same ADHD etiologies can actually provide us with many ideas, to approach them as a whole, and perhaps by combining the right parts with each other, more appropriate experimental animal models can be created. Another point is to look at the development of ADHD by combining it with different diseases. Researchers will enable us to make progress in ADHD by understanding the appropriate molecular mechanism for ADHD in the future. In particular, conducting multidisciplinary studies using the right animal models and use different disciplines (such as imaging studies) will be supportive for this purpose. Furthermore, the cortex areas in our frontal lobe responsible for behavior are very difficult to model structurally on the experimental animal because there are many differences between the experimental animal and the human behavioral mechanism. In addition, ADHD does not have a definite etiology based on sound neurobiologically evidence, and the reason is that neuronal activity transforms into behavior cognitively and the connection between it is not fully established on a solid foundation. With the information obtained from many animal model molecular studies conducted in recent years, dopaminergic and other neurochemical neuron cells, gene, and protein analyzes, cell cultures such as astrocytes, and knock-out and transgenic models that will provide the most possible reflection of these in behavior have begun to be made. Fortunately, it can be argued that a better step has been taken to replace animal models such as spontaneously hypertensive rats that do not have a strict molecular basis, but the studies need to be carried forward. When we put together all the studies we have compiled, it is clearly seen that the brain is divided into different neuron types and lobes responsible for different functions, in fact, they are characterized by cell communications and basically by different associations with other lobes. Therefore, single viewpoints and combinations of neurobiological, neurochemical and neuroimaging, behavior, and neuroanatomy will not be sufficient, and multidisciplinary studies of brain diseases by expanding into different areas can solve many brain diseases in the future. Based on the scientific competence measures of experimental animal models while developing drugs, it has been observed that many behavioral tests and animal models cannot meet the structural competence criteria. All of them have quite a lot of disadvantages. In general, drugs developed for the symptom through visual and predictive competence achieved a certain success in experimental animals with some behavioral tests on ADHD and did not have completely satisfactory results. It is also reported in the literature that drug tolerance develops as a result of taking and discontinuing drugs at regular intervals, which is supported by studies that develop addiction to DA-derived drugs.[125-128] The side effects of the symptom, rather than the treatment, can sometimes be overlooked in experimental animals and these side effects can be observed in humans when it comes to clinical studies.[129] The emergence of such adverse situations reveals that the animal models and behavioral analysis tests used are quite open to discussion and the importance of drawing attention to a good disease etiology and pathogenesis is also important. Finally, an animal model can be created, and an ADHD model can be developed, characterized by an ACG lesion in which the sensorimotor system is adversely affected by neurochemistry. By applying drugs and tests on these disease models, more therapeutic agents can be developed as well as different animal models can be developed. In addition, the PPI test can be used to measure the degree of startle, especially in accordance with this model. As a result, this review provides suggestions and ideas that will be useful to scientists while emphasizing the studies and their shortcomings in the literature about ADHD.

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Rümeysa Rabia Kocatürk (34%) Data collection and wrote the manuscript.

Özge Öznur Özcan (33%) Designed the review, data collection and supervised the article write-up. Wrote the manuscript.

Mesut Karahan (33%) Designed the review, data collection and supervised the article write-up. Wrote the manuscript.

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Review Article

Update on Promising Biomarkers for Multiple Sclerosis

Abstract

Multiple sclerosis (MS) is a chronic autoimmune disease, in which there is chronic inflammation leading to neurodegeneration and demyelination. To detect MS at an early stage is impossible as it includes environmental factors and genetic factors as it varies from person to person. There are various methodologies that have been developed for the treatment of this disease; however, several complications as well as obstacles have been seen which are yet to be resolved. This review describes the biomarker for MS including microRNA and vaccine as a biomarker. Some of the drugs which are under phase II clinical trials are also discussed here. Testing and continuous validation is required for improvement where MS biomarkers are brought into clinical settings.

Keywords: *Biomarker, diagnosis, multiple sclerosis*

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Introduction

Multiple sclerosis (MS) is the most chronic autoimmune disease affecting the central nervous system (CNS) and generally starts at the cerebellum, spinal cord, and optic nerve.[1,2] In this, myelin sheath gets degenerated and myelin gets removed by the microglial cell. After demyelination, conduction of nerve impulses gets distorted. According to the research, MS causes one's own human body to attack the myelin. The most common symptoms are fatigue, vision problem, muscle weakness, and spasm. Some of the symptoms are very less common such as sexual dysfunction, mood swing, depression, cognitive dysfunction, bladder and bowel dysfunction, and speech and swallowing problem.[3] There are four phases of MS, i.e., relapsing–remitting disease, secondary progressive disease, and primary progressive disease. It causes functional disability which generally shows its symptoms at early childhood and is characterized by relapsing and progressive courses.[4] A large number of people are diagnosed with MS between 20 and 40 years of age. The ratio of women versus men in MS is 2:1. The number of cases reported is more in the northern state than southern states of the equator.[5] It affected approximately 2.3 million people worldwide. Around the globe, Canada is most affected by MS, followed by the UK and USA. According to surveys, the prevalence ranges from 74 to 112. There is a myth that "UK and Scootish people have MS mutated genes in their ancestors."[6] According to a recent survey done in India, the prevalence rate had increased from 1.3/1,000,000 to 8.35/1,000,000. In Kashmir, till now, no case of MS has been recorded because of the environmental (cold climate) factor. Obese individuals with high leptin levels are more vulnerable toward MS. Cigarette smoking is considered one of the major environmental factors in MS. Smoking causes DNA methylation through blood and there is a change in gene expression in the AHRR gene. Now, Vitamin D metabolism is emphasized as the environmental and genetic risk factor as before hypovitaminosis is considered as the major risk factor.[7,8] According to the current finding, Vitamin D influences the regulation of T lymphocytes. Based on the worldwide study, still hypovitaminosis is considered as the major risk factor for the globe.[9,10] High salt intake is also considered as the cause of MS rise in the level of immunoglobulin G (IgG) in cerebrospinal fluid (CSF) is considered as the major genetic factor which causes MS.[11] Epstein–Barr virus causes infection mononucleosis (IM), which is associated with an increased rate of causing MS. Change in major histocompatibility

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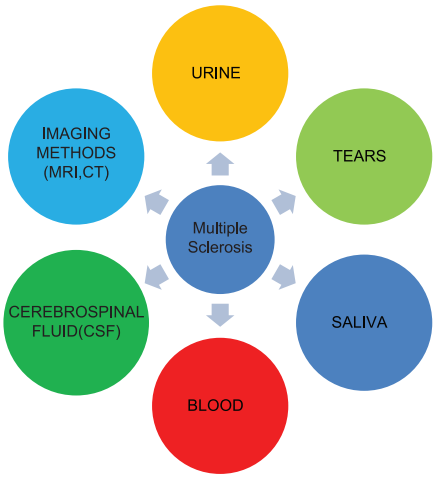

Figure 1: Different biomarkers for multiple sclerosis

complex (MHC) is also considered as the major cause of MS.[12,13]

Treatment for this disease is still not effective. The US Food and Drug Administration (FDA) and the European Medicines Agency approved injectable[1] therapies such as interferon beta (INF beta) and glatiramer acetate,[2] oral therapies (teriflunomide, dimethyl fumarate, fingolimod, and infusion therapies. In relapsing–remitting disease, IFN-β1a, IFN-β1b, and glatiramer acetate show promising effect in reducing magnetic resonance imaging (MRI) lesions.[3] It is believed that MSC transplantation in MS will reduce CNS inflammation and severe clinical disability by controlling inflammation and reducing relapsing phases.[14-18] This review focuses on the various developments and mechanisms for the treatment of MS along with its future perspectives and challenges in the advancement of MS cure.

Mechanism

MS is the most chronic autoimmune disease which causes chronic progressive neurological disability. It affects the CNS.[19] It originates from the spinal cord and optic nerve. It starts in early to middle adult life between 20 and 40 and it affects women more than men. It is idiomatic in nature and some recent evidence proves that genetic (class II MHC) and environmental factors play a major role. In environmental factors, cigarette smoking and[4] vitaminosis are considered a major cause.[20]

Two different types of episodes were seen during disease. According to neurologists, it has two phases combined active progressive and general active phase. Patient with combined active progressive MS, demyelination and neuronal axon damage whereas in normal MS there is only demyelination.[2,21] However, during the management, there is a change in the symptoms of disease, which made it difficult to diagnose 85% of the people are diagnosed with relapsing–remitting MS, 10% people with primary progressive MS, and 5% with progressive relapsing MS. After first exacerbation, the patient does not get any symptom of disease for many years. The symptoms of MS are fatigue, vision problems, vertigo and dizziness, muscle weakness and spasms, and problems with balance and coordination.[22,23] Symptoms which are less commonly seen are speech and swallowing problems, cognitive dysfunction, sexual dysfunction, depression, and mood swings. More than 30% of MS patients have moderate-to-severe jerkiness in the legs and have neuropathic pain. The most accurate test to diagnose MS is MRI, which shows accuracy in 85%–95% in symptomatic people.[24]

The diagnosis is not based on a single test. There are also few more parameters as follows:

1. Presence of two difference types of lesions (scares) in the white matter of CNS
2. Chronic inflammation in CNS is based on CSF.

In relapsing–remitting disease, three agents such as IFN-β1a, IFN-β1b, and glatiramer acetate are able to reduce the number of lesions and exacerbation. Aggressive physiotherapy is considered as the promising long-term treatment.[Figure 1]

Advancement on the diagnosis of multiple sclerosis with magnetic resonance imaging

MRI technique has proven its major impact in the last 10-20 years in the diagnosis of MS. It is able to detect lesions. At present, researchers are focusing on MRI T2 sequences. Fast spin echo-lied turbo spin echo and fluid-attenuated inversion recovery help to visualize lesions. In a recent study in Manitoba, Canada, 2763 MS cases were reported, in which individuals were less than 50 years. Gray matter is the most common finding in all MRI reports. Research performed an experiment and monitored a brain to find association between NFN level and last 10-year BPF (whole-brain atrophy). The results show a negative correlation between 5-year NFN level with 10-year NFN level and we found that there is an increase in fatigue level. These data prove that the patient needs more aggressive rehabilitation. When we study the brain at 3 Tesla, there is NAWN without tissue or GM atrophy and these data prove that functional dissociation can be the main cause of fatigue.[25,26]

Advancement on the diagnosis of multiple sclerosis with cerebrospinal fluid – human data

The pathogenesis of MS is still unknown. The typical feature of MS is the presence of oligoclonal immunoglobulin in CSF.[27] In a recent study out of 107 patients, 40 children with less than 11 years had higher CSF-NBC count than 67 adolescents. Young children have higher neutrophil count than that in CSF in the first sign of MS. The above study was done on 254 patients with PPMS. From 4 different university hospitals in Germany. In these routine CSF parameters, there was no change in cell

count and albumin concentration in CSF and no change in normal values. 24.6% of the patients with elevated CSF serum albumin quotient (QALB) while 91.1%intrathecal IgG oligoclonal (OCBS) bound was detected in person. Expanded disability statement scale says that CSF lactate level, as well as IgM and IgA synthesis, are correlated with progression in disease every year.[28,29] When oligoclonal immunoglobulin is present on CSF, it is called oligoclonal bands (OCB), which is detected by isoelectric focusing.[30,31] Genetic polymorphisms in loci on the human chromosome 6, 14, 18 had been identified as major determinants of CSF antibody level in MS.

Advancement on the diagnosis of multiple sclerosis by checking pathway on mouse model

The NRF2 pathway is considered as a potential biomarker for dimethyl fumarate in the treatment of MS. Interleukin 33 (IL-33) pathway in CNS under MS is still unknown.[32] A researcher checks the cellular expression of IL-33 and its receptor ST2 by immunohistochemistry in the brain tissues of MS patients under appropriate controls *in vitro* using a myelinating culture system. The results show that IL-33 is expressed by neurons, astrocytes, and microglia as well as oligodendrocytes, while ST2 is expressed in the lesions by oligodendrocytes and within and around axons, and the expression levels and patterns of IL-33 and ST2 in the lesions of acute and chronic MS patients' brain samples are enhanced compared with the healthy brain tissues.[11] When this experiment data were performed using rat myelinating cocultures show that IL-33 plays an important role in MS development by inhibiting CNS myelination. IL-1RI induces human Th17 cell differentiation in an IRF4-dependent manner. It has been identified that IL-1RI-mediated signaling pathway is constitutively activated, which increases Th17 cell differentiation in IRF4-dependent manner in patients with RRMS.[33] It will be a useful therapeutic approach in remyelination in MS patients if we target the PI3K/mTOR pathway.[34,35]

Methods for Biomarker Development – State of the Art and Future Strategies

There is no need for ethics committee approval.

Diagnosis of MS with functional MRI at an early age should fulfill two criteria. First, the lesion should spread across the various regions of CNS and the second formation of the new lesion over baseline time. The advancement in the field of proteomics leads to the development of biological fluid marker CSF.[36] In PPMS phase, the level of oxidation products is fourfold higher than other phase patients, but there is no clinically proven evidence between the worse clinical course and oxidative stress. Neurovax and MIS416 is a vaccine, which is under the phase II clinical trial. Personalized medicine is the latest therapeutic approach, which states which therapy suits well for which single individual patient.[37,38] Bone marrow infusion improves visual acuity and response latency (reflex action). microRNAs are noncoding RNAs and their function is post-transcriptional regulation of gene expression and RNA silencing. The upregulation of miR-376c-3p is seen in PPMS and overexpression of miR-191-5p was seen in both subtypes of progressive MS.[39]

Countering multiple sclerosis

Through the development of adult stem cells, it is believed that adult stem cells can treat MS. There is a hope that MSCs have the immunomodulatory and neuroprosthetic effect that adult stem cells can repair CNS and differentiate into neural cells. The ideal therapy for MS to prevent disability to improve quality of life. The US FDA and the European Medicine Agency have proved dimethyl fumarate as an effective drug as it has a neuroprotective effect and immunomodulatory activity on MS patients. Another drug, fingolimod, was approved in 2010 for the treatment of the patient from relapsing–remitting (RR) form of MS. It has the capability to reduce disability and exacerbations. Teriflunomide (pyrimidine), it synthesis Mitox Amare inhibit T cells, B cells, and macrophages which reduce SPMS, relapsing MS, and CRMS.[40,41] Current therapies for MS include inferno beta and glc pirate acetate, which decrease the number of replaces partially and prevent disability. According to the latest research, dimethyl fumarate gives better response than teriflunomide in RRMS phase. Disease-modifying therapies reduce inflammation in relapsing MS and provide neuroprotection and neuropain in progressive MS.[42,43]

Biotin is vitamin B which shows it results in SPMS and PPMS phase of MS. Hematopoietic stem cell transplantation boosts up the immune system to defend against an advanced form of MS.[44,45]

Future Challenge and Conclusion

Future research should be related to daily life as an environmental and genetic factor has an equal contribution in causing MS. It was clearly highlighted in the review that the reason for it is still unknown. The drug can only reduce the symptoms in RRMS. Some drugs such as fluoxetine, lithium, oxcarbazepine, riluzole, and amiloride are under clinical trials for the treatment of MS. Phase II clinical trial of adrenocorticotropic hormone therapy is still going, which seems to be effective in progressive MS. Ibudilast and Idebenone are in the phase trial II PPMS and lipoic acid for SPMS phase II clinical trial.[6] MRI and CSF are still playing a major role in detecting MS, but to detect MS at first stage is impossible. The development of novel biomarkers now seems impossible because several candidates lack reproducibility, accessibility, and specificity. There is no actual treatment because of lack of study of PMS pathogenesis. PMS is still considered due to axonal damage and myelin loss. The patient's response to drugs

depends on various genetic factors. For complex mechanism disease like MS, multiple biomarkers are needed to detect the phase of disease at different levels. Pharmacogenetics is also considered to play a major in MS as it links the genetic mechanism and drug with the MS. As the genetic component also plays a major role in a biomarker for MS, different patients have different responses toward the treatment. Protein level, immune dysfunction, oxidative stress, and neural degeneration will prove better therapeutic biomarkers if they become successful in clinical trials. The aim of the review is to focus on all types of biomarker available. To bring biomarkers into validation, continuous testing is required and considered as a time-consuming process.

Patient informed consent

There is no need for patient informed consent.

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Faizan Ahmad (50%- Conducting a literature review)

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Original Article

The Effect of Memorizing the Quran on Cognitive Functions

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Abstract

Background: Memorizing the Quran is an education continuing from the early periods of Islamic education until today. Although this education started in the past to protect the Quran, nowadays, it is continuing as a tradition. **Aims and Objectives:** The main purpose of this study is to investigate the effects of memorizing the Quran on certain cognitive functions of individuals. **Materials and Methods:** The scope of the study is limited to 18 female and 15 male students who have been studying in the 5th, 6th, and 7th grades of Anatolian Imam Preacher Secondary Schools in different districts of İstanbul. After Demographic Information Questionnaire was used, California Verbal Learning Test children's version, Wechsler Memory Scale revised visual reproduction subtest, Trail Making Test, and Verbal Fluency Test were applied twice to collect data about individuals before and after memorization training. **Results:** Findings demonstrated that there is a statistically significant difference in verbal learning, visual learning, attention speed, and phonemic and semantic fluency before and after memorization training. **Conclusion:** In conclusion, memorizing the Quran has positive impacts on verbal and visual memory, attention processes, and lexical and semantic fluency of individuals. It is important with regard to eliminate emptiness in the literature. In future studies, it can be investigated the effects of textual memorization in a foreign language on brain structures and connections.

Keywords: *Childhood education, cognitive processes, memorizing Quran, memory, neuropsychological tests*

Introduction

Hıfz is an education system that is based on memorizing the holy book Quran by using encoding, storage, and retrieval processes of memory.[1] This education system requires to memorize an increasing number of words day by day; therefore, it is also called textual memorization.[2] Since the Ottoman period, traditional hıfz education system is applied in Turkey. Quran is divided into 30 chapters and each chapter is comprised 20 pages. Traditional method starts with memorization of the last page of every chapter and then the second last page of every chapter and so on.[3]

According to the information processing theory, attention and consolidation significantly affect learning. In hıfz education, texts are first stored in sensory memory through visual and auditory senses, then moved to short-term memory with attention and then transferred to long-term memory with consolidation Salehuddin (2018) is found that texts are first stored in sensory memory through visual and auditory senses, then moved to short term memory with attention and then transferred to long term memory with consolidation, in hıfz education. As texts are strengthened by reading continuously and regularly, synaptic connections get more stronger in the brain, and so changes occur in cell and brain circuits.[4] Studies show that textual memorization causes an increased gray matter in certain brain regions and a direct change in brain structures.[2] When the literature and the results are reviewed, there is no such study on the effect of memorizing the Quran on cognitive functions.

With the change of education policy since 2012 in Turkey, hıfz school projects have been activated. It is a good opportunity for those who want to memorize the Quran during the period of secondary school.[5] "The Project of Hıfz with Formal Education" that carries out together by the

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Presidency of Religious Affairs (DİB) and Ministry of National Education provides students the opportunity of memorizing the Quran after 4 years of primary school.[6]

The aim of this study is to seek an answer what is the effect of memorizing the Quran on cognitive functions such as verbal memory, visual memory, attention, and verbal fluency processes. The difference in the current study is that it evaluates hıfz education in the context of mentioned cognitive functions and it is a quantitative study about hıfz education.

Materials and Methods

The ethics committee approval has been obtained from Uskudar University Non Interventional Research Ethics Committee report number of B.08.6.YÖK.2. ÜS.0.05.0.06/2018/1033 (24 December 2018).

The study is started after the ethics committee approval was obtained from Üsküdar University on December 24, 2018, with the number 1033. This research was conducted with 18 female and 15 male students who have been studying in the 5th, 6th, and 7th grades of Anatolian Imam Preacher Secondary Schools in different districts of İstanbul. Participants get involved in the hıfz education program which is applied in Mehmet Akif Ersoy and Mustafa Can Quran Courses within the Presidency of Religious Affairs. While this study was conducted with female students from January to June in 2019, it was handled with male students from December 2019 to August 2020.

This study is a quantitative research with pre- and posttest experimental design. This experimental design was used to determine the changes over time in cognitive functions as a dependent variable. Four neuropsychological tests were applied to evaluate certain cognitive performances before starting the study. These tests were applied once again 5½ months later for females and 8 months later for males. The cognitive functions that measured by the neuropsychological tests are verbal memory, visual memory, attention, and verbal fluency processes. To examine the effect of memorizing the Quran (as an independent variable) on cognitive functions (as a dependent variable), the data obtained from pre- and posttest values were compared with each other and converted into statistics.

Instruments

Demographic Information Questionnaire

This form involves information about student's age, number of siblings, medication use, studying environment, hand preference, education, and socioeconomic levels of parents.

California Verbal Learning Test-children's version

The California Verbal Learning Test-children's version is used to examine in many aspects of auditory and verbal learning for children.[7] It consists of 11 subtests: immediate recall (IR) measures learning slope and continuity of learning in time; distraction variable measures proactive interference which means that old memories disrupt new memories; short-delay free recall measures short-term verbal memory; long-delay free recall measures long-term verbal memory and retroactive interference which means that new memories disrupt old memories; short-delay cued recall measures short-term memory with category clued; long-delay cued recall measures long-term memory with category clued; perseveration (P) measures words repeated in a trial; intrusions (I) represent to say extra-list intrusions other than target words; semantic clustering (SC) shows the efficiency of learning styles and strategies; discriminability (D) gives information about the ability to distinguish target words from other category words; and response bias (RB) is the tendency to identify words as belonging on the target list.[8,9]

Wechsler Memory Scale-revised visual reproduction subtest

The Wechsler Memory Scale-revised is one of the most common and useful neuropsychological testing.[10] Visual Reproduction Subtest which measures the visual capacity of individuals is used in this study. The score of immediate visual reproduction (IVR) gives information about short-term visual memory. The score of delayed visual reproduction (DVR) provides information about long-term visual memory.[11]

Trail Making Test

Trail Making Test (TMT) is a neuropsychological test which is used to assess visual attention, task switching as well as executive functions. It consists of A and B forms.[12] Trail making A form (TMT-A) provides information about visual search speed and scanning, it measures psychomotor and attention speed. Trail making B form (TMT-B) provides information about shift attention between one task and another, it measures response inhibition, mental flexibility, and visual search speed.[13] When A duration is subtracted from B duration TMT (A-B), the effect of the speed variable disappears and it gives a clearer information about attention, flexibility, and task switching. When A duration is added B duration TMT (A + B), it gives general information about visual scanning and attention.[14-16]

Verbal Fluency Test

The Verbal Fluency Test provides information on the ability of producing as many as words possible from a category in a certain time period. The test is used to evaluate executive functions and it consists of three different parts and their perseverations.[17] Counting animal (CA) measures semantic fluency; CA perseveration measures stereotypes repetitions; Controlled Oral Word Association (COWA) measures phonemic fluency; COWA perseveration (COWAP) measures repetition in phonemic fluency; sequential category naming (SCN) measures the ability to switch between two categories; and SCN perseveration measures repetition in semantic fluency.[18,19]

Data analysis

The data obtained from this study were analyzed using the software package SPSS® version 20.0, IBM Inc., Chicago, IL, USA. Paired sample *t*-test was used for normally distributed data, Wilcoxon signed-rank test was used for not normally distributed data to examine differences between before and after cognitive performances, and also independent sample *t*-test was used to evaluate gender differences in their performances. The data were analyzed at a 95% confidence interval and $P < 0.05$ significance level.

Results

A total of 33 participants took part in the study. About 54.5% of them were girls, 87.9% of them do not use a medication at full strength, 57.6% of them have separate rooms, and 87.9% of them use their right hands. It has been defined that 45.5% of monthly income was at the middle level. Majority (36.4%) of students' mother were at the primary education level and 24.2% of their fathers were at the high school education level. The average age of the students was 11.52 ± 1.25, and the average number of siblings was 3.18 ± 1.01.

The results from Table 1 show that memorizing the Quran significantly influences the IR, predisposition of distractive variables, short- and long-delay free and cued recalls, SC, and discriminability processes of individuals ($P < 0.01$). Moreover, there is no statistically significant difference in perseveration, RB, and intrusions ($P > 0.05$).

As shown in Table 2, memorizing the Quran significantly influences the immediate and delayed visual reproduction of individuals ($P < 0.001$).

As shown in Table 3, there is a statistically significant difference in terms of duration to complete TMT A and B Form between pre- and postmemorization training of individuals ($P < 0.001$). Besides that, there is a statistically significant difference in durations of TMT A ± B Form between before and after memorization training ($P < 0.01$).

As shown in Table 4, individuals' pre and post performances in CA, controlled oral word association, and sequential category naming are significantly influenced from memorizing Quran education ($P < 0.05$). However, there is no statistically significant difference before and after education in terms of perseveration of CA, controlled oral word association, and sequential category naming performances ($P > 0.05$).

As shown in Table 5, there is no statistically significant difference in terms of changes in IR, short- and long-delay free recall, immediate and delayed visual reproduction, trail making B form duration, CA, controlled oral word association, and sequential category naming before and after memorization training according to gender ($P > 0.05$). There is only found a statistically significant difference in duration to complete TMT B form pre and post training in favor of females ($P < 0.05$).

Table 1: California Verbal Learning Test-children's Version changes

CVLT-C subtests	Pretest (*n*=33)	Posttest (*n*=33)	*t*	*P**
IR	46.61±7.35	59.70±7.09	−11.192	0.000
DV	5.18±1.91	6.82±2.22	−3.708	0.001
SDFR	9.33±2.61	12.09±2.11	−6.183	0.000
SDCR	9.45±2.29	12.52±2.21	−8.470	0.000
LDFR	9.61±2.20	12.82±1.92	−8.065	0.000
LDCR	9.70±2.20	12.79±1.76	−8.292	0.000
P	6.85±5.56	8.03±4.74	−1.126	0.268
SC	20.79±6.00	35.48±13.91	−6.081	0.000
RB	0.041±0.35	0.032±0.15	0.141	0.889
CVLT-C subtests	**Pretest (*n*=33)**	**Posttest (*n*=33)**	***Z***	***P****
D	94.54±4.55	97.97±2.17	−4.013	0.000
I	2.61±3.24	2.79±3.87	−0.135	0.892

*Paired sample *t*-test, **Wilcoxon signed-rank test. IR: Immediate recall, DV: Distraction variables, SDFR: Short-delay free recall, SDCR: Short-delay cued recall, LDFR: Long-delay free recall, LDCR: Long-delay cued recall, P: Perseveration, SC: Semantic clustering, RB: Response bias, D: Discriminability, I: Intrusions

Table 2: Wechsler Memory Scale-revised visual reproduction subtest changes

WMS-R subtests	Pretest (*n*=33)	Posttest (*n*=33)	*t*	*P**
IVR	8.91±2.40	12.36±2.23	−9.415	0.000
DVR	7.58±2.82	11.91±2.67	−9.423	0.000

*Paired sample *t*-test. IVR: Immediate visual reproduction, DVR: Delayed visual reproduction

Table 3: Trail Making Test changes

TMT subtests	Pretest (*n*=33)	Posttest (*n*=33)	*t*	*P**
TMT (A)	42.58±12.99	32.82±10.20	7.191	0.000
TMT (B)	102.97±35.25	75.33±20.56	5.133	0.000
TMT (A-B)	60.39±32.53	42.52±21.38	3.044	0.005
TMT (A+B)	145.55±42.01	108.15±24.42	7.176	0.000

*Paired sample *t*-test. TMT (A): Trail making A duration, TMT (B): Trail making B duration, TMT (A−B): Trail making A minus B duration, TMT (A+B): Trail making A plus B duration

Discussion

This study was conducted to determine the effect of memorization training on cognitive functions. Individuals who took the education of Quran memorization were examined in terms of verbal memory, visual memory, attention speed, and verbal fluency performances. There are many studies related to the qualification of hıfz education in the literature, but there is no quantitative study related to the effect of hıfz education on cognitive functions. Therefore, this research will set light to future studies.

In literature, it has been reported that memorizing the Quran includes many benefits for improving memory.[1,20] Methods such as visualization of words, consecutive succession, individually mnemonic coding, and grouping are used

Table 4: Verbal Fluency Test changes

VFT subtests	Pretest (*n*=33)	Posttest (*n*=33)	*t*	*P**
CA	17.42±4.56	19.30±5.16	−2.125	0.041
COWA	21.24±9.61	27.58±8.72	−5.837	0.000
COWAP	0.39±0.65	0.61±0.82	−1.269	0.214
SCN	7.15±2.06	8.30±1.94	−2.510	0.017
SCNP	0.15±0.36	0.33±0.47	−1.644	0.110
VFT subtests	**Pretest (*n*=33)**	**Posttest (*n*=33)**	***Z***	***P*****
CAP	0.58±1.20	0.24±0.50	−1.268	0.205

*Paired sample *t*-test, **Wilcoxon signed-rank test. CA: Counting animal, COWA: Controlled oral word association, COWAP: Controlled Oral Word Association perseveration, SCN: Sequential category naming, SCNP: Sequential category naming perseveration, CAP: Counting animal perseveration

Table 5: *T*-test results comparing males and females pre- and posttest changes

Pre-post test changes	Male (*n*=15)	Female (*n*=18)	*P**
IR	12.33±5.93	13.72±7.41	0.563
SDFR	2.26±3.03	3.16±2.09	0.323
LDFR	3.40±2.58	3.05±2.07	0.674
IVR	3.80±1.82	3.16±2.33	0.399
DVR	5.13±2.74	3.66±2.42	0.114
TMT (A)	12.66±7.36	7.33±7.48	0.049
TMT (B)	34.60±39.41	21.83±21.03	0.244
CA	3.46±5.57	0.55±4.34	0.102
COWA	0.26±1.03	0.16±0.92	0.771
SCN	1.00±2.29	1.27±2.94	0.768

*Independent sample *t*-test. IR: Immediate recall, SDFR: Short-delay free recall, LDFR: Long-delay free recall, IVR: Immediate visual reproduction, DVR: Delayed visual reproduction, TMT (A):Trail making A duration, TMT (B): Trail making B duration, CA: Counting animal, COWA: Controlled oral word association, SCN: Sequential category naming

during hıfz education.[1] As a result of researches, it has been revealed that if more and more words are memorized every day, it will prepare and develop the memory by increasing its capacity (Salehuddin, 2018). Researchers found that individuals who took the education of Quran memorization show high academic success because several cognitive functions are activated at the same time in textual memorization.[1] Furthermore, they found that individual's posttraining cognitive performances were positively affected.[20]

According to a study conducted on individuals who took hıfz education for 1 year, it has been found increased gray matter volumes in the anterior cingulate gyrus, orbitofrontal cortex, left inferior temporal gyrus, right occipitotemporal gyrus, left inferior parietal gyrus, right perirhinal cortex, superior parietal cortex, and posterior and anterior cingulate cortex.[2] These brain regions are generally associated with sensory, decision-making, adaptation to unexpected results, memory, recognition, reading, and pronunciation. It is an indication that the cell and brain circuits change with experiences.[4] Individuals who memorize the Quran constantly can do that activity with the ability of neuroplasticity.

If words or texts are memorized in a foreign language by repeating word by word without learning of meaning deeply, it is called rote memorization. This situation has an important place in word retrieval.[21] Rote memorization takes a large place in hıfz education. A statistically significant difference in short- and long-term verbal memory skills of participants after hıfz education is compatible with literature. Besides, the results of literature show that memorization training causes increased discrimination skill, continuity of learning in time, and efficiency in learning strategies. These are indicators of a good memory process. Ebbinghaus who worked on memorization of nonsense syllables suggested that association is the basis of remembering and he showed the effect of environmental variables and associations on remembered information.[22,23] In this study, the increase of short- and long-delay cued recall supports previous researches, and the increase of predisposition of disruptive stimuli after memorization training shows that the old learning does not make later learning difficulties. In addition to all these, this study showed that there is no statistically significant difference in the individuals' intrusions by saying new words other than the target words and recognizing words which is learned previously.

Individuals who recite verses from any page visualize and recall written words in detail. In the light of literature, photographic memory term is used to represent this situation.[24] This study revealed increased immediate- and long-term visual memory capacity of individuals after memorization training.

According to the lexical approach, language consists of word information. Reading in a foreign language using encoding and recalling processes positively affects on working memory.[25,26] In Quran memorization training, words and texts are learned based on vocabulary rather than grammar. This study shows the increased psychomotor and attention speed, response inhibition, cognitive flexibility, visual scanning speed, general visual monitoring, and working memory performances of participants after hıfz education. The findings from the current study are consistent with previous studies.

Studies on memory show that semantic and syntactic factors have facilitating effect on learning. Semantic fluency represents semantic factors and it is based on producing words related to the category; phonemic fluency represents syntactic factors and it is based on generating sound-related words.[27,28] In this study, a statistically significant difference in phonemic and semantic fluency of participants is found after memorization training, it supports the relevant literature studies. The frontal lobe has an important function in phonemic fluency according

to the researches.[29,30] The phonemic fluency result of this study suggests that frontal lobe functioning of the individuals became syntactically better after memorization training. According to the current study, there is a fact that a statistically significant difference in phonemic fluency is stronger than the statistically significant difference in semantic fluency, so this suggests that words are realized with a sound-oriented rather than a category-oriented in hıfz education. In addition, the sample in this study did not know the Arabic language, this phenomenon supports the idea related to phonemic fluency. Furthermore, it emerges as a new research topic in semantic fluency. Along with these, it is determined that there is a significant increase in students' ability to switching between categories.

Studies have shown that if the retrieval process is extremely emphasized, texts will be permanent in long-term memory.[31] Therefore, it is thought that there might be a statistically significant difference in perseverations of individuals who took hıfz education. However, the term of perseveration mentioned in the literature does not represent transferring information from short-term to long-term memory. For this reason, the lack of a statistically significant difference in verbal learning, phonemic and semantic fluency perseverations in this study could not be explained in the light of the information in the literature.

The changes pre and postmemorization education were evaluated according to gender. It was examined whether there is a brain-based relationship between gender and learning new word processes in literature studies. Researchers have been found that female students perform better than boys in planning and attention processes.[32] In this study, it is revealed that continuity of learning over time, long- and short-term verbal memory, long- and short-term visual memory, cognitive flexibility, and phonemic and semantic fluency changes between pre and post training do not differ by gender, however, it is found a difference in psychomotor and attention speed in favor of female students.

This research is limited to the results of the scales applied to students who took memorizing Quran education and 2018–2019 and 2019–2020 academic years. It is assumed that the sample represents the general population in this study. To eliminate these limitations, it is important to carry out studies with a larger sample that represents the general population.

Sapuan *et al*.[2] are found that textual memorization creates extensive connections in the brain using brain imaging methods. In future studies, it can be provided to determine the effect of memorizing the Quran on possible brain regions. In addition, it can be studied whether the significant increase in cognitive functions is permanent or short term. However, it can be considered the effect of memorizing a text without understanding its meaning on cognitive functions in terms of semantic processing. If it is considered mentioned factors in further studies, it will be made important contributions to the literature.

Patient informed consent

There is no need for patient informed consent.

Ethics committee approval

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Conflicts of interest

There are no conflicts of interest to declare.

Author contribution area and rate

Sümeyye Şirin (%50): Data acquisition, interpretation of data for the study, collection of review of literature, wrote the manuscript.

Barış Metin (%40): conception/design of the work, help in data analysis, critical revision for important intellectual content.

Nevzat Tarhan (%10): guided in developing the extent of the study and contributed to the manuscript with his critiques.

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Original Article

Comparison and Examination of the Death Anxiety of Parents with and Without Having Mental Retarded Children

Abstract

Aims and Objectives: The aim of this study is to have children with and without mental retardation (MR) (diagnosed with MR), it is to compare and examine parents' death anxiety. **Materials and Methods:** The research is based on the screening model. The sample group of the study consists of 120 people in total, consisting of parents (n = 60) of children who are followed up in a private counseling and research center due to the presence of intellectual disability, and parents with typically developed children (n = 60) as the comparison group. Sociodemographic information of the participants, who could be included in the study on a voluntary basis, was filled in by the researcher using face to face interview method using the Sociodemographic Information Form, and their death anxiety levels were evaluated with the Multidimensional Evaluation Inventory for Death and Dying. In comparing the quantitative data of the study, the t test, which is the two independent variable tests, was used to analyze the difference between the two parametric groups. The relationship between the scales was tested with Pearson Correlation analysis. Multiple linear regression was used to see the effect of independent variables on the dependent variable. **Results:** As a result of the research findings, it was found that there are statistically significant differences ($P < 0.05$) between the scores of the compared groups. Death anxiety of parents with mentally retarded children was found to be higher than parents of typically developed children. **Conclusion:** This research is important in terms of providing the opportunity for cross cultural comparison and contributing to the policies to be developed on the subject..

Keywords: *Death, death anxiety, mental retardation, parents*

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Introduction

Mental retardation (MR), which is among neurodevelopmental disorders, is the inadequacy of adaptive skills and behaviors according to the person's own age and culture.[1] Adaptive skills cover areas related to communication, self-care, family life, interpersonal relationships, academic skills, health, and safety. Confirmed by both clinical evaluation and an accepted measure of intelligence, it is characterized by deficiencies in intellectual functions such as reasoning, problem-solving, abstract thinking, designing, judging, learning, and experiencing at school.[2,3] MR often occurs with other developmental disabilities, and the term "mental and developmental disabilities" is used to denote the comorbidity associated with both conditions.[4]

MR could be a condition, a syndrome, or a symptom. According to the definition made by the American Mental Retardation Association (American Association on Mental Disabilities), it is a below-average intelligence function that occurs in the developmental period and is found with dysfunctions in adaptive behavior. This definition stipulates the current compliance problem and limitation in functionality in MR.[5] Along with below-average intelligence function, difficulties are experienced in communication, self-care, life at home, social skills, and social usefulness. In addition to these, it is predicted to have two or more disorders in self-orientation, health protection, academic functioning, and field of study. Causes such as hereditary factors, chromosomal abnormalities, pregnancy and birth problems, drug use during pregnancy, and close blood ties during marriage lead to the development of mental disability.[6]

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It has been reported that mental problems such as somatic complaints, depression, and anxiety disorder are more common in parents with mentally retarded children compared to other parents.[7] In a meta-analysis examining 162 studies on the mental and physical health of caregivers of children with special needs, 23 different factors that may have an impact on the health of caregivers have been identified. It has been reported that social determinants, caregiver-related variables, characteristics of the disabled child, family characteristics, and support factors can affect caregiver health.[8] On the other hand, an increasing number of studies indicate a relationship between parent coping strategies and mental health.[9,10]

Families of children with special needs may face stigma and social isolation.[11] Social isolation is an important issue that needs to be addressed, experienced by mentally retarded children and their parents, and can cause depression. Families using rehabilitation, mental health, or general health services are thought to have a very high probability of financial loss, job change, and sleep disturbance.[8] The level of disability, problematic behaviors, caregiver health, social and individual characteristics affect the quality of life of caregivers and children with MR. It has been reported that there is a relationship between social support and parental stress management and resilience, and the stress and depression levels of mothers who think that they receive little support increase.[12] Social services of countries are effective on the stress levels of families with mentally retarded children. The level of competence of services is an important determinant. It is thought that there is a relationship between social support and parental stress management and resilience.[10]

Death is a phenomenon that has occupied the minds that have been understood throughout human history.[13] The desire to live and to survive drive is the greatest inspiration of man. What provides this is the fear created by the reality of death in man. This fear enables the person to make quick and instant decisions in the face of any threat perception and to survive by activating the whole organism.[14] The perception of death as creepy, frightening, and desperate stems from the psychological structuring of the human being. Existential theorists have argued that the main source of anxiety is death anxiety.[15] As a multidimensional concept, death contains many dynamics within it. The philosophical, religious, moral, legal, social, emotional, and mystical dimensions of death are the results of trying to understand the phenomenon of death since the existence of humanity.[16] Some of these dimensions include the anxiety of the unknown, the fear of losing or leaving loved ones behind, the belief that death can be painful, the feeling of unfinishedness, and the sadness created by the fact that no longer exists. Death anxiety is universal. Denying death, challenging it, wanting or accepting death are attitudes that can develop in the face of death.[17]

The number of children with special needs mental deficiency is showing 29% according to data Turkey Statistical Institute.[18] New regulations are made to increase the quality of life of children with special needs and caregivers around the world. This issue is on the agenda of many countries' health and social policies. In this context, any research that will raise awareness will serve public health. Those with mental disabilities among children with special needs show significant individual differences among themselves. A better understanding of the mentally disabled individuals and their families requires new social policies and global structuring. The insufficiency of social policies created to benefit disadvantaged groups can cause negative consequences. Death anxiety experienced by parents with mentally retarded children is considered as one of these negative consequences. Among the concerns of parents who have a disabled child are the belief that no one will take care of their children after death, and the lack of social facilities and support.[19]

One of the reasons for this study is that death anxiety has an important place in human life for whatever reason. In this study, it was aimed to compare the death anxiety of parents with and without mentally retarded children and to investigate the relationship with sociodemographic variables. Death anxiety-related research both in Turkey investigating the death anxiety of parents of mentally retarded children is limited, although there are very few studies in the world. Ongoing research on individuals with special needs is important for the development of new policies and services.

Methods

The ethics committee approval has been obtained from the Uskudar University noninterventional research ethics committee (2018/897).

Sample

The sample group of the study consists of 120 people in total, consisting of parents of children (n = 60) who are followed up in a special guidance and research center due to mental disability, and parents with children who do not show mental disability (n = 60) as the comparison group. The individuals in the study and comparison groups were informed by the researcher about the study and their written consent was obtained that they agreed to participate in the study. The sample of the study consisted of people selected on the basis of appropriate sampling methods and volunteering. Participants' response times ranged from 15 to 20 min. Inclusion criteria for the study group of the research; being a parent with a child with special needs, being over the age of 18, not having a permanent psychiatric disorder with continuing treatment, having literacy and mental competence to understand reading, and being volunteer. Although the inclusion criteria are the same for the comparison group of the study, there is

a condition of having a parent with a child without any disability.

Measurement instruments

Sociodemographic information of the participants, who could be included in the study on a voluntary basis, was filled in by the researcher using face-to-face interview method using the Sociodemographic Information Form, and their death anxiety levels were evaluated with the Multidimensional Evaluation Inventory for Death and Dying.

Sociodemographic information form

With the form prepared by the researcher, information such as gender, age, marital status, number of children, physical-mental illness, and employment status was questioned and filled in by the researcher with a face-to-face interview.

Multidimensional evaluation inventory for death and dying

The inventory measure death anxiety and death acceptance of the validity and reliability study in Turkey by Zorlu and Ünübol were made in 2018,[13] the scale was adapted to Turkish. The scale has two dimensions as fear and acceptance. The ratio of explaining the total variance of the fear subscale is 43.44%, and the reliability coefficient of Cronbach is 0.950. The explanation rate of the total variance of the acceptance subscale is 50.21%; Cronbach's reliability coefficient is 0.678. The factor distribution of the subscales is different from the original scale. Subscale names have been adapted according to Turkish culture. According to these results, it has been shown that the Turkish Form of ÖÇDE-F is a scale with high validity and reliability.[13]

Data analysis

While analyzing the data obtained in this study, the data were entered into the computer as numerical expressions and statistical analyzes were made using the IBM Corp. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp, Released 2017. Before starting the analysis, the data were examined in terms of normal distribution. It was observed that all scales showed normal distribution in the control of Kurtosis-Skewness values performed

Table 1: Distribution of the sample by demographic variables

	Frequency (%)	
	Without having children with MR diagnosis	**Having children with MR diagnosis**
Gender		
Male	30 (50.0)	30 (50.0)
Female	30 (50.0)	30 (50.0)
Total	60 (100.0)	60 (100.0)
Age		
25-35	17 (28.3)	11 (18.3)
36-45	21 (35.0)	23 (38.3)
46-55	1 (1.7)	16 (26.7)
55 and above	2 (3.3)	1 (1.7)
Total	41 (68.3)	51 (85.0)
Missing	19 (31.7)	9 (15.0)
Total	60 (100.0)	60 (100.0)
Education		
Secondary school	5 (8.3)	32 (53.3)
High school	10 (16.7)	16 (26.7)
Undergraduate	20 (33.3)	2 (3.3)
Graduate	10 (16.7)	5 (8.3)
Total	45 (75.0)	55 (91.7)
Missing	15 (25.0)	5 (8.3)
Total	60 (100.0)	60 (100.0)
Marital status		
Single	1 (1.7)	0 (0)
Married	54 (90.0)	58 (96.7)
Divorced	5 (8.3)	2 (3.3)
Total	60 (100.0)	60 (100.0)
Religion		
Muslim	59 (98.3)	60 (100.0)
Missing	1 (1.7)	
Total	60 (100.0)	

MR: Mental retardation

for the analysis of normality distribution in the sample group of research variables. Since the values in all scales and subscales are between −2 and +2, it shows a normal distribution. In the analysis applied, 95% reliability level was taken as basis. In order to analyze the difference between the two parametric groups in comparing quantitative data, two independent variables tests, the *t*-test, were used. The relationship between the scales was tested with Pearson Correlation analysis. Multiple linear regression was used to see the effect of independent variables on the dependent variable. For statistical significance, $P < 0.05$ was taken.

Results

This section contains the findings obtained from the demographic information form prepared by the researcher.

As seen in the table [Table 1], 50.0% of the group without MR children were male, 50.0% were female, 28.3% were between the ages of 25 and 35, 35.0% were between the ages of 36 and 45, 1.7% were between the ages of 46 and 55, and 3.3% are 55 years or older. About 8.3% of this group are secondary school graduates, 16.7% are high school graduates, 33.3% are university graduates, 16.7% are graduate and above, 1.7% are single, 90.0% are married, 8.3% are divorced, 98.3% are Muslim. In the group with MR children, 50.0% male, 50.0% female, 18.3% between 25 and 35 years old, 38.3% between 36 and 45 years old, 26.7% between 46 and 55 years old, 1.7% 55 years and above, 53.3% secondary school graduate, 26.7% high school graduate, 3.3% university graduate, 8.3% master's and above, 96.7% married, 833% divorced, and 100.0% of the participants are Muslim.

As seen in the table [Table 2], the mean of the Fear Sub-Dimension is 2.11 (standard deviation [SD] = 0.68), the average of the Acceptance Sub-Dimension is 3.38 (SD = 0.60), the average of the Insurgency Sub-dimension is 1.41 (SD = 0.63), and its average is 2.55 (SS = 0.83).

As can be understood from the table [Table 3], as a result of the independent group *t*-test conducted to determine

Table 2: Descriptive statistics of the multidimensional evaluation scale for death and dying

Subscales	*n*	Minimum	Maximum	$\bar{X}$	SD
Fear	120	1.04	4.00	2.11	0.68
Acceptance	120	1.43	4.00	3.38	0.60
Rebellion	120	1.00	4.00	1.42	0.63
Denial	120	1.00	4.00	2.55	0.83

SD: Standard deviation

Table 3: Results of the independent group *t*-test conducted to test the significance of the difference between the scores of the multidimensional scale of death and death and its subdimensions according to the group variable of the sample

	n	$\bar{X}$	SS	*t*	SD	*P*
Fear						
Having children without MR	60	1.98	0.54	−2.112	118	0.037
Having children with MR	60	2.24	0.78			
Acceptance						
Having children without MR	60	3.44	0.62	1.018	118	0.311
Having children with MR	60	3.33	0.59			
Rebellion						
Having children without MR	60	1.19	0.27	−4.149	118	<0.001**
Having children with MR	60	1.64	0.79			
Denial						
Having children without MR	60	2.35	0.68	−2.711	118	0.008**
Having children with MR	60	2.75	0.92			

**P<0.01, ***P<0.001. MR: Mental retardation, SD: Standard deviation

Table 4: Results of the independent group *t*-test conducted to test the significance of the difference between the scores of the multidimensional scale of death and dying and its subdimensions according to the group variable of the sample (female)

Group	*n*	$\bar{X}$	Ss.	*t*	SD	*P*
Fear						
Having children without MR	30	2.03	0.59	−1.634	58	0.108
Having children with MR	30	2.31	0.73			
Acceptance						
Having children without MR	30	3.45	0.75	1.149	58	0.255
Having children with MR	30	3.24	0.67			
Rebellion						
Having children without MR	30	1.22	0.30	−1.917	58	0.060
Having children with MR	30	1.48	0.70			
Denial						
Having children without MR	30	2.62	0.71	−0.289	58	0.774
Having children with MR	30	2.68	0.92			

**P<0.01, ***P<0.001. MR: Mental retardation, SD: Standard deviation

Table 5: Results of the ındependent group t-test conducted to test the significance of the difference between the scores of the multidimensional scale for death and dying and its subdimensions according to the group variable of the sample (male)

Group	*n*	$\bar{X}$	Ss.	*t*	SD	*P*
Fear						
Having children without MR	30	1.94	0.49	−1.343	58	0.185
Having children with MR	30	2.18	0.83			
Acceptance						
Having children without MR	30	3.43	0.46	0.104	58	0.917
Having children with MR	30	3.42	0.48			
Rebellion						
Having children without MR	30	1.17	0.23	−3.878	58	<0.001**
Having children with MR	30	1.79	0.86			
Denial						
Having children without MR	30	2.08	0.54	−3.771	58	<0.001**
Having children with MR	30	2.82	0.93			

**P<0.01, ***P<0.001. MR: Mental retardation, SD: Standard deviation

whether the scores of the sample group from the Fear Sub-Dimension differ significantly with respect to the group variable, It has been determined that there is a statistically significant difference at the P < 0.05 level between the groups because the group with MR children got more points. No statistically significant difference was found at the $P > 0.05$ level from the results of the independent group *t*-test performed to determine whether the scores of the sample group from the Acceptance Sub-Dimension differ significantly according to the group variable.

As can be understood from the table [Table 3], as a result of the independent group *t*-test conducted to determine whether the scores of the sample group from the Rebellion Sub-Dimension differ significantly according to the group variable, It has been determined that there is a statistically significant difference at the P < 0.05 level between the groups because the group with MR children got more points. As a result of the independent group *t*-test performed to determine whether the scores of the sample group from the Denial Sub-Dimension differ significantly according to the group variable, a statistically significant difference was found at the $P < 0.05$ level between the groups, since the group with an MR child got more points.

As can be seen from the table [Table 3], there was no statistically significant difference at the level of $P > 0.05$ from the results of the independent group *t*-test conducted to determine whether the scores of the sample group from the Fear Sub-Dimension differ significantly according to the group variable. No statistically significant difference was found at the $P > 0.05$ level from the results of the independent group *t*-test conducted to determine whether the scores of the sample group from the Acceptance Sub-Dimension differ significantly according to the group variable.

As can be understood from the table [Table 4], no statistically significant difference was found at the level of $P > 0.05$ from the results of the independent group *t*-test, which was conducted to determine whether the scores of the sample group from the Rebellion Sub-Dimension differ significantly according to the group variable. No statistically significant difference was found at the level of $P > 0.05$ from the results of the independent group *t*-test performed to determine whether the scores of the sample group from the Denial Sub-Dimension differ significantly according to the group variable.

As can be seen from the table, there was no statistically significant difference at the level of $P > 0.05$ from the results of the independent group *t*-test conducted to determine whether the scores of the sample group from the Fear Sub-Dimension differ significantly according to the group variable. No statistically significant difference was found at the $P > 0.05$ level from the results of the independent group *t*-test conducted to determine whether the scores of the sample group from the Acceptance Sub-Dimension differ significantly according to the group variable.

As it can be understood from the table [Table 5], as a result of the independent group *t*-test conducted to determine whether the scores of the sample group from the Rebellion Sub-Dimension differ significantly according to the group variable, there is a statistically significant difference at the $P < 0.05$ level between the groups because the group with MR children got more points has been determined. As a result of the independent group *t*-test conducted to determine whether the scores of the sample group from the Denial Sub-Dimension differ significantly according to the group variable, a statistically significant difference was found at the $P < 0.05$ level between the groups because the patient group received more points.

Discussion

In this study, the death anxiety of parents with and without MR was compared and examined. Although there are many studies on parents of children with intellectual disabilities (Burke and Stelter, 2019; Lee *et al.*, 2016),[4,7,12,20-22] few studies are related to parents' death anxiety.[19] As a result of the study, it was found that the fear, rebellion, and denial subscales of the death anxiety scale of parents with mentally retarded children were significantly higher than parents without mentally retarded children. The findings of the research support the results of the research by Oktar and Yıldız[19] examining the death anxiety of mothers with mentally disabled children. Parents with mentally retarded children are thought to have a fear of dying before their children. This finding can be explained by the possibility of death anxiety in parents due to the inadequacy of official or private support systems that can care for children with special needs.

Another finding of this study is the gender difference between the results of the subscales. No significant difference was found in the fear, acceptance, denial, and rebellion subscales of the mothers with and without mentally retarded children. However, the denial and rebellion subscale scores of the fathers with mental retarde children were found to be statistically significantly higher than the healthy group. The importance of father–child interaction in child development is known (Davys *et al.*, 2016). In this context, it is important to examine the death anxiety of fathers as well as mothers. The difference between fathers' and mothers' attitudes regarding their children with disabilities could be related to the fact that the primary caregivers are mostly mothers and they can spend more time with their children than fathers. Behavioral theory suggests that exposure may reduce anxiety, have a therapeutic effect, and avoidance will reinforce fear. In addition, it is thought that gender difference may be effective in experiencing and expressing emotions.

The adequate and quality social support that parents receive from official institutions has a positive effect on

their quality of life.[23] The meta-analysis results of Scherer *et al*.[4] provide evidence that parenting a mentally retarded child is associated with high levels of depressive symptoms. It has been suggested that if the mentally retarded child has comorbid disabilities, the risk of depression, which presents a mixture of physical and cognitive impairments, may increase.[4] In the study of Marquis *et al*.[8] examining 162 studies on the mental and physical health of caregivers of children with disabilities, many different factors that could have an impact on the health of these caregivers were identified. Social determinants, individual caregiver variables, characteristics of the disabled child, family characteristics, and support systems are among these factors. Raising a mentally retarded child includes stressors such as stigma, financial burden, need for constant care, and behavioral problems that arise in children.[24] In addition, it has been reported that parents may be at a greater risk of depression and anxiety due to stress factors such as increased caregiver demands and financial burden.[4]

In the study of Gogoi *et al*.,[7] the psychological responses of parents with mentally retarded children were examined. It was found that anxiety and depression levels were higher and their quality of life was lower than mothers with healthy children. As people with mental and developmental disabilities live longer, they may need not only disability-related support but also services related to aging adults.[25] However, families often provide such support themselves, due to the inadequacy of most service delivery systems.[26] Although future planning should include every family member, very few families of mentally retarded people make future planning. The main reason for this is that future planning can cause stress due to the uncertainty of the future.[21] Moreover, as parental stress can negatively affect children, supporting the well-being of parents can contribute to supporting children's development in a positive way.

Increasing the quality of life of children with special needs and their families is among the important parameters of public health.[27] This topic has created a growing research area in recent years in all countries of the world.[28] A good understanding of the factors that shape the quality of life of this disadvantaged group can inform the development of better policies and better practices to support families. While many studies have defined the quality of life of these families in the last decade,[29-33] some of them are more among these families. Attempted to identify the cluster of factors that could contribute to higher quality of life (Zuna *et al*., 2010).[34-37]

All families, including those affected by disability, deserve a high quality of life. Mentally disabled individuals have lived an isolated life for centuries. Functional service programs are needed to be socially acceptable and social integration.[38] In a study conducted to determine the difficulties and family burden experienced by the families of children with intellectual disability, 48.8% of the mothers stated that they did not have anyone to help care for their children, they felt disappointed, surprised, shocked, desperate, anger and guilty, and blamed others. In the same study, it was reported that mothers had suicidal thoughts, 28.1% experienced depression, most of them looked at their future with anxiety and thought that their burdens were too heavy to bear.[39] It is known that social support has an effect on the life satisfaction of families with children with special needs, seeking help, coping with depression, and stress.[40] In this context, determining the need for support of parents with mentally disabled children as a part of the society, increasing the quality of life with the services to be provided, and trying to eliminate all concerns including death anxiety are within the scope of social responsibility.

Among the positive features of the study are the adequacy of the number of cases, the acceptable ratio of women to men in the sample group, and the use of the scale whose validity and reliability have been made in our country. Additionally, conducting a research in one institution with participant living in the same city, studying limited number of factors related to death anxiety can be included in the study as limitations. The necessary support can be provided by ensuring the integration of children with mental disabilities and their families into society, increasing their quality of life, developing necessary health and social policies, and increasing research that will draw attention to this issue.

It is beneficial to prepare and implement various psychosocial support programs such as making new regulations on social and health policies in order to reduce the death anxiety of families, providing some social security for disabled children, providing support for caregiver problems of their children, and managing stress.

Patient informed consent

Informed consent was obtained.

Ethics committee approval

The ethics committee approval has been obtained from the Uskudar University Noninterventional Research Ethics Committee (2018/897).

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Conflicts of interest

There are no conflicts of interest to declare.

Author contribution subject and rate

Zeynep Gümüş Demir (50%): Design the research, data collection, and analyses and wrote the whole manuscript.

Kahraman Güler (20%): Contributed with on research design and analyses

Emel Aner Aktan (10%): Supervised the article write-up.

Deniz Sevimli (20%): Contributed with comments on research design and slides interpret

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Original Article

The Relationship between Obsessive-Compulsive Symptoms and Religious Attitudes

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Abstract

Objective: This study aimed to examine the relationship between obsessive compulsive symptoms and religious attitudes. **Method:** A total of 80 people, 40 females and 40 males, randomly selected between the ages of 18 and 65 participated in the study. Participants were given Sociodemographic Information Form, the Padua Inventory, and Ok Religious Attitude Scale. **Results:** Based on the findings, there was no statistically significant relationship between obsessive compulsive symptoms subscales and religious attitudes. According to results related to sociodemographic variables, no statistically significant difference was found between sociodemographic variables of the participants and obsessive compulsive symptoms. No statistically significant difference was found between the religious attitudes of the participants and their sociodemographic variables. **Conclusion:** Because the number of study for understanding these variable is limited in Turkey, It can be considered that the findings of the study related to obsessive-compulsive symptoms and religious attitudes is contributive in terms of providing further information for future research.

Keywords: *Obsessive-compulsive disorder, obsessive-compulsive symptoms, religious attitudes, religious compulsions, religious obsessions*

Introduction

Obsessive-compulsive disorder (OCD) is a psychiatric disorder caused by neurobiological dysfunctions. Obsession is a collection of all kinds of dreams, impulses, and thoughts that are a product of the individual's own mind, involuntarily and repetitive, persistent, and compelling. This situation is an event that specifically influences the functionality of the individual. Therefore, the individual tries to get rid of, remove, or keep this disturbing event from his mind, but on the contrary, this event occupies the mind of the individual.[1] The average age of onset of OCD is between 20 and 26, and symptoms usually settle in 2/3 of patients before the age of 25.[2]

Religious obsessions and compulsions, which are a subtype of OCD, are seen in an average of 5% of OCD patients.[3] Examples of the most common religious obsessions are blasphemy and disrespect for God and other religious elements, doubting, fear of doing things that are considered sin, the thought of being a sinner and having sinned without being aware of it, and obsessions that occur during washing rituals during preparation for prayers. Obsessions during the period can be listed as obsessions related to the fulfillment of any religious decree. Examples of common religious compulsions are repentance, prayer and repetition compulsions, and compulsions that occur in cleansing rituals.

OCD was once believed to be an uncommon disease.[4] Although there is no definite information about the process and onset of OCD, certain approaches have made proving statements. Accordingly, it has been discussed that OCD is not a homogeneous disease, that is, it is a heterogeneous condition.[5] The effects of social factors in the etiology of OCD have not yet been revealed in terms of

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its uncertainty. However, there is information about the social or environmental effects that may have role in the etiology of obsessive-compulsive personality.[6] Based on the few studies conducted about the related topic, it is thought that cultural differences may play a role in OCD etiology. However, no gender difference was found in OCD prevalence.[7]

OCD and religion have long been linked in the psychology research. However, the relationship between the two is still not fully understood.[8] Studies on the relationship between religiosity and religion based on OCD have often been conducted with Jewish or Christian participants selected from Western countries. There are very few comparative studies that Muslims have participated.[3]

It has been suggested that religion may play an important role in the development of some of the OCD cases. OCD can be seen commonly in people who have been raised as strictly religious.[9] Ritualistic practices (such as repetitive prayer) common in the Catholic faith were thought to be associated with increased OCD rates in sensitive individuals.[10] In fact, according to a study conducted in Egypt, the role of religious upbringing was clearly seen in the etiology of OCD.[4] While some of the studies on this topic indicate that OCD and religiosity are related to each other, some studies cannot find a relationship.[11]

Studies conducted in our country on this participant have shown that the reason for the lower rate of religious OCD compared to other countries (such as Saudi Arabia and Egypt) of the same religion; religious life and the concept in Turkey, people's role in influencing their living by understanding of religious factors in being at a different level in these countries, interpretation and may influence conditions such as sectarian changes brings to mind.[12]

In a study conducted in 2009, no significant difference was found between the level of obsessive thoughts and OCD symptoms between Turkish students and Canadian students. However, the rate of religious obsession between Turkish students and Canadian students was higher for Turkish students. When the groups were examined about obsession subscales, there was no difference between the two groups in the levels of obsession and compulsion symptoms, while significant findings were found about cultural differences between the two groups in the subscales of religious obsessions and obsessive thoughts. A significant positive correlation was found between religiousness level and religious obsession severity, OCD symptoms, and beliefs. This result supports similar previous studies.[3]

In another study conducted in Turkey on religious obsessions and compulsions in 2013, the rate of religious obsession in women was almost two and a half times higher than men, when obsessions were evaluated, it was found that 100% of obsessions of blasphemy and disobedience against God and an obsession of doubting was 71%. It was found mostly in men. Compulsions occurring during prayers with washing behavior were more common in women.[13]

This study is important in terms of helping to provide the necessary support for future studies on similar issues and to bring the subject of obsessive-compulsive symptoms and religious attitudes, which have been studied in a very limited number in our country, to the literature.

Considering in the context of the relevant literature, the purpose of this study is to examine the relationship between obsessive-compulsive symptoms and religious attitude.

Methods

The ethics committee approval has been obtained from the Uskudar University Committee on Non-Interventional Research Ethics (B.08.6.YÖK.2.ÜS.0.05.0.06/2018/965).

Ethics committee approval was obtained for this study, and informed consent forms were signed by all participants.

Mimar Sinan district in Kocaeli which is a province Korfez district was chosen as the center of the study for the sample group in this study. In the region selected as the research center, 80 people (40 women and 40 men) older than 18 and under 65 participated in the study. The inclusion criteria were determined as being in the 18 and 65 age range, being literate, and volunteering to participate in the study.

The study was conducted with randomly selected people in this specified region. Participants were first informed about the identity and qualification of the person conducting the study and then about the study to be conducted.

Measurement Instruments

Sociodemographic information form

The sociodemographic information form is a 7-item form (gender, age, marital status, educational status, employment status, occupation, and chronic illness) prepared by the researcher to determine the points that may affect or be related to the hypotheses in the study.

Padua inventory

The Padua Inventory is a scale that helps patients with OCD to determine the predominant symptom, as well as measuring the severity of the disease in general. Padua Inventory consists of 60 questions. These questions were created by selecting from among 200 different symptoms indicated by patients with OCD. Each question consists of 5 answers and only one is selected and answered. Each question is scored between 0 and 4 points according to the answer type. The way of answering the questions and scoring; It has been prepared as None (0) points, Very little (1) points, A lot (2) points, Quite a lot (3) points, and Excessive (4) points.[14] Since there is no overall cutoff score in the Padua Inventory, the average categories for the scores in this study were organized.

According to the scoring stated by Tan,[1] in this study, a category was prepared as follows, which is not certain but dependent on the estimation and average scoring:

- 0–40 average score = normal
- Average score of 41–70 = obsessive above than average
- Average score 71–85 = obsessive
- Average score of 86 and above = severely obsessive.

For subscales, subscales based on imprecise estimation and mean scoring are categorized as follows.

There are a total of 11 questions in the contemplation subscale, and the total score range that can be taken is 0–44 points. According to this score, an approximate average was taken and according to this, the 0–11 mean score range is normal; the 12–22 average score range is a little more obsessive than normal; the 23–33 average score range is obsessive; and the 34–44 average score range is seriously obsessive. It was calculated according to the subscale of having thoughts. There are a total of 10 questions in the washing/contamination subscale, and the total score range that can be obtained is 0–40 points. According to this score, an average score was taken and accordingly, the 0–10 mean score range is normal; the 11–20 average score range is a little more obsessive than normal; the 21–30 average score range is obsessive; and the 31–40 average score range is seriously obsessive. It was calculated according to the washing subscale. There are 8 questions in total in the control subscale, and the total score range that can be taken is 0–32 points. According to this score, an approximate average was taken and according to this, the 0–8 mean score range is normal; the 9–16 average score range is a little more obsessive than normal; the 17–24 average score range is the obsessive patient; and the 25–32 average score range is seriously obsessive. It was calculated according to the control subscale. There are a total of 6 questions in the impulses subscale, and the total score range that can be taken is 0–24 points. According to this score, an approximate average was taken and accordingly, the 0–6 mean score range is normal; the 7–12 average score range is a little more obsessive than normal; the 13–18 average score range is obsessive; and 19–24 average score range is seriously obsessive. It was calculated according to the impulses subscale. There are a total of 3 questions in the counting subscale, and the total score range that can be obtained is 0–12 points. According to this score, an approximate average was taken and accordingly, the 0–3 mean score range is normal; the 4–6 average score range is a little more obsessive than normal; the 7–9 average score range is obsessive; and the 10–12 average score range is seriously obsessive. It was calculated according to the counting subscale. There are a total of 3 questions in the precision (repetitive behavior) subscale, and the total score range that can be obtained is 0–12 points. According to this score, an approximate average was taken and accordingly, the 0–3 mean score range is normal; the 4–6 average score range is a little more obsessive than normal; the 7–9 average score range is obsessive; and the 10–12 average score range is seriously obsessive. It was calculated according to the repetitive behaviors subscale.

Ok-religious attitudes scale

Ok, developed this scale in 2011, based on behavioral knowledge and emotional elements that are emphasized in the field of social psychology, and it was prepared to measure the emotional, cognitive, behavioral, and relationship-related factors regarding religion. The scale, consisting of 6 positive and 2 negative questions in total, was named "Ok-Religious Attitude Scale" by combining with the surname of the person to avoid confusion with other religious attitude scales.

This scale, designed as Likert, is answered according to the frequency levels. Frequency levels are strongly disagree (1), disagree (2), somewhat agree (3), agree (4), and definitely agree (5). The alpha coefficient of the scale, which has four factors, was 0.90, and the percentage of explaining the total variance was 86. The way of scoring the scale is as follows: the lowest score with $8 \times 1 = 8$ and the highest score with $8 \times 5 = 40$. Accordingly, lower scores indicate that the level of religious attitude is low and higher scores indicate that the level of religious attitude is high. According to the average of the scores obtained from the options of the items in the scale, the level of religiousness of the individual can be approximately as follows:

- 1.00–1.49 average score = little or no religious person
- 1.50–2.49 average score = less religious
- 2.50–3.49 average score = moderately religious
- 3.50–4.49 average score = highly religious
- 4.50–5.00 average score = very religious.[15,16]

Data analysis

Statistical analysis of the data in the study was carried out using the SPSS 18 (SPSS Inc., 2009) software including independent t test, Pearson correlation, one way ANOVA, and Chi square tests.

Reference: SPSS Inc. Released 2009. SPSS Statistics for Windows, Version 18.0. Chicago: SPSS Inc.

Results

Sociodemographic variables

Based on the descriptive data obtained from the participants regarding their sociodemographic variables, 50% (n = 40) of the participants in the study were women and the other 50% (n = 40) were men, and the total number of participants was 80. The average age of the participants was determined as 27.7 ± 7.3. There is no statistically significant difference between the average age of women and men. 7.5% (n = 6) were primary school graduates, 41.3% (n = 33) were high school graduates, 48.8% (n = 39) were university graduates, and 2.5% (n = 2) also constitute graduate students, while

66.3% of the participants (53 people) were employed and 33.8% (27 people) were unemployed.

According to Table 1, 25% of the participants (20 people) were normal, 37.5% (30 people) were more obsessive than normal, 8.8% (7 people) were obsessive, and 28.7% (23 people) were scored as having severe OCD symptoms.

1.3% of the participants (n = 1) are little or no religious, 6.3% (n = 5) are poorly religious, 16.3% (n = 3) are moderately religious, 40% (n = 32) were quite religious, and 36.3% (n = 29) were found to be very religious or strictly believers. As a result of the t-test, no statistically significant difference was found between gender, educational status, age groups, marital status, employment status, and religious attitude ($P > 0.05$).

In Table 2, the relationship between the obsessive-compulsive subscales of the participants and their religious attitudes is shown with the Pearson correlation analysis results. According to the table, no significant relationship was found between the obsessive-compulsive symptoms and subscale symptoms and their religious attitudes.

Discussion

In this study, the relationships between obsessive-compulsive subscale symptoms and religious attitudes of randomly selected individuals were investigated. There is no scientific determination that indicates that religious attitude can cause religious OCD when looking at etiological explanations. In addition to this situation, there are not many differences between non-religious OCD and religious OCD due to etiological interventions and treatments in the studies conducted.[17] This situation supports the conclusion that there is no relationship between religious attitude and OCD in our study.

According to the study of Bayraktar in 2007, a significant relationship was not detected between the symptoms of OCD and prayers.[18] This study also supports our study with its findings.

The study conducted by Tek and Ulug found out that 42% of OCD patients had religious obsessions in Turkey. Afterward, the washing rituals required for all the participants to belong to the religion of Islam and to be able to worship according to Islam was carried out in accordance with Islamic rules in a specific order. Therefore, the contamination obsessions about religious issues among OCD patients may include the washing, counting, and checking compulsions. They stated that their compulsions were noticed. They underlined that washing behavior due to being unclean occupies a large place in Islamic practice, the concept of being clean in religious terms can easily be disrupted in some situations that may cause repetition of washing, and therefore, contamination and washing obsessions and repetition compulsions in OCD patients are in the line of religious ritual.

In this study, there is no relationship between religiousness and the clinical features of OCD, and the concept of religion may be a point where this disease can emerge and manifest rather than being a factor that determines OCD.[19] This study of Tek and Ulug also supports our research results.

In the study of Uyaver in 2010,[20] no significant difference was found between religious obsessions and sociodemographic characteristics. In addition, there was no statistically significant difference between the participants' religious obsessions and their level of OCD severity.[20]

According to the obtained data, no statistically significant difference was found between the religious obsession and knowledge about religion and belief in God. No statistically significant difference was found between the perceptions and attitudes indicating religiousness between the groups of participants with and without religious obsessions. The results of our study support the results of Tek and Ulug, Bayraktar, and Uyaver.[18-20]

Religion factor in OCD may vary from culture to culture, and the possible effects of this factor on OCD symptoms have also been investigated. According to studies conducted in Saudi Arabia and Egypt, obsessions are generally related to religious issues. It made us think that the issue of washing, which has an important place in Islam, may have an effect on this situation.

In the intercultural studies conducted by Yorulmaz, Gencoz, and Woody in 2010, the effect of being religious on OCD

Table 1: Distribution of participants by obsessive-compulsive symptom levels

	N	%
Normal	20	25
Obsessive above than average	30	37.5
Obsessive-compulsive disorder	7	8.8
Severe obsessive-compulsive disorder	23	28.7
Total	80	100

Table 2: The relationship between obsessive-compulsive symptoms and sub-scales of participants and their religious attitudes

	Obsessive-compulsive symptom severity	Intrusion	Contamination	Checking	Obssessive impulses	Counting	Repetition (accuracy)
Religious attitudes (r, P)	−0.061, 0.593	0.008, 0.943	0.203, 0.071	0.075, 0.506	−0.105, 0.354	−0.155, 0.169	−0.172, 0.128

*P<0.05. r: Correlation coefficient

symptoms was investigated. In this study, Turkish and Canadian participants were compared. According to the findings of the study, a significant relationship was found between OCD symptoms and the religiousness factor in the group with only Turkish participants. In addition, religion emerges as a factor that affects obsessions and compulsions in terms of content and severity. In fact, it is thought to be a factor that can affect cross-cultural differences in OCD symptoms.[21]

According to the nonclinical research of 298 Muslim participants aged 16–66, conducted by Ok and Goren in 2018;[22] a positive relationship was found between religiosity and OCD scores.[22] In addition, the relationship between OCD and religiosity in the study of Yorulmaz, Gencoz and Woody (2010) and Ok and Goren (2018) does not support our study. As a possible reason for this situation, it can be considered that the sociocultural structures of the participants and the scales used, as well as the difference in the number of participants, may have an effect.

This study was conducted with randomly selected individuals from Mimar Sinan district in Kocaeli province Korfez district. The results of this study may not reflect the general population. In the planning of the study, one of the limitations affecting this study was the fact that randomly selected individuals also did not want to participate in the study and could not fill in the scales appropriately and seriously, although they agreed to participate.

According to the results of this study, no statistically significant relationship was found between obsessive-compulsive subscale symptoms and religious attitudes. The relationship between OCD and religious attitude in different cultures and different religious beliefs should be examined with larger samples.

Patient informed consent

Patient informed consent was obtained.

Ethics committee approval

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Conflicts of interest

There are no conflicts of interest.

Author contribution subject and rate

Tayfun Cinar (50%): Design the research, data collection and analyses and wrote the whole manuscript.

Oguz Tan (20%): Organized the research and supervised the article write-up.

Remziye Keskin (15%): Contributed with comments on manuscript organization and write-up.

Gokben Hizli Sayar (15%): Contributed with comments on research design.

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Original Article

Investigation of Obsessions and Compulsions in Terms of Psychological Resilience in the Epidemic Period

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Abstract

Aims and Objectives: In this study, obsessions and compulsions observed during the epidemic period were investigated in terms of psychological resilience. **Materials and Methods:** The research was conducted on a voluntary basis with 208 people (51.4% women, 48.6% men) who were exposed to the COVID 19 epidemic. Participants were given a Sociodemographic Information Form including questions about COVID 19, Vancouver Obsession–Compulsion Inventory (VOCI), and Adult Psychological Resilience Scale. Data were analyzed with Statistical Package Program for Social Science 21.0 program. **Results:** When the findings were examined, no difference was found between obsession–compulsion and psychological resilience in terms of total score. However, there are relationships in subdimensions. Contamination subscore of VOCI and social resources subscore of Resilience Scale for Adults were found to be higher than the others. Hoarding was higher in men, while self perception, structural style, and family cohesion were higher in women. Single participants had higher obsession–compulsion scores, whereas married participants had higher self perception and family adjustment. It was concluded that as individuals' age increased, their self perception and social competence increased. Relationships were also found in terms of both obsession–compulsion and psychological resilience with variables, such as the frequency of COVID 19 news and case follow up, the frequency of body screening for COVID 19 symptoms, the change in the frequency of cleaning, and the idea of getting psychological support. **Conclusion:** This research is significant when it comes to seeing the effect of a compulsive life event, such as an epidemic disease on obsessive and compulsive behaviors.

Keywords: *COVID-19, epidemic disease, obsession–compulsion, psychological resilience*

Introduction

Epidemic diseases have severely affected human and animal health, economy, and psychology from the past till today and have led to losses.[1] These effects have been studied in various dimensions and fields (such as psychology, sociology, history, economy, and tourism) and have been the subject of research. COVID-19 (coronavirus) is one of these epidemic diseases. These effects have been studied in various dimensions and fields (such as psychology, sociology, history, economy, and tourism) and have been the subject of research. COVID-19 (coronavirus) is one of these epidemic diseases. It started in Wuhan, China, in December 2019 and rapidly spread to the whole world. The first case seen in our country was in March. There has been intense anxiety and stress since the first case was seen. It is a predictable result that the epidemic will cause and create physical disorders in people. However, the psychological consequences of the epidemic are as significant as the physiological consequences. Psychology has a prominent role in how individuals exposed to the epidemic will do in the face of such a crisis, as well as how to deal with the problems of social isolation, staying at home, washing hands, and fear of contamination.[2]

Whether the individual is infected or not can be quite psychologically worn out. However, it is unknown how corrosive it will be and how long the negative effect will last.[3] Negative effects and psychological disturbances will expect in people in line with what has been learned

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from previous pandemics and epidemics, even though the long-term psychiatric consequences of the pandemic period are not yet known.[4] The issue of how it will be affected by this crisis period may vary depending on many factors. Individuals with an anxious personality may become more anxious.[3] Fear of infection, financial difficulties, quarantine practices, increased losses, incomplete or misinformation in the media, increased concerns about the death of oneself, or others can lead to a psychological disturbance that did not exist before, as well as can increase an already existing ailment and symptom.[5,6] Warnings such as paying attention to hygiene, washing hands frequently, and using disinfectants, which are part of COVID-19 precautions, are likely to increase the contamination obsession and cleaning compulsion that the individual already has.[7] The COVID-19 outbreak can exacerbate obsessions and compulsions in individuals with obsessive–compulsive disorder (OCD). However, it can be the opposite. The individual who has excessive thoughts about the contagion realizes that everyone is behaving like her/him. This situation may relax the person and obsessive fears about the coronavirus may not occur.[8]

Since the emergence of psychology science, the effects of adverse and challenging situations psychological health have been researching from different perspectives in many studies.[9] COVID-19 is also described as a global crisis and a challenging situation. Which events will lead to the crisis and how they will affect it vary from person to person.[10] The reactions and behaviors put forward as a result of the crisis are temporary. On the other hand, long-term effects on the psychology and well-being of individuals can be seen.[11]

Physiology and psychology are a whole that affects each other. "Neuro-immunomodulation" describes this situation well. It means that the mood of the person, how he/she feels, affects the immune system.[1] One of the previous studies supports this opinion. In the study, being psychologically resilient and physiologically resilient was found interrelated. Psychological well-being brings along physical well-being. Resilient individuals were able to deal with stressful events more comfortably without seeing them as a threatening factor.[12] Resilience also brings along physical and psychological health. It can be said that individiuals with higher endurance think in a more positive way.[12] and therefore, anxiety symptoms are not common in these individuals.[13] Woodard (2004) mentioned that psychological resilience can explain physical resilience and is a protective factor for diseases. In another study,

Table 1: Descriptive statistical findings of sampling (*n*=208)

Factor	Variable	*n* (%)
Gender	Female	107 (51.4)
	Male	101 (48.6)
Marital status	Single	150 (72.1)
	Married	58 (27.9)
Frequency of following COVID-19 news and case numbers	Several times a day	58 (27.9)
	Every 2-3 days	68 (32.7)
	Once a week	17 (8.2)
	If it coincides	65 (31.3)
Self-examination for representation of COVID-19 symptom	Almost always	53 (25.5)
	Sometimes	76 (36.5)
	Rarely	61 (29.3)
	Never	18 (8.7)
Change in cleaning frequency	Yes	149 (71.) 6
	No	59 (28.4)
The frequency of cleaning and disinfection of the place experienced in the pandemic process	Several times a day	45 (21.6)
	Once a day	72 (34.6)
	2-3 times a week	54 (26.0)
	4-5 times a week	37 (17.8)
The frequency of cleaning and disinfection of the place before the pandemic	Several times a day	16 (7.7)
	Once a day	51 (24.5)
	2-3 times a week	102 (49.0)
	4-5 times a week	39 (18.8)
Psychological support	Yes	31 (14.9)
	No	177 (85.1)
Thought of getting psychological support in the following days	Yes	26 (12.5)
	No	139 (66.8)
	Indecisive	43 (20.7)

COVID-19: Coronavirus-2019

resilience was found to be associated with positive affect, positive social support, life satisfaction, and optimistic coping.[14] In the study conducted by Altuntaş and Genç,[15] psychological resilience was found to be associated with happiness. It is thought that the individual with high strength will be happier, and therefore, the resilient individual will be happier.

In a study conducted with approximately 130 individuals in Canada to examine the psychological effects of the severe acute respiratory syndrome (SARS), which has a contagious epidemic feature and emerged in 2003, a high level of stress was observed in people. Individuals showed signs of posttraumatic stress disorder (PTSD) and depression. Furthermore, it was concluded that close contact with the individual who tested positive for SARS and the process of long-term social isolation increased these symptoms.[16]

Postepidemic research is as important as the researchers conducted during the epidemic period, as psychological symptoms can be observed. In a study conducted with 233 individuals who survived the disease 3–4 years after the SARS-CoV-1 epidemic, psychiatric disorders were found in nearly 50% of them. Panic disorder, PTSD, chronic fatigue, depression, and OCD are among the observed disorders.[17]

In a study conducted after the onset of the COVID outbreak in China, participants have rated the psychological impact of the epidemic as moderate or severe and reported symptoms of depression and anxiety.[18]

This research was needed because the COVID-19 outbreak is all over the world and caused problems for people. This study aimed to examine the obsessions and compulsions observed during the epidemic period, in terms of psychological resilience. Although research on the epidemic is very limited, it has been observed that previous studies have generally focused on PTSD or depression. Therefore, it is thought that looking at the epidemic from a perspective of obsession– compulsion and psychological resilience can be important to cope with the period more easily.

Table 2: Mean scores and score ranges of the scales

	n	$\bar{X}$	SD	Minimum	Maximum
VOCI	208	68.31	40.28	4	186
Contamination	208	18.31	10.14	1	46
Checking	208	7.76	6.37	0	24
Obsessions	208	12.26	9.56	0	39
Hoarding	208	5.52	5.22	0	20
Absolute accuracy	208	16.34	10.32	0	46
Indecision	208	8.10	5.47	0	23
RSA	208	102.90	9.00	75	143
Perception of the self	208	19.03	2.66	8	27
Planned future	208	12.61	1.84	6	18
Structured style	208	13.00	2.57	6	20
Social competence	208	19.25	2.58	12	30
Family cohesion	208	18.72	2.94	10	29
Social resources	208	20.28	3.37	11	33

VOCI: Vancouver Obsessive-Compulsive Inventory, RSA: Resilience Scale for Adults, SD: Standard deviation

Methods

The ethics committee approval has been obtained from the Uskudar University Non-Interventional Research Ethics Committee (613551342/2020-360).

Sample

The study sample is 208, of which 107 are female (51.4%) are 101 are male (48.6%). Their age is between 18 and 60 years. The sample was selected by the inclusion and exclusion criteria. Inclusion criteria were being in the age range of 18–60, not having a psychiatric diagnosis, and agreeing to participate in the study voluntarily. Exclusion criteria were that being younger than 18 and older than 60 years old is to have a psychiatric diagnosis. All participants submitted a volunteer consent form.

Table 3: Analysis of variance results on the relationship between the scale scores of the sample and the frequency of following coronavirus-19 news and case numbers

Frequency of following	*n*	$\bar{X}$	SS	Minimum	Maximum	*F*	*P*	Difference
Indecision								
Several times a week	58	7.77	5.56	0	18	6.453	0.000*	1-3
Every 2-3 days	68	7.41	4.52	0	21			2-3
Once a week	17	13.47	6.87	1	23			3-1
If it coincides	65	7.70	5.27	0	23			3-2
								3-4
								4-3
Structured style								
Several times a day	58	13.81	2.51	6	18	2.760	0.043*	1-4
Every 2-3 days	68	12.79	2.50	8	17			4-1
Once a week	17	12.64	1.57	10	16			
If it coincides	65	12.60	2.78	7	20			

*$P \leq 0.05$: Statistically significant. SD: Standard deviation

Table 4: Analysis of variance results of the relationship between scale scores of the sample and self-examination for the representation of coronavirus-19 symptoms

Examination	*n*	$\bar{X}$	SD	Minimum	Maximum	*F*	*P*	Difference
VOCI								
Almost always	53	85.18	41.65	8	186	5.578	0.001*	1-3
Sometimes	76	67.82	39.47	9	175			1-4
Rarely	61	59.45	35.32	8	152			3-1
Never	18	50.72	40.87	4	133			4-1
Contamination								
Almost always	53	23.62	10.97	2	46	10.354	0.000*	1-2
Sometimes	76	18.34	8.67	1	42			1-3
Rarely	61	15.78	9.47	1	40			1-4
Never	18	11.11	8.40	2	29			2-1
								3-1
								4-1
Checking								
Almost always	53	9.86	6.49	0	24	2.772	0.043*	1-2
Sometimes	76	7.11	6.07	0	24			1-3
Rarely	61	7.22	6.14	0	24			1-4
Never	18	6.16	7.13	0	22			2-1
								3-1
								4-1
Obsession								
Almost always	53	15.05	10.15	0	18	2.924	0.035*	1-3
Sometimes	76	12.36	9.61	0	18			3-1
Rarely	61	9.81	7.97	0	20			
Never	18	11.88	10.98	0	12			
Absolute accuracy								
Almost always	53	20.20	11.23	0	23	4.633	0.004*	1-3
Sometimes	76	16.23	9.84	0	22			1-4
Rarely	61	14.52	9.35	0	18			3-1
Never	18	11.55	9.57	0	19			4-1
Indecision								
Almost always	53	10.03	5.32	88	126	3.985	0.009*	1-3
Sometimes	76	8.10	5.97	83	132			1-4
Rarely	61	7.00	4.64	87	143			3-1
Never	18	6.11	4.99	75	121			4-1
Perception of the self								
Almost always	53	19.79	2.91	8	17	2.957	0.033*	1-2
Sometimes	76	18.64	2.47	10	17			1-3
Rarely	61	18.63	2.38	6	18			2-1
Never	18	19.77	3.19	8	17			3-1

*$P \leq 0.05$: Statistically significant. VOCI: Vancouver Obsessive-Compulsive Inventory, SD: Standard deviation

Measurement instruments

The Vancouver obsessive–compulsive inventory (VOCI) and the Resilience Scale for Adults (RSA) were used with the form prepared to collect the sociodemographic information of the participants.

Sociodemographic Information Form

The questions on this form used in the first section of the search: participants' genders, ages, marital status, frequency of following COVID-19-related news and cases, how often they performed body screening to determine if they showed symptoms of COVID-19, whether the frequency of cleaning during the epidemic period has changed, whether participants' have received psychological support before, whether participants' have previously received a psychiatric diagnosis, and whether they want psychological support in the following days.

Table 5: *t*-test results of the relationship between the sample scale scores and the change in cleaning frequency

Change	*n*	$\bar{X}$	SD	*t*	*P*
Contamination					
Yes	149	19.32	10.01	2.320	0.021*
No	59	15.74	10.10		
Hoarding					
Yes	149	6.04	5.22	2.267	0.024*
No	59	4.23	5.02		
Self-perception					
Yes	149	18.80	2.66	-1.974	0.050*
No	59	19.61	2.61		

*$P \leq 0.05$: Statistically significant. SD: Standard deviation

Vancouver obsessive–compulsive inventory

This scale frequently uses to evaluate the severity of OCD, both in research and clinical practice. The original form of the scale had created by Thordarson *et al*.[19] Validity and reliability studies of the Turkish form were conducted by İnözü and Yorulmaz.[20] The scale is in the form of five-point Likert scale and consists of six subdimensions and 55 substances. Subdimensions are contamination, checking, obsessions, hoarding, absolute accuracy, and indecisiveness. As the score from the scale, the severity of OCD symptoms also increases. Internal consistency of the original version of the scale was 0.94 for the total scale and 0.88–0.96 for subscales.[19] The total internal consistencies were 0.96 in the study of the validity and reliability of the Turkish form. Internal consistencies of subscales were 0.89 for contamination, 0.90 for checking, 0.86 for obsessions, 0.81 for hoarding, 0.87 for absolute accuracy, and 0.77 for indecisiveness.[20]

Resilience Scale for Adults

It has created by Fribog *et al*.[21] to include five subdimensions: personal strength, structural style, family cohesion, social competence, and social resources. However, considering that these dimensions were not enough, they divided the dimension of "personal strength" into self and future perception. Thus, the scale consisted of six dimensions in total. The validity and reliability study of the Turkish form was carried out by Basim and Cetin[22] through two groups of 262 employees and 350 students. There are 33 items on the scale and five boxes in the answer key. Positive and negative answers are on different sides for each question. Scoring is released and the scores that can obtain from the scale vary between the values 33 and 165. Cronbach alpha coefficients for subscales of the original form of the scale range from 0.67 to 0.90 and test–retest correlations vary between 0.69 and 0.84. In the validity and reliability study of the Turkish form, Cronbach alpha coefficients for subscales range between 0.66 and 0.81 in the study group and between 0.68 and 0.79 in the employee group. The total Cronbach alpha coefficient of the scale was 0.86 in both groups.[22]

Data analysis

The data were collected online by sending them to the participants. Data analysis was used IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp. One-way analysis of variance and independent *t*-test were used to determine differences in participant scale scores based on Sociodemographic Information Form variables. Pearson's correlation analysis was used to determine the relationship between scores obtained from scales.

Results

When the distribution of 208 participants in the study by gender variable is examined, it is seen that there are 107 (51.4%) women and 101 (48.6%) men. It was determined that 150 (72.1%) participants were single and 58 (27.9%) participants were married. It has determined that most of the participants (31.7%) followed the COVID-19 news and the number of cases every 2–3 days. It has concluded that the majority of the participants (36.5%) sometimes performed body scans for COVID-19 symptoms. The cleaning frequency of 149 (71.6%) participants changed during the COVID-19 period. Most of the participants, 72 (34.6%), clean or disinfect their place of living once a day during the pandemic period. Most of the participants, 102 (42%), clean or disinfect their place of living 2–3 times a week before the pandemic period. The number of participants who have not received psychological support before is 177 (85.1%), and 139 (66.8%) people do not consider receiving psychological support in the following days. [Table 1]

The contamination average score, which is one of the subdimensions of VOCI, was determined as 18.31. Accordingly, the contamination subdimension score is higher than the other subdimension scores of the scale. Social resources' average score of the participants, which is one of the subdimensions of resilience scale for adult, was determined as 20.28. Accordingly, the social resources score is higher than the other subdimension score of the scale. [Table 2]

According to the analysis results, there is a significant difference between the indecision scores ($F_{(3,204)} = 6.453$; $P = 0.000$), structural style scores ($F_{(3.204)} = 2.760$; $P = 0.043$), and the frequency of following the COVID-19 news and case numbers. According to the results of the Tukey *post hoc* test conducted to determine which group caused the difference, for indecision: it was determined that the indecision scores of the participants with weekly follow-up frequency were higher than other participants; for the structural style: it has been determined that the structural style scores of the participants who have several follow-ups every day were higher than the participants who looked if coincidentally. [Table 3]

According to the analysis results, VOCI ($F_{(3.204)} = 5.578$; $P = 0.001$), contamination ($F_{(3.204)} = 10.354$;

Table 6: Analysis of variance results of the relationship between the frequency of cleaning and disinfection of the place experienced in the pandemic with the scale scores of the sample

Frequency	*n*	$\bar{X}$	SD	Minimum	Maximum	*F*	*P*	Difference
VOCI								
Several times a day	45	80.84	37.17	8	152	4.958	0.002*	1-2
Once a day	72	60.13	37.15	5	166			1-3
2-3 times a week	54	59.51	37.88	4	157			2-1
4-5 times a week	37	81.83	46.60	9	186			3-1
Contamination								
Several times a day	45	21.24	11.00	3	45	3.877	0.010*	1-3
Once a day	72	17.65	9.84	1	41			3-1
2-3 times a week	54	15.16	8.74	2	37			
4-5 times a week	37	20.62	10.41	3	46			
Checking								
Several times a day	45	9.97	6.14	0	22	2.852	0.038*	1-2
Once a day	72	6.63	6.20	0	24			2-1
2-3 times a week	54	7.14	6.05	0	24			
4-5 times a week	37	8.18	6.95	0	24			
Obsessions								
Several times a day	45	14.33	8.32	1	29	4.777	0.003*	1-2
Once a day	72	9.65	8.09	0	31			1-4
2-3 times a week	54	11.44	9.33	0	33			2-1
4-5 times a week	37	16.02	12.22	1	39			4-1
Hoarding								
Several times a day	45	7.22	5.63	0	20	5.173	0.002*	1-2
Once a day	72	4.11	4.50	0	19			1-4
2-3 times a week	54	4.87	4.72	0	17			2-1
4-5 times a week	37	7.18	5.83	0	18			4-1
Absolute accuracy								
Several times a day	45	18.84	9.30	0	38	3.773	0.011*	3-4
Once a day	72	14.84	9.77	1	45			4-3
2-3 times a week	54	13.96	10.11	0	43			
4-5 times a week	37	19.67	11.63	2	46			
Indecision								
Several times a day	45	9.22	5.31	0	19	3.912	0.010*	2-4
Once a day	72	7.23	5.43	0	23			3-4
2-3 times a week	54	6.92	4.86	0	23			4-2
4-5 times a week	37	10.13	5.97	1	22			4-3

*$P \leq 0.05$: Statistically significant. VOCI: Vancouver Obsessive-Compulsive Inventory, SD: Standard deviation

Table 7: *t*-test results of the relationship between the scale scores of the sample and psychological support

Support	*n*	$\bar{X}$	SD	*t*	*P*
Family cohesion					
Yes	31	17.45	2.77	-2.643	0.009*
No	177	18.94	2.91		

*$P \leq 0.05$: Statistically significant. SD: Standard deviation

P = 0.000), checking (F (3.204) = 2.772; P = 0.043), obsessions (F (3.204), absolute accuracy (F (3.204) = 4.633; P = 0.004), indecision (F (3.204) = 3.985; P = 0.009), and one of the RSA subdimensions self-perception (F (3.204) = 2.957; P = 0.033), it is found that there is a significant difference between the scores and self-examination for the representation of COVID-19 symptoms. [Table 4] According to the results of Tukey *post hoc* test, in participants who almost always examine themselves for symptoms, VOCI, contamination, checking, obsessions, absolute accuracy, indecision, and self-perception scores were higher.

The contamination (P = 0.021) and hoarding (P = 0.024) scores were significantly higher in participants with a change in cleaning frequency. [Table 5] On the other hand, the self-perception (P = 0.050) score was significantly higher in participants with no change in cleaning frequency. [Table 6]

There was a significant difference in VOCI (F (3.204) = 4.958; P = 0.002), contamination (F (3.204) = 3.887; P =

Table 8: Analysis of variance results of the relationship between the scale scores of the sample and the thought of obtaining psychological support

Thought	*n*	$\bar{X}$	SD	Minimum	Maximum	*F*	*P*	Difference
VOCI								
Yes	26	79.92	41.79	24	186	16.958	0.000*	1-2
No	139	58.04	36.99	4	157			2-1
Indecisive	43	94.51	36.37	11	166			2-3
								3-2
Contamination								
Yes	26	19.23	9.95	7	46	7.618	0.001*	2-3
No	139	16.61	9.35	1	40			3-2
Indecisive	43	23.25	11.21	2	45			
Checking								
Yes	26	8.15	6.88	0	24	6.549	0.002*	2-3
No	139	6.79	5.94	0	24			3-2
Indecisive	43	10.69	6.62	0	24			
Obsessions								
Yes	26	15.76	9.86	2	39	20.832	0.000*	1-2
No	139	9.56	8.31	0	36			2-1
Indecisive	43	18.86	9.49	2	38			2-3
								3-2
Hoarding								
Yes	26	6.57	4.98	0	18	7.114	0.001*	2-3
No	139	4.62	5.04	0	20			3-2
Indecisive	43	7.81	5.21	0	17			
Absolute accuracy								
Yes	26	19.03	10.73	5	46	14.861	0.000*	1-2
No	139	13.86	9.47	0	43			2-1
Indecisive	43	22.72	9.75	2	45			2-3
								3-2
Indecision								
Yes	26	11.15	6.55	2	23	18.860	0.000*	1-2
No	139	6.58	4.97	0	23			2-1
Indecisive	43	11.16	4.25	1	21			2-3
								3-2
Family cohesion								
Yes	26	17.46	3.47	12	26	4.783	0.009*	1-2
No	139	19.13	2.67	11	29			2-1
Indecisive	43	18.13	3.16	10	26			

*$P \leq 0.05$: Statistically significant. VOCI: Vancouver Obsessive-Compulsive Inventory, SD: Standard deviation

0.010), checking (F (3.204) = 2.852; $P = 0.038$), obsessions (F (3.204) = 4.777; $P = 0.003$), hoarding (F (3.204) = 5.173; $P = 0.002$), absolute accuracy (F (3.204) = 3.773; $P = 0.011$), and indecision (F (3.204) = 3.912; $P = 0.010$) scores depending on the frequency of cleaning and disinfection of the place lived in the pandemic process. According to the Tukey *post hoc* test conducted to determine which group caused the difference, VOCI and its subdimensions contamination, checking, obsessions, and hoarding scores are higher in participants who had a frequency of cleaning several times a day compared to others. [Table 7] For absolute accuracy and indecision: The scores of the participants who had 4–5 times of cleaning per week were higher than the others. [Table 8]

The family cohesion ($P = 0.009$) scores of the participants who did not receive psychological support have found to be significantly different and higher than the participants who received psychological support.

There was a significant difference in VOCI (F (2.205) = 16.958; $P = 0.000$), contamination (F (2.205) = 7.618; $P = 0.001$), checking (F (2.205) = 6.549; $P = .002$), obsessions (F (2.205) = 20.832; $P = 0.000$), hoarding (F (2.205) = 7.114; $P = 0.001$), absolute accuracy (F (2.205) = 14.861; $P = 0.000$) and indecision (F (2.205) = 18.860; $P = 0.000$) scores, depending on the idea of getting psychological support, and there is a significant difference between the

Table 9: *t*-test results of the relationship between scale scores of the sample and gender

Gender	*n*	$\bar{X}$	SD	*t*	*P*
Hoarding					
Female	107	4.68	4.69	-2.422	0.016*
Male	101	6.42	5.61		
RSA					
Female	107	104.86	9.33	3.310	0.001*
Male	101	100.83	8.17		
Self perception					
Female	107	19.68	2.45	3.717	0.000*
Male	101	18.34	2.72		
Structural style					
Female	107	13.38	2.69	2.203	0.029*
Male	101	12.60	2.38		
Family cohesion					
Female	107	19.28	3.12	2.872	0.004*
Male	101	18.12	2.61		

*$P \leq 0.05$: Statistically significant. RSA: Resilience Scale for Adults, SD: Standard deviation

Table 10: *t*-test results of the relationship between the scale scores of the sample and marital status

Marital status	*n*	$\bar{X}$	SD	*t*	*P*
VOCI					
Single	150	73.033	40.96	2.758	0.006*
Married	58	56.12	35.99		
Contamination					
Single	150	19.59	10.14	2.983	0.003*
Married	58	15.00	9.46		
Hoarding					
Single	150	6.16	5.26	2.851	0.005*
Married	58	3.89	4.77		
Absolute accuracy					
Single	150	17.55	10.52	2.767	0.006*
Married	58	13.20	9.14		
Indecision					
Single	150	8.78	5.71	3.322	0.001*
Married	58	6.32	4.37		
Self perception					
Single	150	18.73	2.58	-2.647	0.009*
Married	58	19.81	2.73		
Family cohesion					
Single	150	18.45	2.99	-2.130	0.034*
Married	58	19.41	2.69		

*$P \leq 0.05$: Statistically significant. VOCI: Vancouver Obsessive-Compulsive Inventory, SD: Standard deviation

idea of getting psychological support. According to the results of Tukey *post hoc* test conducted to determine which group caused the difference, VOCI and its subdimensions contamination, checking, obsessions, hoarding, absolute accuracy, and indecision scores were found higher in participants who were indecisive at the idea of getting psychological support than others. [Table 9] For family cohesion: scores of the participants who had no idea of getting psychological support were higher.

According to the analysis, female participants' RSA ($P = 0.001$), self-perception ($P = 0.000$), structural style ($P = 0.029$), and family cohesion ($P = 0.004$) scores are significantly different and higher than male participants. On the other hand, hoarding ($P = 0.016$) scores of the male participants are significantly different and higher than female participants. [Table 10]

According to the analysis, VOCI ($P = 0.006$), contamination ($P = 0.003$), hoarding ($P = 0.005$), absolute accuracy ($P = 0.006$), and indecision ($P = 0.001$) scores of the single participants were found to be significantly different and higher than married participants. On the other hand, the scores of self-perception ($P = 0.009$) and family cohesion ($P = 0.034$) of married participants were found to be significantly different and higher than single participants.

According to the analysis result, There was significant negative correlation between age and VOCI ($r = -0.250$; $P = 0.000$), contamination ($r = -0.235$; $P = 0.001$), obsessions ($r = -0.196$; $P = 0.005$), stacking ($r = -0.241$; $P = 0.000$), absolute accuracy ($r = -0.234$; $P = 0.001$), indecision ($r = -0.274$; $P = 0.000$) and future perception ($r = -0.148$; $P = 0.033$), social resources ($r = -0.149$; $P = 0.032$). On the other hand, a positive and statistically significant relationship was found between age and the subdimensions of RSA - self-perception ($r = 0.162$; $P = 0.019$) and social competence ($r = 0.167$; $P = 0.016$). According to these results, as individual's age increases, self-perception and social competence increase, while VOCI, contamination, obsessions, hoarding, absolute accuracy, indecision, future perception, and social resources scores decrease.

According to the correlation results, Accordingly, there was a statistically significant and positive correlation between VOCI and contamination ($r = 0.812$; $P < 0.01$), checking ($r = 0.808$; $P < 0.01$), obsessions ($r = 0.887$; $P < 0.01$), hoarding ($r = 0.820$; $P < 0.01$), absolute accuracy ($r = 0.941$; $P < 0.01$), indecision ($r = 0.804$; $P < 0.01$), future perception ($r = 0.173$; $P < 0.05$), structural style ($r = 0.139$; $P < 0.05$), and social resources ($r = 0.211$; $P < 0.01$). [Table 11] A statistically significant and positive relationship has found between RSA with self-perception ($r = 0.617$; $P < 0.01$), planned future ($r = 0.491$; $P < 0.01$), structural style ($r = 0.572$; $P < 0.01$), social competence ($r = 0.495$; $P < 0.01$), family cohesion ($r = 0.610$; $P < 0.01$), and social resources ($r = 0.566$; $P < 0.01$). On the other hand, there is a statistically significant and negative relationship between obsessions and family cohesion ($r = -0.163$; $P < 0.05$). [Table 12]

Discussion

There are studies conducted during the pandemic period on people diagnosed with OCD. These studies indicate that contamination obsession and cleaning compulsion increased during the epidemic period.[23,24] In our study,

Table 11: The correlation analysis results of the relationship between the scale scores of the sample and age

	Age
VOCI	
r	-0.250
P	0.000**
Contamination	
r	-0.235
P	0.001**
Obsessions	
r	-0.196
P	0.005**
Hoarding	
r	-0.241
P	0.000**
Absolute accuracy	
r	-0.234
P	0.001**
Indecision	
r	-0.274
P	0.000**
Self-perception	
r	0.162
P	0.019*
Planned future	
r	-0.148
P	0.033*
Social competence	
r	0.167
P	0.016*
Family cohesion	
r	0.135
P	0.052
Social resources	
r	-0.149
P	0.032*

VOCI: Vancouver Obsessive-Compulsive Inventory, ** P<.001

the contamination subdimension score has found to be higher on the obsession–compulsion scale. It is a known fact that COVID-19 spreads through contact. Accordingly, the result found is quite meaningful and compatible with the literature. In the psychological resilience scale, the social resources subdimension score is higher than the other subdimensions. All subdimensions of psychological resilience were positively correlated with each other. Despite the isolation process, it can be said that strong social ties and communication with other individuals have a significant effect on resilience. The total obsessive–compulsive score and future perception, structural style, and social resources were found to be significantly and positively related. That's not what we expected. The characteristics of the sample are significant in this sense. It can be said that the pandemic period reinforces the obsessions–compulsions that are present in every individual, even if only a little, and causes them to be internalized. It can be thought that the process taking longer than expected creates a habituation situation. Since psychological resilience is expressed as the ability to adapt despite adverse conditions, even if people show signs of obsession–compulsion, they may cope more easily thanks to their high endurance. Besides, a negative relationship was found between obsessions and family cohesion. Affecting the whole family from a problem experienced by the person and there may be troubles in the family.

When the previous studies are examined, individuals generally prefer to receive support from the family and social environment and do not want to seek professional support unless there is a serious problem. In a study with university students, it says that students meet their needs for psychological support from friends or family, rather than someone who is an expert in the field. They are generally looking for psychological support due to emotional, personality, and family problems.[25] Participants who were indecisive about the psychological support had higher scores of obsession compulsion total score, contamination, checking, obsessions, absolute accuracy, hoarding, and indecision subdimensions. The result found overlaps with the characteristics of OCD and the indecision subdimension. No differentiation was observed in the total score of psychological resilience. Family adjustment, which is the subdimension of psychological resilience, was found higher in participants who did not think of getting support. Studies confirm that people prefer family members first, rather than psychological support. It can be said that an individual with harmonious family relationships and support will not need expert help. In this case, it is seen that positive interaction and communication with individuals at home are too important during the pandemic process. It can be said that the stronger and more harmonious the relationships with the people living together are, the less affected individuals will be affected by this process.

When we look in terms of news and case follow-up frequency, weekly news and case follow-ups were found to be associated with the indecision subdimension. The uncertainty experienced considering it is quite possible to see it in its indecision with the uncertainty in this period. The structural style score, which is the psychological resilience subdimension, was found higher in participants who had a frequency of following several times a day. Structural style can also express as the ability to make daily, weekly, and monthly plans. In fact, in this case, it is necessary to take into account of people's news-watching habits. News and case tracking can be part of the daily routine. Structural style is also the ability to control one's self. Individuals with a high structural style may prefer to stay away from events and news when they think they are affected. Some studies support our findings as well as studies that do not. In a previous study, it has concluded that the psychological resilience of people differentiates depending on the following COVID-19 development.[26] In

Table 12: The correlation analysis results of the relationship between the scales

		(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)	(13)	(14)
(1) VOCI	R	1													
(2) Contamination	R	0.812**	1												
(3) Checking	R	0.808**	0.602**	1											
(4) Obsessions	R	0.887**	0.591**	0.652**	1										
(5) Hoarding	R	0.820**	0.582**	0.542**	0.742**	1									
(6) Absolute accuracy	R	0.941**	0.689**	0.763**	0.809**	0.743**	1								
(7) Indecision	R	0.804**	0.532**	0.571**	0.690**	0.669**	0.751**	1							
(8) RSA	R	0.116	0.146*	0.113	0.091	0.045	0.091	0.080	1						
(9) Self perception	R	-0.019	0.065	0.033	-0.039	-0.099	-0.048	-0.047	0.617**	1					
(10) Planned future	R	0.173*	0.072	0.160*	0.229**	0.095	0.137*	0.201**	0.491**	0.205**	1				
(11) Structural style	R	0.139*	0.174*	0.096	0.101	0.038	0.126	0.138*	0.572**	0.337**	0.159*	1			
(12) Social competence	R	-0.045	-0.030	0.038	-0.041	-0.036	-0.044	-0.130	0.495**	0.121	0.096	0.108	1		
(13) Family cohesion	R	-0.059	0.066	0.005	-0.163*	-0.128	-0.056	-0.051	0.610**	0.343**	0.138*	0.188**	0.243**	1	
(14) Social resources	R	0.211**	0.131	0.081	0.245**	0.256**	0.193**	0.181**	0.566**	0.094	0.286**	0.164*	0.113	0.078	1

*$P<0.05$: Statistically significant; **$P<0.01$: Statistically significant. VOCI: Vancouver Obsessive-Compulsive Inventory, RSA: Resilience Scale for Adults

another study, it was stated that the psychological resilience of the participants who learned the information about COVID-19 from official institutions was higher than the participants who learned on social media.[27] There are also studies stating that there is no relationship between following the COVID-19 news, cases, and being psychologically healthy.[28]

Participants were asked how often they examined themselves for the COVID-19 symptom. According to the analysis results, participants who answered "almost always" had high scores of obsession–compulsion overall score and contamination, checking, obsessions, absolute accuracy, and indecision. When considering anxiety and contamination concerns, the result found is quite meaningful. Often dealing with somatic symptoms reminds us to obsessions. Self-perception, which is one of the subdimensions of psychological resilience, was found to be associated with body scan frequency. Self-perception is also associated with physical well-being (Tutar *et al.*, 2009).[29] In a study, it was stated that people with high self-perception had fewer symptoms of anxiety.[30] Individuals with high self-perception may be doing body scanning, not because of anxiety, but to take the necessary precautions if they show symptoms.

The frequency of cleaning and disinfection behavior had examined to determine how long the participant was busy with this situation in a week. There was no difference between psychological resilience and the frequency of cleaning before and during the pandemic period. In a study, it was concluded that as the anxiety increased, the efforts regarding cleaning increased.[31] In another study on hygiene, it was stated that individuals have more hygiene and hygiene-oriented behaviors who have disease anxiety.[32] In another study, psychological resilience was found associated with the cleaning and disinfecting behaviors during the epidemic period.[27] When examined in terms of obsession and compulsion scores, although there was no difference before the pandemic, there were significant differences in the frequency of cleaning during the pandemic period. It was found that the VOCI, contamination, checking, obsessions, and hoarding scores of the participants whose cleaning and disinfection frequency were several times a day were higher than the other participants. Although the findings were not at the desired level in terms of psychological resilience, predictable results were obtained in terms of obsession–compulsion. In another study, it is considered that obsessions and compulsions should be investigated in terms of alternative variables. Besides, the question was asked, "Did your cleaning frequency change during the pandemic period?" as the subjective assessment of the participant is important, and as can be predicted, a majority stated that they have changed.

There are different studies and different findings analyzing the relationship between psychological resilience and

gender. Haring *et al*.[33] stated as a result of their research that men have higher psychological well-being levels than women. They found gender as a significant predictor of subjective well-being. In a study examining the relationship between COVID-19 and psychological resilience, women's resilience was found to be higher than men's.[27] In our study, a significant difference was found between gender and psychological resilience level. The psychological resilience level of women is significantly higher than men's. In a study, it has been noted that obsessive–compulsive behaviors and anxiety levels increase in pregnant women on the COVID-19 outbreak.[34] The number of samples and sample characteristics is thought to be effective in finding the different results.

Psychological resilience scores of married individuals were found higher than singles in a study conducted with adult participants (Türker, 2018). In some studies, no significant relationship is found between marital status and psychological resilience.[27,35] When we look at our findings, no difference had found between psychological resilience total score and marital status. However, when the subdimensions were examined, it was found that married participants' self-perception and family adjustment were significantly higher than single participants. Another study indicates that married individuals have higher self-perception than singles.[29] Some factors have a positive effect on psychological resilience. All kinds of supportive attitudes felt among family members can be expressed as strong family ties, a romantic relationship, nurturing the parenting aspect.[36] It can be thought that the support that married participants receive from their partners and children, their romantic relationship with their partner and their commitment to each other, and their parenting roles and their skills in this regard reinforce resilience. From another perspective to approach the result, the high subdimensions may be due to the difference between the number of married participants and the number of single participants.

Looking at the literature, in a study conducted, a low-level positive relationship has been found between OCD scores and age. In other words, as age increases, OCD scores increase.[37] Some studies support our findings.[38] According to the results of our analysis, as the age of the individual's increases, the scores obtained from the subscales of obsession–compulsion total score, contamination, obsessions, hoarding, absolute accuracy, and indecision decrease. There was no differentiation in terms of total score in the relationship between psychological resilience and age. However, when we look at the subdimensions, it was found that as individuals' age increases, their self-perception and social competence are increased, while their future perception and social resources scores decrease. As the experiences of individuals increase depending on age, it will be possible to reach a level that they can understand and analyze them better and give clearer answers to the question of "who am I." Accordingly, individuals can increase their self-perception and social competence as their age increases. However, when the person reaches a certain age, although their social competence increases, the bonds in their social relationships may weaken. In a study conducted with healthcare professionals during the pandemic period, it was stated that as age increases, psychological resilience also increases.[39,40]

Patient informed consent

Informed consent was obtained.

Ethics committee approval

The ethics committee approval has been obtained from the Uskudar University non-interventional research ethics committee (613551342/2020-360).

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There is no conflict of interest to declare.

Author contribution area and rate

Zeynep Atalay (60%): She designed the research, data collection and analysis and wrote the entire article.

Merv Çebi (30%): Contributed with comments on research design and slides interpret.

Zeynep Gümüş Demir (10%): Supervised the article write-up.

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Original Article

Examining the Relationship between the Knowledge of Sexually Transmitted Diseases and Sexual Myths among University Students in Turkey

Abstract

Objective: The purpose of this study is to evaluate the level of knowledge among university students on sexually transmitted diseases (STDs) and to compare the level of knowledge of this sample on STDs and their sexual myths. **Methods:** The sociodemographic data of 200 university students studying at several universities in Turkey randomly selected between January and March 2019 were evaluated with the "Sociodemographic Questionnaire," their knowledge of STDs with the Sexually Transmitted Diseases Knowledge Questionnaire (STDKQ), and their beliefs in sexual myths with the Sexual Myths Scale (SMS). **Results:** There was no difference between the STDKQ and the SMS in terms of demographic variables. However, differentiation was seen between the "sexual behavior," which is one of the subscales of sexual myths, and STDs. The STDKQ scores revealed that individuals who were previously informed received higher scores than those who did not. The level of knowledge about STDs was higher in men than in women. **Conclusion:** The knowledge of STDs among university students and their beliefs in sexual myths were evaluated based on sociodemographic variables. According to the results, we obtained from our research to increase the level of knowledge about STDs, and for the healthy development of sexual behavior, formal education including sexual health issues should be provided, research should be done for each region in Turkey on this subject, and in line with the results, necessary information should be provided regarding sexual health.

Keywords: *Sexual myths, sexually transmitted diseases, university students*

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Introduction

Sexuality is one the fundamental components of human life. Sexual act is influenced by attraction, availability, fantasy, and the actual act.[1] Gender is defined as the pattern of characteristics pertaining to masculinity and femininity and has been seen as binary. There is a distinction between biological sex and gender as a role: Gender role is the manner in which individuals express their status in the society.[2] Gender identity refers to one's sense of oneself as male, female, or of unidentified gender.[3] Sexual orientation refers to the sex of those to whom one is sexually and romantically attracted.[4] Although it was presented by Kinsey about 60 years ago, the recognition of sexual orientation as a spectrum happens gradually.[5] Sexual fluidity has been defined as situation-dependent flexibility in sexual responsiveness, which may manifest in changes in sexual orientation identity over time.[6]

Sexually transmitted diseases (STDs) are one of the factors that adversely affect public health. STDs are transmitted from person to person through sexual intercourse. STDs are transmitted through blood, semen, different body fluids, or by direct contact with the infected body area. There are many STDs including hepatitis B and C, urogenital fungal infections, trichomoniasis, and AIDS.[7] According to the World Health Organization, sexually transmitted infections (STIs) are one of the five types of disease, for which adults around the world most commonly

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seek medical help.[8] Physicians and other healthcare providers play a critical role in preventing and treating STDs.[9] More than 1 million STIs are acquired every day worldwide. Each year, there are an estimated 376 million new infections with 1 of 4 STIs: chlamydia, gonorrhea, syphilis, and trichomoniasis.[10,11] The UNAIDS released in July 2019 the updated estimates for HIV figures worldwide. Overall, 37.9 million people are currently living with HIV, more than 80% in developing countries and mostly in Sub-Saharan Africa. Roughly, 1.7 million 12 new HIV infections occurred during the year 2018, which represents 5000 new infections per day Overall, 61% of these new infections occur in Sub-Saharan Africa, 10% in children, half of them in women, and one-third in adolescents and youth. Finally, 770,000 persons died from AIDS during the year 2018, being a significant proportion of them late presenters. Clearly, the AIDS pandemic is slowing down but not as rapidly as desirable.

Rise in marriage age in Turkey is related to the increase in education level and job status. Therefore, having sexual intercourse at a younger age and having sexual intercourse before marriage are rising further. Since young people start having sexual intercourse at an earlier age, the risk of contracting these STDs is also increased. Failure of young people to get accurate information about sexuality or to be misinformed can cause difficulties when struggling with these diseases.[12] From a public health perspective, it is necessary to ensure that young people receive education from the right sources about STDs in the early stages and know how to prevent these diseases.

Sexual myths consist of exaggerated and unrealistic expectations. They are also referred to as sexual fabulation, and these sexual myths have a very important effect on living a healthy sex life in the society. Beliefs that are spreading by word of mouth, have changed shape with the imagination of people in society, and are not linked to any scientifically proven data are called sexual myths, and these negative thoughts have nothing to do with the reality of sexuality.[13]

The primary purpose of this study is to compare different sociodemographic groups in terms of information about STD and sexual myths. The second purpose of the study is to investigate the relationship between the level of knowledge about STDs and sexual myths.

Methods

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Üsküdar University noninterventional studies ethics committee on April 25, 2019, with the number 61351432-/2019-197.

Participants

The population subject to the research is university students, and the sample is university students studying at several universities in the Marmara region of Turkey, enrolled by simple random selection between January and March 2019, interviewed face to face or by mail.

The design of our study is cross-sectional, observational, and descriptive. The sociodemographic data of the participants were evaluated using the "Sociodemographic Questionnaire," their knowledge of STDs with the Sexually Transmitted Diseases Knowledge Questionnaire (STDKQ), and their beliefs in sexual myths with the Sexual Myths Scale (SMS).

In addition, sexual orientation, gender, age, sexual behavior, masturbation, sexual violence, sexual intercourse, and sexual satisfaction scores, which are SMS subscales, were also included in our study. Independent categorical variables were the sociodemographic data of the participants, and dependent (outcome) numerical variables were the scores of STDKQ, SMS, and SMS subscales. Using the G*POWER 3.1 program, the sample size was determined as $n = 200$ with 2 hypotheses, type 1 error = 0.05, power = 0.80, effect size $d = 0.40$.[14]

The criteria for inclusion were volunteering to participate in the study and the absence of any physical or mental illness.

Materials

Sociodemographic Data Form

The sociodemographic data form is used to obtain detailed information about the individuals who contributed to the questionnaires applied. The information obtained will provide information on the effect of different variables in the research. This form filled in by the interviewer.

Sexual Myths Scale

SMS is a scale consisting of 28 questions. The Sexual Myth Assessment Form was developed by Zilbergeld, 1999.[15] Although being a Likert-type scale, it is considered valid with 0.91 points. Possible answers are "I Never Agree," "I Disagree," "I am Undecided," "I Agree Partially," and "I Strongly Agree."

It was adapted to Turkish by Golbası *et al*., 2016.[16]

Sexually Transmitted Diseases Knowledge Questionnaire

This is a knowledge questionnaire about STDs. This test, originally called STI/HIV pretest, consists of 40 items. STDKQ was developed by Brislin, 1970.[17] It was adapted to Turkish by Siyez and Siyez, 2009,[18] and the number of items was reduced to 36 by removing four items that are not suitable for the country conditions and Turkish students. Possible answers are "correct," "false," and "I don't know."

Data analysis

Two hundred people participating in the research were divided into groups according to the sociodemographic variables. Normal distribution was assessed by skewness and sharpness in the histogram, Q-Q plot and Kolmogorov–Smirnov tests. Variance homogeneity was evaluated by Levene test. The differences between the means of two independent groups were tested with the *t*-test, while the differences between the means of more than two groups were tested with one-way ANOVA. Type-I error value was accepted as $\alpha = 0.05$.

Results

Sixty percent (n = 120) of the 200 participants were women and 40% (n = 80) were men. According to the age data of the participants, 9.5% (n = 19) aged between 17 and 19 years, 26% (n = 52) aged between 20 and 22 years, 42% (n = 84) aged between 23 and 25 years, and 22.5% (n = 45) were older than 26 years. According to the data on the marital status of the participants, 13% (n = 26) were married. According to the status of getting information about STD, 79.5% had prior information while 20.5% did not. When they were asked whether they request to get information about STDs, 89.5% were willing to get information about STDs, while 10.5% were not [Table 1a].

When the "barrier," "oral contraceptive," and "withdrawal" options under "protection status during sexual intercourse" variable related to protection from sexual diseases were examined, no significant difference was found between sexual myths and sexual myths subscales. While the percentage of students who marked

Table 1a: Comparison of participants' scale scores according to sociodemographic data

Variables	*n* (%)	STDKQ total		SMS total		Sexual orientation†		Gender†	
		Average (SD)	*t* (*P*)	Average (SD)	*t* (*P*)	Average (SD)	*t* (*P*)	Average (SD)	*t* (*P*)
Gender									
Women	120 (60)	12.12 (4.15)	−3.183*	50.70 (15.84)	−1.121	10.57 (4.64)	1.946*	8.83 (3.33)	−3.196*
Men	80 (40)	14.26 (5.30)	(0.002)	53.41 (18.06)	(0.264)	9.32 (4.86)	(0.049)	10.62 (4.58)	(0.002)
Marital status									
Married	26 (13.0)	13.69 (5.30)	0.818	59.38 (20.91)	2.509	13.73 (5.18)	4.388**	10.69 (4.92)	1.578
Single	174 (87.0)	12.87 (4.67)	(0.414)	50.64 (15.83)	(0.013)	9.52 (4.45)	(<0.001)	9.37 (3.79)	(0.116)
Sexual act within last year									
Yes	126 (63.0)	13.12 (4.94)	1.578	48.78 (16.19)	−3.384**	9.06 (4.29)	−4.704**	9.37 (3.96)	−0.821
No	74 (37.0)	12.72 (4.43)	(0.116)	56.89 (16.63)	(<0.001)	11.79 (5.04)	(<0.001)	9.85 (3.98)	(0.412)
STD prior information									
Yes	151 (79.5)	11.48 (4.69)	−3.011*	51.22 (17.32)	−0.937	10.01 (4.86)	−0.328	9.51 (4.12)	−0.240
No	49 (21.5)	13.02 (4.54)	(0.003)	53.97 (14.45)	(0.357)	10.29 (4.37)	(0.743)	9.68 (3.37)	(0.811)
STD request for information									
Yes	179 (89.5)	13.02 (4.66)	0.415	50.87 (16.5)	−2.257*	9.76 (4.64)	−2.730*	9.32 (3.88)	−2.376*
No	21 (10.5)	12.57 (5.59)	(0.678)	59.52 (17.15)	(0.025)	12.71 (4.99)	(0.007)	11.47 (4.29)	(0.018)
Characteristic	***n* (%)**	**post-hoc**	***F* (*P*)**	**post-hoc**	***F* (*P*)**	**post-hoc**	***F* (*P*)**	**post-hoc**	***F* (*P*)**
Methods of sexual protection									
Withdrawal	62 (31.0)	1, 3	3.139*	-	0.364	-	2.139	-	0.383
OCs	27 (13.5)		(0.046)		(0.695)		(0.120)		(0.682)
Barrier	111 (55.5)								
Education level (mother)						-			
Illiterate	7 (3.5)	-	0.385	2, 5	4.067*		1.809	2, 5	2.798*
Primary school	47 (23.5)		(0.820)	3, 5	(0.003)		(0.129)	3, 5	(0.027)
Secondary school	32 (16.0)								
High school	60 (30.0)								
University	54 (27.0)								
Education level (father)								-	
Illiterate	2 (1)	-	0.405	-	1.912		1.396		2.007
Primary school	41 (20.5)		(0.805)		(0.110)		(0.237)		(0.095)
Middle school	32 (16.0)								
High school	61 (30.5)								
University	64 (32.0)								

*P<0.05, **P<0.001, †SMS subscales. SD: Standard deviation, n: Number of sample, t: Independent group t-test value, F: One-way ANOVA F test

the barrier variable was 55.5%, those who selected the oral contraceptive option were 13.5% and the withdrawal were 31.0% [Tables 1a-c].

A significant relationship was found between the "sexual behavior" subscale of sexual myths and the scores of STD. All the subscales of the SMS had a positive significant correlation with each other. The comparison of STDKQ, SMS, and sexual myths subscales in terms of gender revealed higher STDKQ scores in men than in women. With regard to the "sexual orientation," which is one of the SMS subscales, women's scores were higher than men, and in other SMS subscales, the scores of men in "gender," "age and gender," and "sexual violence" were higher than that of women [Tables 1b and c].

Marital status, which is a demographic variable, did not show a statistically significant difference in terms of STDKQ scores. The level of belief in sexual myths was higher in married individuals compared to singles. "Sexual orientation" and "sexual violence," which are the subscales of sexual myths, differed significantly between married and single people. Sexual orientation and sexual violence scores were found higher in married students. Belief in sexual myths has been evaluated according to the variable of "having sexual intercourse within the past year," and students who have not had sexual intercourse within the past year had higher levels of belief in sexual myths. There was a significant difference in the demographic variable of "request for information about STDs" in terms of sexual myths. People who do not want to receive information about STDs had higher sexual myth scores [Tables 1a-c].

When the demographic variable "education level of the mother" was examined, no significant difference was found

Table 1b: Comparison of participants' scale scores according to sociodemographic data

Variables	*n* (%)	Age and gender†		Sexual behavior†		Masturbation†	
		Average (SD)	*t* (*P*)	Average (SD)	*t* (*P*)	Average (SD)	*t* (*P*)
Gender							
Women	120 (60)	7.11 (2.81)	−2.487*	4.40 (2.07)	−3.221*	4.09 (1.96)	1.284
Men	80 (40)	8.28 (3.83)	(0.014)	5.51 (2.76)	(0.001)	3.73 (1.83)	(0.201)
Marital status							
Married	26 (13.0)	7.26 (3.25)	−0.521	5.57 (2.83)	1.642	4.42 (2.17)	1.354
Single	174 (87.0)	7.63 (3.31)	(0.603)	4.74 (2.35)	(0.102)	3.87 (1.86)	(0.177)
Sexual act within the last year							
Yes	126 (63.0)	6.88 (2.81)	−4.034**	4.65 (2.37)	−1.456	3.52 (1.75)	−4.283**
No	74 (37.0)	8.77 (3.72)	(<0.001)	5.17 (2.51)	(0.147)	4.67 (1.97)	(<0.001)
STD prior information							
Yes	151 (79.5)	7.49 (3.32)	−0.742	4.83 (2.41)	−0.155	3.91 (1.95)	−0.461
No	49 (21.5)	7.92 (3.23)	(0.459)	4.90 (2.52)	(0.877)	4.07 (1.78)	(0.645)
STD request for information							
Yes	179 (89.5)	7.38 (3.22)	−2.527*	4.79 (2.35)	−0.963	3.94 (1.95)	−0.006
No	21 (10.5)	9.28 (3.57)	(0.012)	5.33 (3.00)	(0.337)	3.95 (1.59)	(0.995)
Variables	***n* (%)**	**post-hoc**	***F* (*P*)**	**post-hoc**	***F* (*P*)**	**post-hoc**	***F* (*P*)**
Methods of sexual protection							
Withdrawal	62 (31.0)	-	0.203	-	0.740	-	2.045
OCs	27 (13.5)		(0.816)		(0.479)		(0.132)
Barrier	111 (55.5)						
Education level (mother)							
Illiterate	7 (3.5)	3,5	3.883*	-	1.604		0.519
Primary school	47 (23.5)		(0.005)		(0.175)		(0.722)
Secondary school	32 (16.0)						
High school	60 (30.0)						
University	54 (27.0)						
Education level (father)							
Illiterate	2 (1)	-	1.554	-	0.385		0.055
Primary school	41 (20.5)		(0.188)		(0.819)		(0.994)
Middle school	32 (16.0)						
High school	61 (30.5)						
University	64 (32.0)						

*P<0.05, **P<0.001, † SMS subscales. SD: Standard deviation, *n*: Number of sample, *t*: Independent group *t*-test value, F: One-way ANOVA F test

Table 1c: Comparison of participants' scale scores according to sociodemographic data

Variables	*n* (%)	Sexual violence†		Sexual intercourse†		Sexual satisfaction†	
		Average (SD)	*t* (*P*)	Average (SD)	*t* (*P*)	Average (SD)	*t* (*P*)
Gender							
Women	120 (60)	5.99 (2.26)	0.270 (0.788)	4.81 (1.93)	−0.928 (0.355)	4.86 (2.04)	−0.239 (0.811)
Men	80 (40)	5.90 (2.48)		5.08 (2.15)		4.93 (2.07)	
Marital status							
Married	26 (13.0)	7.07 (2.66)	2.652* (0.009)	5.26 (2.14)	0.930 (0.353)	5.34 (2.03)	1.206 (0.229)
Single	174 (87.0)	5.78 (2.25)		4.87 (2.00)		4.82 (2.94)	
Sexual act within the last year							
Yes	126 (63.0)	5.89 (2.44)	0.456 (0.649)	4.71 (2.00)	−1.936 (0.054)	4.66 (2.06)	−2.074* (0.039)
No	74 (37.0)	6.05 (2.17)		5.28 (2.01)		5.28 (1.96)	
STD prior information							
Yes	151 (79.5)	5.87 (2.39)	−0.958 (0.339)	4.84 (2.06)	−1.133 (0.258)	4.71 (2.01)	−1.451 (0.115)
No	49 (21.5)	6.26 (2.15)		5.24 (1.84)		5.58 (2.04)	
STD request for information							
Yes	179 (89.5)	5.88 (2.35)	−1.175 (0.241)	4.91 (2.01)	−0.293 (0.770)	4.86 (2.06)	−0.698 (0.486)
No	21 (10.5)	6.52 (2.24)		5.04 (2.10)		5.19 (1.88)	
Characteristic	***n* (%)**	**post-hoc**	***F* (*P*)**	**post-hoc**	***F* (*P*)**	**post-hoc**	***F* (*P*)**
Methods of sexual protection							
Withdrawal	62 (31.0)	-	1.787 (0.170)	-	0.087 (0.917)	-	0.084 (0.920)
OCs	27 (13.5)						
Barrier	111 (55.5)						
Education level (mother)							
Illiterate	7 (3.5)	-	2.105 (0.082)	2, 4	5.191* (0.001)	2, 4	3.601 (0.007)
Primary school	47 (23.5)			2, 5		2, 5	
Secondary school	32 (16.0)						
High school	60 (30.0)						
University	54 (27.0)						
Education level (father)							
Illiterate	2 (1)	-	1.825 (0.126)	-	2.019 (0.093)	-	2.275 (0.063)
Primary school	41 (20.5)						
Middle school	32 (16.0)						
High school	61 (30.5)						
University	64 (32.0)						

*P<0.05, †SMS subscales. SD: Standard deviation, *n*: Number of sample, *t*: Independent group *t*-test value, F: One-way ANOVA F test

in terms of STD, but a significant difference was seen in sexual myths. Children of university graduate mothers had lower myths scores than other options. When the demographic variable "education level of the father" was examined, no significant difference was found between STD, sexual myths (SM), and sexual myths. The demographic variable "protection method during sexual intercourse" showed a significant difference. There is a significant difference in terms of STDs between "withdrawal" and "barrier" methods of protection during sexual intercourse. There was no significant difference between sexual myths and sexual myths subscales [Tables 1a-c].

There was no statistically significant correlation between STDKQ and SMS total scores. When the sexual myths subscales were evaluated in terms of STDs, there was no statistically significant relationship between "sexual orientation" and STD scores, between "gender" and STD scores, between "age and gender" and STD scores, between "masturbation" and STD scores, between "sexual violence" and STD scores, between "sexual intercourse" and STD scores, and between "sexual satisfaction" and STD points. However, there was a statistically significant weak and positive correlation between "sexual behavior" and STD scores (P = 0.049, rho = 0.140). All the subscales of the SMS had a positive significant correlation with each other [Table 2].

Discussion

In this study, it was found that female students have less knowledge about STDs than male students. However, myths related to gender, age and gender, sexual behavior, and sexual intercourse were less common among female students than male students. In male students, sexual myths related to sexual orientation and masturbation were found less than female students. According to marital status, the level of knowledge and total sexual myth scores

Table 2: Correlation between scales

Scales and subscales		1	2	3	4	5	6	7	8	9	10
1. STDKQ	ρ	-									
	P										
2. SMS	ρ	0.033	-								
	P	0.639									
3. Sexual Orientation†	ρ	0.025	0.781**	-							
	P	0.722	<0.001								
4. Gender†	ρ	0.099	0.742**	0.512**	-						
	P	0.162	<0.001	<0.001							
5. Age and gender†	ρ	0.003	0.753**	0.469**	0.506**	-					
	P	0.963	<0.001	<0.001	<0.001						
6. Sexual behavior†	ρ	0.140*	0.662**	0.393**	0.523**	0.520**	-				
	P	0.049	<0.001	<0.001	<0.001	<0.001					
7. Masturbation†	ρ	−0.131	0.653**	0.496**	0.367**	0.432**	0.375**	-			
	P	0.064	<0.001	<0.001	<0.001	<0.001	<0.001				
8. Sexual violence†	ρ	−0.081	0.715	0.606**	0.594**	0.415**	0.356**	0.424**	-		
	P	0.254	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001			
9. Sexual intercourse†	ρ	0.043	0.656**	0.371**	0.385**	0.482**	0.367**	0.381**	0.409**	-	
	P	0.544	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001		
10. Sexual satisfaction†	ρ	−0.026	0.651**	0.394**	0.389**	0.517**	0.396**	0.445**	0.396**	0.671**	-
	P	0.710	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	

*P<0.05, **P<0.001, †SMS subscales. ρ: Spearman correlation coefficient

about STDs do not differ. Sexual myths were less common among university students who had had sexual intercourse within the past year, and there was no difference in terms of information about STDs between these two groups. It has been observed that the students whose mothers were using the withdrawal method as a method of protection have less knowledge about STDs than those who use the barrier method. University students whose mothers are primary or secondary school graduates had higher total sexual myth scores than university students whose mothers are university graduates. There was no relation between the total score of sexual myths and information about STDs.

The literature search showed no differences in the beliefs of university students on sexual myths, according to gender variable.[19-21] In our study, while myths related to gender, age and gender, sexual behavior, and sexual intercourse were less common among female students, sexual myths related to sexual orientation and masturbation were less common in male students than in female students. The results of our study differing from the findings of previous studies indicate that there may have been a sociocultural change in our country in terms of sexual myths in recent years.

According to a study conducted with nurses, people who have had previous sexual intercourse believed less in myths.[22] In our study, similar findings were found in university students. Less belief in sexual myths was detected in students who had sexual intercourse within the past year. People may be less likely to believe in sexual myths not only through sexual information but also through their experience. Another explanation may be that people who believe less in sexual myths are more willing to have sexual intercourse.

Studies suggest that one of the most important factors that threaten the health status and future of the young population is that sexual health and reproductive health involve risky behaviors.[23] It is essential to generalize the education about sexual health to ensure a healthy life.[24] Many studies conducted in Turkey show that the young population gained information about STD from school lessons as well as from printed visual media. In the study conducted by Dağ *et al*., 2012[25] on 331 university students, it was found that 57.1% acquired information about sexual and reproductive health from TV/internet/books, 15.7% from friends, schools, and conferences, 11.2% from family, 8.5% from doctors, and 7.5% from nurses. STDs are one of the important factors for public health. It is necessary to educate the young population on sexual health issues at an early age to prevent these diseases in the future or to treat an individual with the disease without encountering any greater problems.

Reaching some of the thoughts on STDs by experiencing or through the environment and especially the internet is easier than to reach experts of this topic. Sexual myths have been told from childhood and people can turn these thoughts into myths in their minds and even if people have some sexual experiences, potential of sexual myths to

continue may be higher because they do not have obvious symptoms such as sexual diseases.

While people are expected to get information about sexuality from their families first, the parents not having enough information, the perception of sexuality as a taboo in families, and the families probably having traditional values are thought to cause their children not to talk openly about sexual issues.[26] In our study, more sexual myths were detected among the students whose mother's education level is primary and secondary school compared to those whose mothers are university graduates, supporting the aforementioned opinion. In one study, weak-to-moderate correlation was found between the father's education level and belief in sexual myths,[27] whereas in another study, no relationship was found between believing sexual myths in men and the mother's education level.[21] Larger sample size and multicenter studies are warranted to eliminate the inconsistency in this issue.

No difference was found in the students' beliefs in sexual myths based on the marital status variable. In the study of Torun *et al*., 2011,[21] individuals who are married had higher scores in terms of belief in sexual myths than individuals who are single and divorced. This finding supports the result of our study. According to the findings in our sample, married university students have higher belief in sexual myths than single university students.

The literature search showed no study investigating the relationship between sexual myths and knowledge levels about STDs. When the secondary purpose of our study, that is the determination of this relationship, was evaluated, no significant statistical relationship was found. Reaching some of the thoughts on STDs by experiencing or through the environment and especially the internet is easier than to reach experts of this topic. Sexual myths have been told from childhood and people can turn these thoughts into myths in their minds and even if people have some sexual experiences, potential of sexual myths to continue may be higher because they do not have obvious symptoms such as sexual diseases. In addition, it seems more difficult to learn about myths from the environment and the internet than to learn about STDs. Depending on all these processes, these two variables may be unrelated.

Our study has some limitations. Since the sample is selected from a single region and no stratified sample selection is made according to Turkey's geographical regions, the inferences about the population from the sample may not be strong enough. In addition, our study was designed cross-sectionally. By conducting a longitudinal and multicenter study, more comprehensive and longitudinal information can be obtained about the knowledge of the university students in Turkey about their STDs and their belief in sexual myths.

Conclusion

According to the results, we obtained from our research to increase the level of knowledge about STDs, and for the healthy development of sexual behavior, formal education including sexual health issues should be provided. Research should be done for each region in Turkey on this subject, and in line with the results, necessary information should be provided regarding sexual health.

Patient informed consent

Informed consent was obtained.

Ethical clearance

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Üsküdar University noninterventional studies ethics committee on April 25, 2019, with the number 61351432-/2019-197.

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Conflicts of interest

There are no conflicts of interest to declare.

Author contribution area and rate

- Cüneyt Balkanoğlu (28%): Data acquisition, analysis interpretation
- Habib Erensoy (24%): Conception/design of the work, data acquisition, analysis interpretation
- Süleyman Dönmezler (24%): Involved in refining the conception of the work, the interpretation of data for the work and revising it critically for important intellectual content
- Tonguç Demir Berkol (24%): Involved in refining the conception of the work, the interpretation of data for the work and revising it critically for important intellectual content.

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Original Article

Evaluating of Solute Carrier Family 6 Member 4 Gene (SLC6A4) Promoter Polymorphisms with Escitalopram Plasma Levels for Precision Medicine in Major Depressive Disorder

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Abstract

Aim and Objective: Escitalopram (SCT) shows an antidepressant effect due to its mechanism of increasing the serotonin level by inhibiting the serotonin transporter protein (5HTT). 5HTT is encoded by solute carrier family 6 member 4 gene (SLC6A4) in the brain. Recognition of SCT plasma level of patients and pharmacodynamics of individuals during SCT treatment will increase the expected response to the treatment and reduce the adverse effects. This study aims to determine the effect of SLC6A4 promoter long/short polymorphism and the SCT plasma level of patients on the response to treatment during the SCT drug therapy. **Materials and Methods:** Blood and plasma samples of 30 major depressive patients using 20 mg SCT for 8 weeks between the ages of 18 and 65 were analyzed to determine SCT plasma level and SLC6A4 promoter polymorphism. The treatment response level was determined by using the Hamilton Depression Rating Scale at patient files. **Results:** SCT plasma level of the nine patients with LL polymorphism was found to be in the range of 13.40–63.36 ng/mL. For 13 patients with LS polymorphism, SCT plasma level was found to be in the range of 2.93–57.48 ng/mL. For eight patients with SS polymorphism, the SCT plasma level was found to be in the range of 0.95–49.32 ng/mL. **Conclusion:** When the association between SCT plasma level and response to the drug treatment was examined, we had significant results to show that SCT level affected the response to treatment, especially in the LS group, as well as the SLC6A4 promoter variation. This study may lead to a more profound understanding of rational drug therapy as well as to a careful application of pharmacogenetics in psychiatry..

Keywords: *Escitalopram plasma level, response, SLC6A4 promoter polymorphism*

Introduction

Escitalopram (S-CT) is one of the most commonly utilized selective serotonin reuptake inhibitors (SSRIs) for depression and general anxiety treatment.[1,2] S-CT shows an antidepressant effect, as it increases the serotonin level in the presynaptic area by inhibiting the serotonin transporter protein (5-HTT) in the brain.[3,4] S-CT has proven to be effective in treating depression and anxiety disorder after it is administered with an oral dose of daily 10–20 mg.[1] As far as the effects of S-CT in the body is concerned, it is seen in past studies that the effect of S-CT begins when reaching a level higher than 80% of 5-HTT occupancy.[5,6] During S-CT treatment, the knowledge of the genotypic characteristics of individuals and the plasma level of S-CT may be effective in determining therapeutic targets.[7] Polymorphism can change the gene expression or gene activity where they are

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present. Solute carrier family 6 member 4 gene *(SLC6A4)* encodes 5-HTT. The polymorphism exists in the promoter region of *SLC6A4* where a 44 bp GC (Guanine, Cytosine) consisting of 20–22 bp double repeats occurs depending on the repetitions of a rich sequence of insertions/deletions. Bp long (L: L) form consists of 16 repeats resulting from the insertion of the 44 bp repeat sequence. In the case of the deletion, however, the allele that is called as bp short (S) form consisting of 14 repeats occurs. L and S variants have been identified in a variety of studies showing different transcriptional effects.[8] S variant is associated with the lower transcriptional activity of the promoter when compared to the L variant.[4,7]

In addition, determining the appropriate individual drug and dose depends on taking the individual differences into consideration. Furthermore, the severity of side effects and interactions as well as possible adverse drug reactions can be decreased, and in addition, the efficacy of treatment can be increased as well.[9] While genotyping methods are used to determine polymorphisms in enzymes, carrier proteins, and receptors, drug levels in body fluids (e.g., plasma, blood, and urine) have been evaluated by therapeutic drug monitoring (TDM).[9] TDM, which has been widely used in the world, is one of the methods that can be used with the purpose of personalized treatment.

It is thought that besides knowing the S-CT plasma level of patients, the pharmacodynamics of individuals has an essential role in increasing the success of the treatment. Recognition of the S-CT plasma level of patients and pharmacodynamics of individuals during the S-CT treatment will increase the expected response to the treatment and reduce the adverse effects.

The goal of this study is to determine the effect of *SLC6A4* promoter polymorphism and the S-CT plasma level of the patients on their response to treatment during the S-CT drug therapy. Therefore, in this study, the level of S-CT has been analyzed in plasma samples of patients treated by S-CT therapy in depression. Furthermore, *SLC6A4* promoter polymorphism and evaluation of response to treatment have been identified in the same patients. When *SLC6A4* promoter polymorphism and S-CT plasma levels of these patients have been identified and evaluated together, the physician can choose and set an effective drug regimen according to their 5-HTT activity. With this attempt, the side effects of the drug could be reduced more effectively and the desired result could be increased as well.

Materials and Methods

The ethics committee approval has been obtained on June 5, 2017 (ethics committee decision number: B.08.6.Y OK.2.US.0.05.0.06/2017/154) for the blood sampling part of the work.

Sample selection

Between June 1, 2017, and June 1, 2018, blood and plasma samples of 30 patients (males and females), between the ages of 18 and 65, who were using 20 mg S-CT for 8 weeks, were analyzed in Üsküdar University, Clinical Pharmacogenetics Laboratory, to determine the S-CT plasma level and *SLC6A4* promoter polymorphism. Approval of the Ethics Committee from Üsküdar University was obtained on June 5, 2017 (ethics committee decision number: B.08.6.YOK.2.US.0.05.0.06/2017/154) for the blood sampling part of the work.

Inclusion criteria of the present study were as follows: (1) Patients who showed evidence of a diagnosis of major depressive disorder according to Diagnostic and Statistical Manual of Mental Disorders-IV; (2) patients who had a score of at least 18 on the 17-item Hamilton Rating Scale for Depression (HRSD) (Hamilton, 1960)[31] in the patient files; and (3) patients taking monodrug therapy with S-CT. To be in the inclusion list, the patients must also not be taking any drugs or foods that affect (inhibit or induce) the S-CT metabolic pathway during the drug treatment of selected patients. Patients who showed evidence of bipolar or anxiety disorders, psychosis, substance use disorders, pregnancy, or breastfeeding were excluded from the study.

Samples were selected from patients, whose samples were sent to the laboratory within the last 12 months. Samples were taken 24 h after the last dose to determine the plasma S-CT trough level of the patient by using liquid chromatography–tandem mass spectrometry (LC-MS/MS). The blood and plasma samples sent to the laboratory were kept at –20°C until analysis. Treatment response level was found by examining patient files (patients were classified as a responder if there was at least 50% reduction in initial HRSD score at the endpoint by clinicians).

Chemicals and reagents

For TDM analysis, all reference standards (escitalopram oxalate and desipramine hydrochloride (as internal standard [IS]) were purchased from Sigma (Sigma-Aldrich, St. Louis, Missouri, USA). Furthermore, high-performance liquid chromatography (HPLC) grade methanol, HPLC grade acetonitrile, formic acid, and ammonium formate were purchased from Merck (Merck, Kenilworth, New Jersey, USA). For *SLC6A4* genotyping, all other reagents (DNA isolation kits, forward and reverse primers [to and from] and Taq polymerase enzyme) were purchased from Invitrogen (Germany).

DNA sample collection

DNA was isolated by using Invitrogen DNA isolation kits (Germany). The procedure of the manufacturer's instructions was followed for isolation. The purity of the

isolation was confirmed according to the OD260/OD280 ratio. Values between 1.60 and 2.00 were accepted as pure and used for amplification.

SLC6A4 genotyping

To genotype *SLC6A4* promoter polymorphism, conventional polymerase chain reaction (PCR) was carried out by using the forward primer 5'-TCCCAGCAACTCCCTGTA-3 and reverse primer 5'-GGAATACTGGTAGGGTGCAA-3'. The PCR conditions were previously described.[10] Long allele (L) and short allele amplicons gave rise to 317 bp and 272 bp, respectively [Figure 1].

Therapeutic drug monitoring analysis of patient samples

The quantitative determination method has been applied for S-CT in plasma considering the publications of bioanalytical method validation.[11-14-30] The validation results of the method were published in our previous study.[15]

Liquid chromatography–tandem mass spectrometry conditions

Agilent 6470 HP-1200 LC series (USA) was used for the analysis. ACE-3 C 8 (3 µm, 3.0 mm 150 mm) column was used for analytical separation. The column temperature was 45°C. Mobile phase conditions in the previous study were applied.[15] The total analysis run time was 8 min at a flow rate of 0.5 mL/min. Quantitative analysis was carried out by multiple reaction modes with an electrospray positive ionization (ES+). Quantitation was based on monitoring precursor ion and product ion for S-CT m/z 325.1 >109.1 and for ISs, desipramine m/z 267.0 >72.0.

Preparation of standard and quality control samples

The stock standard solution was prepared by dissolving 12 mg of escitalopram oxalate in methanol ($c_{S\text{-}CT}$: 0.92 mg/mL). Then, a diluted stock standard solution was prepared by diluting the stock standard solution with methanol ($c_{S\text{-}CT}$: 3.7 µg/mL). To prepare eight calibration standards and five quality control samples for S-CT in plasma, the diluted stock standard solution was spiked in different volumes to the plasma. The limit of quantification that can be used for quantitative assay in plasma for S-CT was found to be 5.9 ng/mL. The calibration range for S-CT was 5.9–441.8 ng/mL.

Analysis of plasma samples*:* 100 µL of IS solution (c: 550 µg/mL) and 400 µL cold acetonitrile were spiked to the 500 µL plasma sample and further vortexed for 30 s and then it was centrifuged at 15,000 rpm for 5 min. Subsequently, 5 µL from the clear portion was injected into the system.

Statistical analysis

Statistical analysis was carried out by descriptive methods. For comparisons between groups, the nonparametric statistical method (Kruskal–Wallis and Mann–Whitney U-tests) was applied.

Results

The patients' demographic data, mean with standard deviations, as well as the minimum and maximum value for S-CT plasma level (for TDM), are displayed in Table 1. The percentage of females was found to be 66.7%. The mean age of the patients was 39.00 ± 10.55 (years). The mean S-CT plasma level of the patients was 27.59 ± 16.05 ng/mL.

There was no statistically significant difference between the males and females in the mean plasma level of S-CT ($P > 0.05$) [Table 1 and Figure 2]. When the relationship between S-CT plasma level and age groups was examined using the Kruskal–Wallis test, no statistically significant difference was found ($P > 0.05$) [Table 1 and Figure 3]. The frequency distribution of the LL, LS, and SS groups for the *SLC6A4* promoter polymorphism

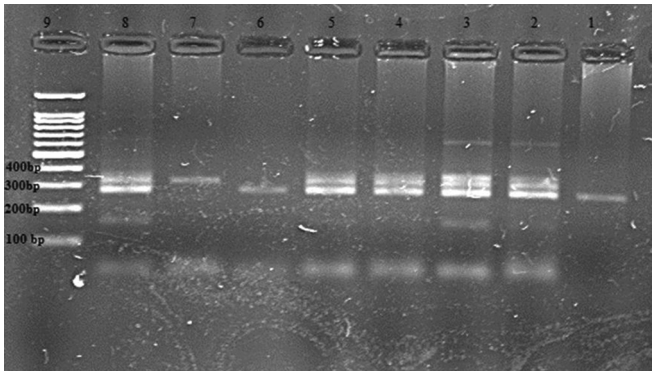

Figure 1: Representetive figure of agarose gel electrophoresis and *SLC6A4* Promoter Polymorphism Results. Lanes; 1: SS genotype (272 bp); 2: LS genotype (317 and 272 bp); 3: LS genotype (317 and 272 bp); 4: LS genotype (317 and 272 bp); 5: LS genotype (317 and 272 bp); 6: SS genotype (272 bp); 7: LL genotype (317 bp); 8: LS genotype (317 and 272 bp); 9: DNA standart marker

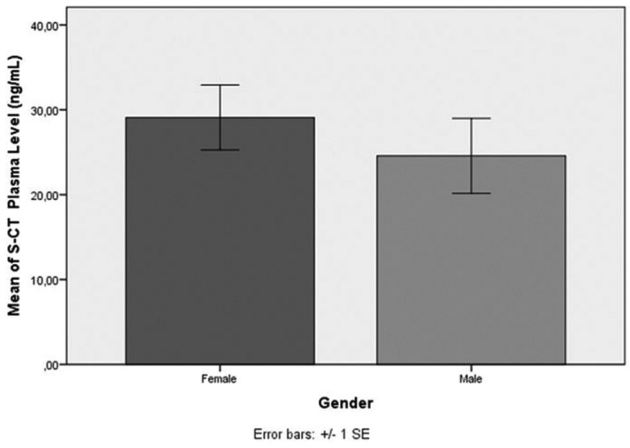

Figure 2: Relationship of Gender and S-CT Plasma Level. Mann–Whitney U-test shows that there is no statistically significant effect of gender difference on S-CT plasma level ($P > 0.05$). Number of samples (N_{female}: 20, N_{male}: 10), mean S-CT plasma level (female: 29.10 ng/mL, male: 24.58 ng/mL), standart deviation S-CT plasma level (female: 16.69, male: 13.28)

of 30 patients is summarized in Table 2. In our study, out of 30 patients, nine patients (30.0%) with LL polymorphism, 13 patients (43.3%) with LS polymorphism, and eight patients (26.7%) with SS polymorphism were detected [Table 2]. Patients with LL, LS, and SS polymorphisms were compared in three different groups using the Kruskal–Wallis and Mann–Whitney U-tests to determine the effect of *SLC6A4* promoter polymorphism to response during the drug treatment. The difference between the groups was found to be statistically significant. When the Mann–Whitney U-test was applied to determine the difference between the groups, the difference between the LL and SS groups was found to be statistically significant ($P \leq 0.05$) in the 95% confidence interval in Table 2 [Figure 4]. Mann–Whitney U-test was used to determine the effect of S-CT plasma level on the response to treatment. S-CT plasma level was found to be statistically significant on the response to treatment ($P \leq 0.05$) [Table 2 and Figure 5].

S-CT plasma level of the nine patients with LL polymorphism was found to be in the range of 13.40–63.36 ng/mL [Table 2]. When the patient files were examined, it was reported that no side effects were observed in nine patients during S-CT administration, and the desired drug response was obtained. For 13 patients with LS polymorphism, S-CT plasma level was found to be in the range of 2.93–57.48 ng/mL. It has been notified in patient files that no treatment response was obtained from four patients with LS polymorphism whose S-CT plasma level was below the therapeutic range. In this group, the drug side effects (insomnia and loss of appetite) have been reported to have appeared in one person. For eight patients with SS polymorphism, S-CT plasma level was found to be in the range of 0.95–55.25 ng/mL. When the patient files have been reviewed, it has been reported that the five nonresponder patients were obtained from these patients. Among these patients, two with S-CT plasma levels below the therapeutic range and three with S-CT plasma levels within the therapeutic range were identified. Furthermore, it has been reported that a response has been obtained for three patients whose S-CT level was within the therapeutic range.

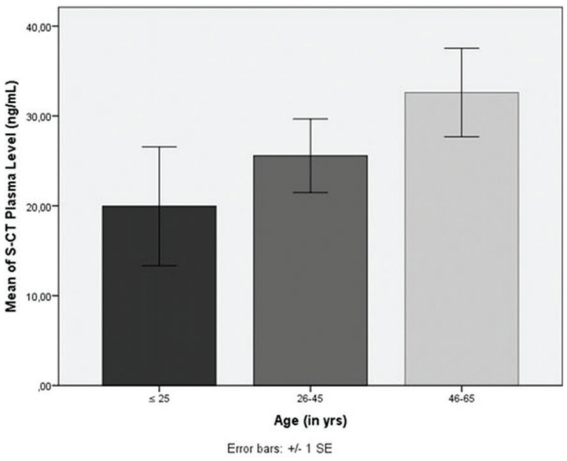

Figure 3: Relationship of Age and S-CT Plasma Level. Kruskal–Wallis test shows that there is no statistically significant effect of age groups on S-CT plasma level ($P > 0.05$). Number of samples ($N \leq_{25\ age}$: 3, $N_{26\text{-}45\ age}$: 16, $N_{46\text{-}65\ age}$: 11), mean S-CT plasma level (≤25 age: 19.96 ± 11.44 ng/mL, 26–45 age: 25.58 ± 16.37 ng/mL, 46–65 age: 32.60 ± 16.34 ng/mL)

Discussion

S-CT is used in the treatment of major depression at a wide range of ages.[16,17] It is reported that the physician can more

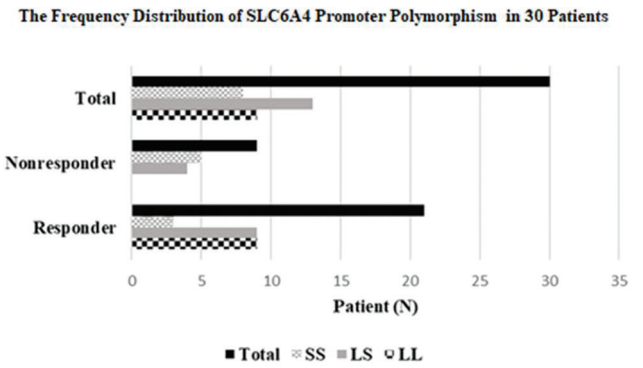

Figure 4: Evaluation of the Association between *SLC6A4* Promoter Polymorphism and Response to Treatment. Out of 30 patients, nine patients (30.0%) with LL polymorphism ($N_{responder}$; 9), 13 patients (43.3%) with LS polymorphism ($N_{responder}$; 9 and $N_{nonresponder}$; 4), and eight patients (26.7%) with SS polymorphism ($N_{responder}$; 3 and $N_{nonresponder}$; 5) were detected

Table 1: Results of descriptive statistic for gender, age, and escitalopram plasma level (ng/ml)

Patient		S-CT plasma level (ng/mL)			Mann-Whitney U-test, *P**
Gender	***n*; %**	**Minimum**	**Maximum**	**Mean±SD**	
Female	20; 66.7	0.95	63.36	29.10±16.69	*P*>0.05
Male	10; 33.3	9.66	57.48	24.58±13.28	
Total	30;100.0	0.95	63.36	27.59±16.05	
Age (years), mean±SD: 39.00±10.55					Kruskal-Wallis test
≤25	3;10.0	7.35	29.71	19.96±11.44	*P*>0.05
26-45	16;53.3	0.95	57.48	25.58±16.37	
46-65	11; 36.7	15.23	63.36	32.60±16.34	
Total	30; 100.0	0.95	63.36	27.59±16.05	

*The mean difference is significant at≤0.05 level in the 95% CI. CI: Confidence interval, SD: Standard deviation, S-CT: Escitalopram

Table 2: The evaluation of the relationship between escitalopram plasma level and *SLC6A4* promoter polymorphism and drug response

Patient (*n*; %)	S-CT plasma level (ng/mL)		SLC6A4 promoter polymorphism			
	Mean±SD	Mann-Whitney U-test (*P**)	LL (*n*; %)	LS (*n*; %)	SS (*n*; %)	Kruskal-Wallis-Mann-Whitney U-test (*P**)
Responder (21; 70.0)	31.42±12.90	≤0.05*	9; 100.0	9; 69.23	3;37.5	≤0.05**(LL-SS)
Nonresponder (9; 30.0)	18.65±19.74		-	4; 30.77	5;62.5	
Total (30; 100.0)	27.58±18.77		9;100.0	13,100.0	8; 100.0	
SLC6A4 promoter polymorphism						
Patient (*n*; %)	**S-CT plasma level (ng/mL)**			**Therapeutic range (15-80 ng/mL)**		
	Minimum	**Maximum**	**Mean±SD**	**Below (*n*, %)**	**Within (*n*, %)**	**Above (*n*, %)**
Responder (21; 70.0)						
LL (9; 42.9)	13.40	63.36	33.15±14.33	1; 11.1	8;88.9	NR
LS (9; 42.9)	16.83	57.48	30.43±13.75	NR	9; 100.0	NR
SS (3; 14.2)	23.90	38.21	29.22±6.39	NR	3; 100.0	NR
Nonresponder (9; 30.0)						
LL (NR; NR)	NR	NR	NR	NR	NR	NR
LS (4; 44.4)	2.93	14.89	8.71±4.98	4; 100.0	NR	NR
SS (5; 55.6)	0.95	55.25	26.60±24.13	2; 40.0	3; 60.0	NR
Total (30; 100.0)						
LL (9; 30.0)	13.40	63.36	33.15±14.33	1; 11.1	8;88.9	NR
LS (13; 43.3)	2.93	57.48	23.74±15.53	4;30.8	9; 69.2	NR
SS (8; 26.7)	0.95	55.25	27.58±18.77	2; 25.0	6; 75.0	NR

*The mean difference is significant at≤0.05 level in the 95% CI, **The difference between the LL and SS groups was found to be statistically significant (*P*≤0.05) in the 95% CI. NR: Not reported, SD: Standard deviation, S-CT: Escitalopram, CI: Confidence interval

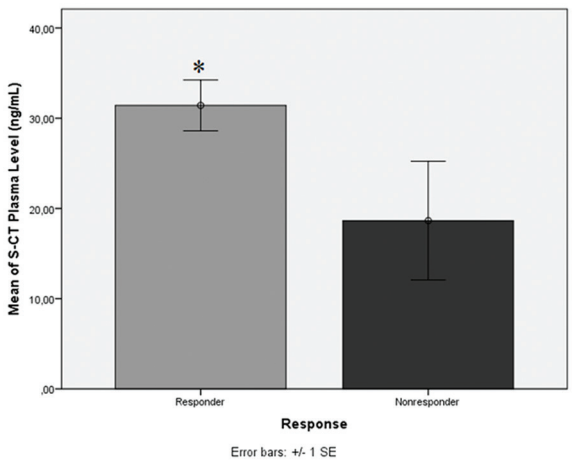

Figure 5: Evaluation of the association between S-CT Plasma Level and Response to Treatment. S-CT plasma level was found to be statistically significant on the response to treatment by Mann Whitney U test (*P* ≤ 0.05). '*' represent significant differences (*P* ≤ 0.05). Number of samples ($N_{nonresponder}$: 9, $N_{responder}$: 21), mean S-CT plasma level ($N_{nonresponder}$: 18.65 ± 19.74 ng/mL, $N_{responder}$: 31.42 ± 12.90 ng/mL)

easily adjust the drug plasma levels by following up TDM to provide the plasma therapeutic drug range when the individual factors affect the plasma drug levels differently.[18]

The expected S-CT plasma level/drug dose ratio (C/D [ng/mL/mg]) was identified to be 0.58–1.54 ng/mL/mg in the study of Hiemke *et al*.[5] When this ratio is taken into consideration, the expected S-CT plasma level range for the 20 mg S-CT can be calculated as 11.6–30.8 ng/mL. In our study, the mean plasma S-CT level of 30 patients using 20 mg S-CT was found to be 27.59 ± 16.05 ng/mL [Table 1]. The mean S-CT plasma level obtained from our study was found to be within the expected S-CT plasma level range (11.6–30.8 ng/mL), as reported by Hiemke *et al*.[5] Jin *et al*.[17] investigated the effect of age on S-CT exposure, indicating that S-CT plasma level is higher than that of younger people because they have lower clearance in elderly people.[17] In our study, however, it was found that there was no statistically significant difference between the S-CT plasma levels in the age groups formed [Table 1]. The reason for the difference between the two studies is that, in contrast to the other study, the age range of the study group is closer to each other and the general age range of the study sample is narrow (range: 20–58 age) in our study, which is why the exact distinction could not be made. Rao[1] study of S-CT pharmacokinetics showed that there was no statistically significant difference in S-CT pharmacokinetics (t_{max}, C_{max}, $t_1/_2$) between adolescents (12–17 age) and adults (18–35 age), whereas the difference between the adults and elderly was found to be significant.[1] Moreover, in the same study, it was stated that gender had no effect on S-CT level.[1] In our study, the age group formed is mainly composed of adolescents and adults. No statistically significant difference was detected in S-CT plasma levels between these age groups ($P > 0.05$). In addition, we found that gender difference did not cause a significant difference in S-CT plasma level ($P > 0.05$) [Table 1]. The results of the comparison between S-CT plasma level and gender and age in our study are similar to those of Rao's study [Figures 2 and 3].[1,17]

In many studies, the pharmacodynamic mechanism of SSRIs is explained by the effect on 5-HTT.[19] S-CT located in the SSRIs group inhibits 5-HTT and prevents serotonin reuptake and increases the level of serotonin in the synaptic region.[20] It is known that the *SLC6A4* promoter has a polymorphic characteristic. In our study, the variant distribution of LL, LS, and SS of 30 patients is given in Table 2. It has been found that nine patients (30%) have the LL variant, 13 patients (43.3%) have the LS variant, and eight patients (26.7%) have the SS variant. In a study by Samochowiec *et al*.,[21] the effect of *SLC6A4* promoter on anxiety disorders was examined.[21] Of the 202 healthy Caucasians in the control group included in this study, 42% were reported as LL, 48% as LS, and 10% as SS. The *SLC6A4* promoter variant distribution of the patients who participated in our study is similar to the variant distribution of the control group in the publication by Samochowiec *et al*.[21] However, the proportion of people with SS variant, in the patients who participated in our study, was found to be slightly higher than that in the healthy control group in the related publication. In many studies, variant variability has been reported to affect the level of 5-HTT expression.[22] The L-homozygous variant increases the transcriptional activity of the *SLC6A4* promoter, which results in a rise of 5-HTT expression relatively more than those of the S variant.[4,7] In related studies, it was noted that the 5-HTT expression decreased in those with the S variant.[23,24] It was reported by Mancama and Kerwin[22] that patients in the LL and LS groups had higher compliance with drug treatment than those in the SS group. When the response of S-CT treatment to 30 patients with *SLC6A4* promoter polymorphism distribution was examined, it was observed that the difference between the groups was statistically significant ($P \leq 0.05$) [Table 2 and Figure 4]. While a statistical significance was detected between LL and SS groups in response to the treatment ($P \leq 0.05$), no statistical significance in the response to treatment was found between the LS group and the other groups ($P > 0.05$) [Table 2]. While the response to treatment was observed in the entire LL group, patients without response to the drug treatment in the SS group were determined. In cases where the SS group failed to respond to the drug treatment, it has been determined from patient files that dose increase and different drug additions were performed to maintain the treatment. Many studies have reported that people with LL variants can respond better to SSRIs than those with SS variant, and it is difficult and long to reach a response in SS group patients.[25-27] The data obtained from our study is similar to the data in the literature.

It has been reported that in many studies studying the association between S-CT plasma level and antidepressant effect, the antidepressant effect of S-CT initiates by occupying at least 80% of 5-HTT (Klein *et al*., 2006).[28] It has been reported that 80% of 5-HTT is loaded when S-CT reaches 15 ng/mL in plasma. The therapeutic interval was reported to be 15–80 ng/mL in previous studies.[6] In our study, the mean plasma level of 30 patients was found to be 27.59 ± 16.05 ng/mL. It was found that nine patients (30%) did not respond to the treatment. In our study, when *SLC6A4* promoter variations of these nonresponder patients were examined, it was observed that five patients were from the SS group and four patients were from the LS group. The minimum and maximum value ranges of S-CT plasma level and mean plasma level in these nonresponder patients with SS group were found to be 0.95–55.25 ng/mL and 26.60 ± 24.13 ng/mL, respectively [Table 2]. Even though the S-CT plasma levels of these patients with the SS variant were within the therapeutic range, these levels were detected to be insufficient for a response to treatment. Taylor *et al*.[29] reported that patients with the SS group had lower rates of remission than LS or LL groups in their studies. The data obtained from our study is similar to the results of Taylor *et al*.[29] However, the TDM level of nonresponder patients with SS variant in our study differs from the literature.[6]

In our study, the mean TDM levels in the nonresponder group (LS versus SS) were found to differ from each other. While the mean TDM level of the LS group that did not respond to treatment was determined to be below the therapeutic range in accordance with the literature, patients who did not respond to the treatment were observed in the SS group, even if the mean TDM level in the SS group was within the therapeutic range. Unfortunately, TDM level may could not be exactly determined in patients, who did not respond due to an insufficient number of samples. Therefore, the limitations of our study include the insufficient number of samples for each group. Hence, it is recommended to determine the mean TDM level in responder and nonresponder patients by planning studies with a higher number of samples.

Florio *et al*.[6] reported that the antidepressant effect of S-CT begins when S-CT plasma levels reach approximately higher than 20 ng/mL.[6] In our study, the minimum–maximum S-CT plasma level of the four nonresponder patients with the LS group was found to be 2.93–14.89 ng/mL [Table 2]. It has been observed that since the S-CT plasma levels of these patients with LS variants have not reached the lower limit of the therapeutic range (15 ng/mL), these levels are not sufficient for the drug response to be seen. The data obtained from our study is similar to the data in the literature. The S-CT plasma level affected the response to treatment, especially in the LS group, as well as the variation of *SLC6A4* promoter polymorphism.

It has been found that the means of S-CT plasma level of 21 responder patients with LL, LS, and SS variants were 33.15 ± 14.33 ng/mL, 30.43 ± 13.75 ng/mL, and 29.22 ± 6.39 ng/mL, respectively [Table 2]. Nine of these patients have the LL variant, nine have the LS variant, and

three have the SS variant. While the S-CT plasma levels of eight patients in the LL variant were found to be within the therapeutic range, the S-CT plasma level of only one patient was 13.40 ng/mL. Although not reaching the lower limit of the therapeutic range (15 ng/mL), it was observed that the patient received the desired response from the treatment at the detected drug level. S-CT plasma levels of patients with LS and SS variants in this group were found in the therapeutic range.

Conclusion

When the association between the S-CT plasma level and response to the drug treatment was examined, significant results were obtained which showed that the S-CT plasma level affected the response to treatment, especially in the LS group, as well as the variation of *SLC6A4* promoter polymorphism. This study may lead to a more profound understanding of drug therapy and to a careful application of pharmacogenetics in psychiatry.

Patient informed consent

There is no need for patient informed consent.

Ethics committee approval

The ethics committee approval has been obtained on June 5, 2017 (ethics committee decision number: B.08.6.Y OK.2.US.0.05.0.06/2017/154) for the blood sampling part of the work.

Financial support and sponsorship

No funding was received.

Conflicts of interest

There is no conflict of interest to declare.

Author contribution subject and rate

Fadime Canbolat (40%): Design the research, sample analyses, data statistically analysis and wrote the whole manuscript.

Dilek Meltem Tasdemir (20%): Sample collection and data interpretation

Canan Sercan Dogan (15%): Sample analyses

Alper Evrensel (10%): Sample collection and data interpretation

Korkut Ulucan (%5): Sample analyses

Ahmet Aydın (%5): Contributed with comments on research design and slides interpretation.

K. Nevzat Tarhan (%5): Supervised the article write-up.

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Original Article

Comparison of Job Satisfaction, Work–Life Quality, and Compassion Level between Psychologists and Psychological Counselors

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Abstract

Introduction: Various studies have been conducted in the literature on job satisfaction, work-related quality of life, and compassion with different sample groups. Our aim is to compare psychologists and psychological counselors (PC) in terms of these variables. **Methods:** It consists of 60 participants; 41 women and 19 men, 30 psychologists and 30 PC, aged between 23 and 52 years, working in schools, clinics, hospitals, and other institutions. Participants filled out a sociodemographic information form and were subjected to the Minnesota job satisfaction scale, the work-related quality of life scale, and the compassion scale. **Ethical Aspect of the Study:** This study was approved by the T.R. University of Üsküdar, Non-Interventional Studies Ethics Committee. **Results:** It was determined that as the age of psychologists and PC increases, their level of disconnection decreases in terms of compassion (r = −0.264; P = 0.041); thus, their ability to create a rapport increases with age, their compassion fatigue decreases as the workplace changes (r = −0.256; P = 0.048), their job satisfaction decreases as the noise level in the workplace increases (r = −0.433; P = 0.001), their job satisfaction increases as the work-related quality of life increases (r = 0.373; P = 0.003), their humaneness increases as their professional satisfaction increases, and their level of indifference and conscious awareness decreases as their compassion fatigue increases. **Conclusion:** Compassion fatigue is considered to be more related to the traumatic burden of the work done, because as the frequency of workplace changes increases, compassion fatigue decreases. The findings indicate that psychologists and PCs not only need to have suitable working areas available for their work but also need to change their work fields from time to time. It can be argued that the job satisfaction and work-related quality of life of psychologists and PCs working in private clinics are higher than those working in schools; moreover, the reason for the lower levels of burnouts may be due to the noise levels, as well as the workload at the workplace, other occupational groups, and the culture of the institution.

Keywords: *Compassion, job satisfaction, psychological counselor, psychologist, work–life quality*

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Introduction

In the literature, it was seen that various studies on job satisfaction, work-related quality of life, and compassion were conducted with different sample groups, but there was no study comparing psychologists and psychological counselors (PCs) in terms of these variables.

Many authors' descriptions of job satisfaction are close to each other. For example, one study suggested that job satisfaction is an important factor driving people to work, job satisfaction will be possible when the hope of success as a result of one's effort happens, and hence, job satisfaction is a way of fulfilling one's ego.[1] Çekmecelioğlu defines job satisfaction as the reactions developed by the employee depending on whether the work conditions, such as the work itself, the physical environment, the attitude of the management, or the outcomes of the job such as wage and job security, meet the employee's own standards, values, and expectations according to the employee's assessment.[2] Akıncı reported that job satisfaction is a dynamic concept, and once job satisfaction is achieved, it does not mean that job satisfaction is sustained.[3]

The concept of compassion has been neglected for many years in psychology

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but has been studied under concepts, such as affinity and empathy (Gilbert, 2005).[32] In recent years, new orientations focusing on well-being, strength, and endurance rather than pathologies in psychology have also accelerated the studies on compassion.[4] Compassion was defined by Gilbert as a concept that includes the desire to relieve someone else's pain, a cognitive process related to understanding the source of pain, and a behavioral process related to performing a compassionate action (Gilbert, 2005). One study suggests that compassion has no correlation with the concept of pity. In the concept of pity, there is no positive participation of the individual, while in compassion, there is an intense interest and respect; including helping, volunteering, and interaction.[5] Since compassion includes helping, volunteering, and interaction, it is behaviorally similar to concepts such as empathy and sympathy. Neff and Pommier stated that empathy and compassion are very similar and sometimes even used interchangeably.[6] Although compassion and empathy are generally defined as different concepts and it is stated that empathy is an important competence related to understanding the pain of others, it is also stated that it does not include motivation and behavior toward eliminating these problems.[7] Sympathy, on the other hand, is a concept included in the emotional aspect of compassion, but compassion includes a more active reaction to the distressed person than sympathy.[8]

PCs working in schools and psychologists working in clinics apply psychotherapy to their clients using various methods and techniques. The aim of this study was to investigate the relationship between job satisfaction, work-related quality of life, and compassion levels of PC working in schools and psychologists working in clinics. In the study, the job satisfaction, work-related quality of life, and compassion levels of psychologists and PCs were also examined taking into account that the noise level in the workplaces may have an effect on those who are working in schools and private clinics.

Methods

The ethical approval of this study was obtained from Üsküdar University Non-Invasive Research Ethics Committee with number B.08.6.YÖK.2. ÜS.0.05.0.06/2018/624 on May 23, 2018.

The study design was observational, cross-sectional, and relational. The sample of the study consists of 60 participants; 41 women and 19 men; 30 psychologists and 30 PC; aged between 23 and 52; working in various schools, clinics, hospitals, and other institutions; selected by simple random sampling method.

Primary outcome variables (dependent variables) were Minnesota job satisfaction scale, work-related quality of life scale, and compassion scale scores, and the independent variable was categorically defined as the individual being a psychologist or a PC. In addition, the relationship between outcome variables was examined in two independent groups.

The inclusion and exclusion criteria of our study were being still actively working as a psychologist or PC, voluntarily accepting to participate in the study, and the absence of any physical and neurodevelopmental disease that would prevent filling the tests in the study. We evaluated the opposite of these criteria as the exclusion criteria of our study.

The sociodemographic questionnaire was prepared by the investigator and consists of questions about the participants' age, gender, education level, profession, and working conditions.

The Minnesota Job Satisfaction Scale consists of 20 items and uses a 5 point-Likert type response format (Weiss et al., 1967)[34] and translated into Turkish by Baycan[9] and whose validity and reliability studies were conducted (Cronbach's alpha = 0.77). Each question contains five options that describe the degree of satisfaction the person has with their job. These options are "very dissatisfied," "dissatisfied," "undecided," "satisfied," and very satisfied." These options were evaluated by giving 1, 2, 3, 4, and 5 points, respectively. The highest score that can be obtained from the scale is 100, the lowest score is 20, and the midpoint of 60 points denotes neutral satisfaction. Scores approaching 20 indicate that the satisfaction level has decreased, and scores approaching 100 indicate that the satisfaction level has increased. Intrinsic satisfaction score consists of elements related to satisfaction associated with the inherent nature of the job, such as success, recognition or appreciation, the job itself, job responsibility, promotion, and job change due to promotion. The sum of the scores obtained from the items of this aspect is divided by 12 to calculate the intrinsic satisfaction score. Extrinsic satisfaction score consists of elements pertaining to the business environment such as corporate policy and management, type of audit, relations with managers, employees and subordinates, working conditions, and wages. The sum of the scores obtained from the items of this aspect is divided by 8 to calculate the extrinsic satisfaction score. The neutral satisfaction score of the scale is 3. If the scale result is <3, job satisfaction is considered low; if it is above 3, job satisfaction is considered high.

The work-related quality of life scale is a self-report assessment tool developed by Stamm (2005)[35] and translated into Turkish by Yeşil *et al*.[10] and consists of 30 items and three subscales. Professional satisfaction (compassion satisfaction) is the first of the subscales and refers to the sense of fulfillment and satisfaction that the employee feels as a result of helping another person who needs help in a field related to his or her job. The high score from this subscale indicates the level of satisfaction or fulfillment as being the helper. Items 3, 6, 12, 16, 18, 20, 22, 24, 27,

and 30 in the scale are items that measure professional satisfaction. The alpha reliability value of the scale is 0.87. The second subscale, the burnout subscale, is a test that measures the feeling of burnout caused by hopelessness and difficulty in coping with problems in business life. A high score on this scale indicates a high level of burnout. The alpha reliability value of the scale is 0.72. Items 1, 4, 8, 10, 15, 17, 19, 21, 26, and 29 in the scale measure burnout. The third scale, compassion fatigue subscale, is a test created to measure the symptoms, resulting from encountering a stressful event. Employees who score high on this scale are recommended to seek support or assistance. Alpha reliability value of the scale is set to 0.80. Items 2, 5, 7, 9, 11, 13, 14, 23, 25, and 28 of the scale are developed to measure compassion fatigue. While evaluating the scale scores, items 1, 4, 15, 17, and 29 should be calculated by reversing them. A six-step chart ranging from "never" (0) to "very often" (5) was used to evaluate the items in the scale.

Compassion scale, developed by Pommier[11] and studied for Turkish validity and reliability by Akdeniz and Deniz,[12] measures the level of compassion of individuals and consists of 24 items. In the validity and reliability study of the scale, subaspects that form the compassion structure were determined. These subaspects include kindness (crα = 0.73), indifference (crα = 0.64), common humanity (crα = 0.66), separation (crα = 0.67), mindfulness (crα = 0.70), and disengagement (crα = 0.60). Kindness subaspect is the sum of items 6, 8, 16, 24, indifference is the sum of items 2, 12, 14, and 18; common humanity is the sum of items 20, 11, 15, and 17; separation is the sum of items 10, 3, 5, and 22; mindfulness is the sum of items 13, 4, 9, and 21; and disengagement is the sum of items 1, 7, 19, and 23. The scale questions were brought to use by Akdeniz and Deniz[12] in the validity and reliability study.

Results

The two groups were tabulated in terms of age, gender, education, and workplaces. Categorical variables are expressed as frequency distribution (percentage), and numerical variables as mean (standard deviation) [Table 1].

When we compared the two independent groups in terms of outcome variables, the mean scores ($\bar{x}$ = 9.67) of the compassion scale indifference subscale of the PCs were found to be statistically significantly higher than the psychologists ($\bar{x}$ = 7.97, P = 0.030). The workplace noise mean of the PCs ($\bar{x}$ = 3.33) was found to be statistically significantly higher than the psychologists' mean workplace noise ($\bar{x}$ = 2.57, P = 0.019). No statistically significant difference was found between the psychologists and the PC's mean scores from the other subscales of the Minnesota job satisfaction scale, the work-related quality of life, and the compassion scale [Table 2].

Another independent variable we want to examine was the workplace. Private school employees (n = 33) and private clinic employees (n = 18) were compared in terms of means of workplace noise, job satisfaction, work-related quality of life, and compassion. The overall job satisfaction means of those working in private clinics ($\bar{x}$ = 4.21) were found to be statistically significantly higher than the mean ($\bar{x}$ = 3.20) of those working at school (P < 0.001) [Graph 1].

Table 1: Statistics on the demographics of psychologists and psychological counselors

	Psychologist, *n* (%)	PC, *n* (%)	Total, *n* (%)
Gender			
Women	28 (93.3)	13 (43.3)	41 (68.3)
Men	2 (6.7)	17 (56.7)	19 (31.7)
Education status			
Bachelor's degree	9 (30.0)	18 (60.0)	27 (45.0)
Y. bachelor's degree	19 (63.3)	11 (36.7)	30 (50.0)
Doctor's degree	2 (6.7)	1 (3.3)	3 (5.0)
Workplace			
School	13 (43.3)	20 (66.7)	55.0
Private clinic	9 (30.0)	9 (30.0)	18 (30.0)
Hospital	2 (6.7)	0 (0.0)	2 (3.3)
Other	6 (20.0)	1 (3.3)	7 (11.7)
Age	30.40 (7.49)	29.37 (5.32)	

PC: Psychological counselors

The mean of professional satisfaction ($\bar{x}$ = 42.22) of those working in private clinics was found to be statistically significantly higher than the mean of those working at school ($\bar{x}$ = 36.76, P = 0.043). The mean noise level perceived by those working at school ($\bar{x}$ = 3.61) was found to be statistically significantly higher than the mean ($\bar{x}$ = 2.00) of those working in private clinics (P < 0.001).

When we look at the relational implications, which is our secondary objective, a significant negative correlation was found between the ages of psychologists and PCs and the scores they received from the separation subscale of the compassion scale (r = −0.264; P = 0.041). A significant negative correlation was found between the number of workplace changes and the scores obtained from the compassion fatigue subscale of the work-related quality of life scale (r = −0.256; P = 0.048). A negatively significant relationship was found between the perceived noise level in the workplace and the total scores from the Minnesota job satisfaction scale (r = −0.429; P = 0.001), a significant negative correlation was found between the total scores from the Minnesota job satisfaction scale intrinsic satisfaction subscale (r = −0.433; P = 0.001), a significant negative correlation was found between the total scores of the Minnesota job satisfaction scale extrinsic satisfaction subscale (r = −0.363; P = 0.004), a significant negative correlation was found between the scores of the work-related quality of life scale professional satisfaction subscale (r = −0.315; P = 0.014), and a positive significant relationship (r = 0.335; P = 0.009) was found between the scores obtained from the work-related

Table 2: Evaluation of psychologists and psychological counselors workplace noise, job satisfaction, work-related quality of life, and compassion levels

Department	*n*	*X*	*S*	*Z*	*P*
General job satisfaction					
Psychologist	30	3.65	0.763	−0.636	0.525
PC	30	3.49	0.944		
Intrinsic satisfaction					
Psychologist	30	3.92	0.756	−0.829	0.407
PC	30	3.70	0.950		
Extrinsic satisfaction					
Psychologist	30	3.25	0.918	−0.267	0.790
PC	30	3.18	1.043		
Professional satisfaction					
Psychologist	30	40.23	6.951	−0.718	0.473
PC	30	37.57	10.500		
Exhaustion					
Psychologist	30	15.27	5.003	−0.719	0.472
PC	30	16.83	7.042		
Compassion fatigue					
Psychologist	30	15.03	10.190	−1.199	0.231
PC	30	17.23	8.274		
Kindness					
Psychologist	30	16.27	3.290	−1.342	0.179
PC	30	15.27	3.237		
Indifference					
Psychologist	30	7.97	4.295	−2.172	0.030*
PC	30	9.67	3.925		
Common humanity					
Psychologist	30	16.70	2.867	−1.856	0.063
PC	30	18.03	2.008		
Separation					
Psychologist	30	7.33	3.575	−1.803	0.071
PC	30	8.73	3.513		
Conscious awareness					
Psychologist	30	17.43	2.622	−1.267	0.205
PC	30	17.03	2.076		
Disengagement					
Psychologist	30	8.13	3.910	−1.391	0.164
PC	30	9.23	3.645		
Noise level					
Psychologist	30	2.57	1.165	−2.344	0.019*
PC	30	3.33	1.295		

*P<0.005. Mann-Whitney U-test results of means, SD and independent samples. PC: Psychological counselor, SD: Standard deviation

quality of life scale burnout subscale [Table 3]. A positive statistically significant relationship was found between the total scores of the psychologists and PCs from the Minnesota job satisfaction scale and the scores from the job satisfaction subscale of the work-related quality of life scale (r = 0.527; P = 0.000). A negatively significant relationship was found between the total scores of the psychologists and PCs from the Minnesota job satisfaction scale and the scores from the burnout subscale of the work-related quality of life scale (r = −0.280; P = 0.030). A positively significant relationship was found between the total scores of the psychologists and PCs from the intrinsic satisfaction subscale of the Minnesota job satisfaction scale and the scores from the job satisfaction subscale of the work-related quality of life scale (r = 0.575; P = 0.000). A negatively significant relationship was found between the total scores of the psychologists and PCs from the intrinsic subscale of the Minnesota job satisfaction scale and the scores from the burnout subscale of the work-related quality of life scale (r = 0.344; P = 0.007). A positively significant relationship was found between the total scores of the psychologists and PCs from the extrinsic satisfaction subscale of the Minnesota job satisfaction scale and the scores from the job satisfaction subscale of the work-related quality of life scale (r = 0.373; P = 0.003). A positively significant relationship was found between the total scores of the psychologists and PCs from the extrinsic satisfaction subscale of the Minnesota job satisfaction scale and the scores from the compassion fatigue subscale of the work-related quality of life scale (r = 0.291; P = 0.024). A positively significant relationship was found between the total scores of the psychologists and PCs from the extrinsic satisfaction subscale of the Minnesota job satisfaction scale and the scores from the separation subscale of the work-related quality of life scale (r = 0.278; P = 0.032). A positively significant relationship was found between the total scores of the psychologists and PCs from the job satisfaction subscale of the work-related quality of life scale and the scores from the kindness subscale of the compassion scale (r = 0.430; P = 0.001). A positively significant relationship was found between the total scores of the psychologists and PCs from the compassion fatigue subscale of the work-related quality of life scale and the scores from the indifference subscale of the compassion scale (r = 0.340; P = 0.008). A negatively significant relationship was found between the total scores of the psychologists and PCs from the compassion fatigue subscale of the work-related quality of life scale and the scores from the common humanity subscale of the compassion scale (r = 0.259; P = 0.046). There was no significant relationship between the scores of psychologists and PCs in other su-scales [Table 4].

Discussion

Job satisfaction and work-related quality of life of those psychologists and PCs working in private clinics were found to be higher than those working in schools, while their burnout levels were lower. It was also determined that as the age of psychologists and PC increases, their level of disconnection decreases in terms of compassion; thus, their ability to create a rapport increases with age, their compassion fatigue decreases as the workplace changes, their job satisfaction decreases as the noise level in the workplace increases, their job satisfaction increases as the

work-related quality of life increases, their humaneness increases as their professional satisfaction increases, and their level of indifference and conscious awareness decreases as their compassion fatigue increases.

Gilbert and Procter[13] defines compassion as cognitive abilities and compassionate behaviors that include the desire to understand and reduce pain and feelings of empathy. The fact that the levels of indifference toward other people's pain in PCs are significantly higher than psychologists can be explained by the higher noise levels perceived by PCs in the workplace than psychologists. As a finding of the current study, the moderate correlation of noise levels with general job satisfaction, professional satisfaction, and burnout levels may indirectly regulate the indifference levels of PCs.

General job satisfaction, intrinsic job satisfaction, extrinsic job satisfaction, and professional satisfaction levels of psychologists and PCs working in private clinics were found to be significantly higher than those working at schools. However, the burnout levels of psychologists and PCs working at schools were found to be significantly higher than those working in private clinics. In addition, the noise level perceived by the psychologists and PCs working at schools was found to be significantly higher than the noise level perceived by those working in the private clinics. In their study on job satisfaction, Köroğlu[14] revealed that workplace-related features such as temperature, light and noise level, ventilation, working hours and rest breaks, cleanliness and quality of the workplace, location, and work equipment affect job satisfaction. Likewise, Özer[15] reported that excessive workload, boring qualities of the job, low wages, impossibility of promotion, excessive working hours, and negative physical working conditions such as noise, insufficient lighting, and heat are sources of stress in the workplace. On the other hand, Avşaroğlu *et al*.[16] reported that job satisfaction can change depending on the feedback employees receive in their work life, which is an emotional feedback and also affects the quality of life. Şengül[17] reported that the level of satisfaction of their clients significantly affects the job satisfaction of healthcare professionals. The higher levels of job satisfaction and professional satisfaction of psychologists and PCs working in private clinics may be due to the fact that they receive more frequent and immediate feedback regarding the satisfaction of their clients. There may be factors that reduce job satisfaction and professional satisfaction levels, such as the high number of clients in schools, consultation with psychologists and PCs working in schools being mandatory due to disciplinary problems rather than voluntary, and the absence of or late feedback from the client on satisfaction.

As the age of psychologists and PCs increases, their level of separation subscale of compassion scale decreases. In their study examining the levels of compassion of health

Table 3: The evaluation between the demographic characteristics of psychologists and psychological counselors and their scores of job satisfaction scale from the Minnesota job satisfaction scale and the compassion scale

	Age	Workplace change	Duration of work	Noise level
General job satisfaction	−0.036	0.074	0.011	−0.429**
Intrinsic satisfaction	0.002	0.097	0.049	−0.433**
Extrinsic satisfaction	−0.114	0.019	−0.034	−0.363**
Professional satisfaction	0.209	0.139	0.234	−0.315*
Exhaustion	−0.149	−0.068	−0.194	0.335**
Compassion fatigue	−0.217	−0.256*	−0.169	0.141
Kindness	−0.007	−0.019	0.073	−0.048
Indifference	−0.236	−0.316*	−0.090	0.226
Common humanity	−0.075	−0.126	0.122	0.074
Separation	−0.264*	−0.245	−0.091	0.136
Consicous awareness	−0.065	−0.173	−0.016	0.036
Disengagement	−0.211	−0.196	−0.050	0.088

*P<0.05. Spearman correlation analysis findings, **p<0.001

Table 4: Relationship between the scores of psychologists and psychological counselors in the Minnesota job satisfaction scale, the work-related quality of life scale, and the compassion scale

	1	2	3	4	5	6	7	8	9	10	11
1. General job satisfaction	-										
2. Intrinsic satisfaction	0.954**	-									
3. Extrinsic satisfaction	0.908**	0.757**	-								
4. Professional satisfaction	0.527**	0.575**	0.373**	-							
5. Exhaustion	−0.280*	−0.344**	−0.159	−0.549**	-						
6. Compassion fatigue	0.174	0.068	0.291*	−0.074	0.432**	-					
7. Kindness	0.059	0.088	0.002	0.430**	−0.215	−0.139	-				
8. Indifference	0.081	0.052	0.139	−0.235	0.219	0.340**	−0.384**	-			
9. Common humanity	0.091	0.103	0.083	0.180	−0.128	−0.014	0.199	0.033	-		
10. Separation	0.174	0.117	0.278*	−0.023	0.020	0.230	−0.250	0.687**	0.062	-	
11. Conscious awareness	−0.010	0.061	−0.109	0.179	−0.044	−0.259*	0.438**	−0.189	0.503**	−0.163	-
12. Disengagement	0.142	0.133	0.166	−0.107	0.127	0.226	−0.496**	0.802**	0.027	0.604**	−0.132

*P<0.05, **P<0.01. Spearman correlation analysis findings

professionals, Polat[18] revealed that separation levels, which are one of the subaspects of compassion, do not differ according to age. This finding indicates that as the age of psychologists and PCs increases, their ability to create a rapport in their communication with their clients increases. Therefore, it can be suggested that the ability to feel an emotional connection with people who are suffering, the ability to create a rapport with people when they are sad, and the ability not to avoid the negative emotions of others increase with age.

Compassion fatigue decreases as the number of workplace changes of psychologists and PCs increases. Hamilton (2008) [29] reported that psychological symptoms such as staying away from colleagues, staying away from patients, and feeling that there is no compassion left for the rest of life, as well as behavioral symptoms such as job absenteeism and anger, may occur in compassion fatigue. In this context, changing the work area or workplace can be seen as a protective factor in reducing the compassion fatigue that can be caused by the fact that psychological health professionals work with individuals who experience various crises and are constantly facing similar crises in the same workplace. For example, considering that a professional who continuously provides psychological support to oncology patients as a subfield of health psychology, developing emotional apathy toward the patients' lives over time is an indicator of compassion fatigue,[19] it may be appropriate to change the working areas of the same professional by rotation. Thus, psychological healthcare professionals will have the opportunity to find purpose and meaning in every new working field and to recognize and understand the positive aspects of the service they provide. Similarly, due to the large number of students who are under the responsibility of psychologists and PCs working at schools, emotional apathy may develop against the problems of the students due to reasons such as not being able to contact each student, not being able to provide service at a level that can provide job satisfaction under the conditions of the workplace. It is considered that if the professionals who provide psychological health services can have the feeling of making a difference in their work and that they are competent in their work, it can prevent the development of compassion fatigue.

As the noise level perceived by psychologists and PCs in the workplace increases, their general job satisfaction, intrinsic job satisfaction, extrinsic job satisfaction, professional satisfaction decrease, and burnout levels increase. This finding complies with the literature. There are many studies demonstrating that the noise level in the workplace negatively affects job satisfaction and professional satisfaction and increases the levels of burnout.[14,15,20-24] In workplaces where the noise level is high or perceived high, job satisfaction and work-related quality of life can be affected, which can reduce the performance of employees, increase their burnout and stress levels, and furthermore cause problems including physical and mental disorders.[24]

As the professional satisfaction of psychologists and PCs increases, their general job satisfaction, intrinsic job satisfaction, extrinsic job satisfaction, and kindness levels increase. This finding complies with the literature. Polat and ve Erdem[25] found a positively significant relationship between professional satisfaction, which is the subaspect of work-related quality of life and kindness, common humanity, and conscious awareness aspects of compassion fatigue. Moreover, there are many studies indicating that job satisfaction increases professional satisfaction.[1,2,10,26-28]

As the compassion fatigue of psychologists and PCs increases, their extrinsic job satisfaction and indifference levels increase and their level of conscious awareness decreases. This finding complies with the literature. Polat and ve Erdem[25] found in their study that with the increase of compassion fatigue, the level of conscious awareness, which is the subaspect of compassion, decreases and the levels of indifference increases. According to Coetzee and Klopper (2010),[30] some emotional, psychological, social, behavioral, and physical changes are observed in individuals with compassion fatigues. Physical symptoms caused by compassion fatigue in individuals can be observed as fatigue, loss of strength, and decrease in physical performance. Mental and emotional symptoms are reluctance, malaise, depersonalization, burnout, irritability, and emotional oppression. Socially, it can seem as impassivity and indifference toward the environment. Mc Holm (2006)[31] reported that compassion fatigue is a form of burnout experienced by healthcare professionals. Gilbert (2010)[32] states that the therapists are more likely to develop compassion fatigue when they do not have a benevolent and positive attitude despite feeling empathy, and they can discover different treatment options when they are friendly toward their clients and adopt the attitude they need. This finding shows that although psychologists and PCs cannot establish emotional rapport internally with their clients at the level of compassion, they have job satisfaction with their work. It may not be possible for psychologists and PCs to constantly experience the state of creating a rapport with their client, creating a rapport emotionally with people who are suffering, not having difficulty in creating a rapport with them when they are sad, and not avoiding the negative emotions of others. For this reason, although they do not feel connected in terms of compassion in reality, they can adopt a positive attitude toward their clients with the empathy they establish at the conscious level and their job satisfaction may increase with the resulting positive feedback.

Limitations of our study

At the beginning of the study, it was considered that psychologists mostly work in the clinical environment and PC work in schools, and the comparison of job satisfaction, work-related quality of life, and compassion levels of these occupational groups in terms of factors, such as the

complexity of the working environment and the intensity of noise, was predicted to be helpful in determining how they can cope. However, collected data showed that the number of psychologists working in schools was almost equivalent to PCs. In private clinics, the numbers of psychologists and PCs were equal. Therefore, comparing psychologists and PC was not considered appropriate considering the adaptation of these individuals to the work environment, depending on their working years. However, these occupational groups were compared for discussion. Although the main purpose of the study is to compare these two occupational groups, it was not possible to observe the differences arising from the training of these occupational groups, considering that adaptation to the workplace may be a confounding variable.

Patient informed consent

Informed consent was obtained.

Ethics committee approval

The ethical approval of this study was obtained from Üsküdar University Non-Invasive Research Ethics Committee with number B.08.6.YÖK.2. ÜS.0.05.0.06/2018/624 on May 23, 2018.

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A Case With Sexual Dysfunction Improved By Vortioxetine Dose Reduction and Sensate Focus Exercises

Abstract

Major depression disorder in its nature and antidepressants as side effects may cause people to have sexual dysfunction. In the literature, it has been shown in a few examples that it may be beneficial for sexual dysfunction to switch drugs from a selective serotonin reuptake inhibitor to vortioxetine. Vortioxetine is an antagonist for 5-HT3 and 5-HT7, a partial agonist for HT1B and agonist for 5-HT1A and has been known for its low level of sexual dysfunctionality. There is a case showing that vortioxetine with high doses might cause sexual impairment and dose reduction might be a treatment option for this side effect. In this case, vortioxetine dose reduction and sexual improvement were simultaneous. Although the sensory exercises might also help the treatment of sexual dysfunction, it should not be ignored that vortioxetine may cause dose-dependent sexual side effects.

Keywords: *Depression, sexual dysfunction, vortioxetine*

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Introduction

Vortioxetine is one of the antidepressants which has been using commonly in clinical practice. Although antidepressants usually have sexual side effects, vortioxetine has been known for its low level of sexual dysfunctionality.[1] There is a case showing that vortioxetine with high doses might cause sexual impairment and dose reduction might be a treatment option for this side effect.

Case Report

A 38-year-old woman admitted to our outpatient clinic with the complaint of a decreased libido for the past 1 month. She has also noticed anhedonia, lack of motivation, and depressed mood for the last 7 months. In her clinical examination, depressive symptoms were apparent and Beck depression scale was applied. The score was 21, which is coherent with her initial diagnosis which is mild depression after a critical psychiatric evaluation. She also pointed out that she become using vortioxetine 20 mg/day upon one of her friend's recommendation 2 months ago. Her symptoms have alleviated; however, she started to complaint about decreased libido for the last 1 month.

She has been married for 20 years. The couple has two children who are 14 and 18 years old. Her husband is 43 years old, graduated from primary school, and working in a textile factory. She graduated from high school and working in the manufacturing sector.

History

She got her first menstrual period at the age of 13. She had known about menstruation at that time, and her family had a neutral attitude. She acquired superficial information about sexual health with her middle school friends, and she masturbated at the age of 17 for the first time. She had continued to masturbate twice a year, and she had been feeling ashamed of this behavior. She had flirted with a boy at the same age with her when they were 16 for 1 year. They did not have any sexual intimacy. She met her husband afterward and she had her first sexual intercourse in the 1st month of her marriage. They have been having sexual intercourse once every 2 months for the last 7 months, while she has had sexual desire frequency of once every 2 or 3

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months. On the other hand, she had the frequency of 2 or 3 times a week before this period. For the last 7 months, after she has begun to work harder at work, she could not have sexual arousal or orgasm during her sexual encounter with her husband although she had before.

Her husband was circumcised at the age of 6, and he acquired sexual information about masturbating from one of his relatives at the age of 13. He began to masturbate once a day when he was 13. After his marriage, he stopped masturbating because he had been feeling guilty and he worried that it could be infidelity to his wife. His first sexual intercourse was with a woman by paying money when he was 18. He experienced sexual arousal and desire, and the intercourse had lasted for 2 min.

They had acquainted with each other with the help of their friends. They got married after 6 months of engagement when they were in love with each other. On the first night of their marriage, they did not have a sexual encounter because she was ashamed. They postponed their first intercourse for 1 month, and they did not have any problem afterward.

Treatment

Evaluation of their history and symptoms has been made during their first psychiatric interview. Interviews were made as couple and individually. They have been told about sexual anatomy and physiology in the next sessions. They had a few questions and they were answered during sessions. The true version of sexual myths was tried to be explained to the couple. In the next weekly sessions, they have been banned from sexual intercourse. As a homework exercise, the woman was told to touch herself in front of a mirror when she was alone. Later, sensate focus-I was explained and the couple was told to do the exercise three times a week. The dosage of vortioxetine has been decreased from 20 to 10 mg/day and ceased gradually. After the woman noted that she got benefit from sensate focus and her sexual desire frequency had increased to once a week, sensate focus-II was explained and told to do the exercise 3 times a week. In the next session, she emphasized that her symptoms had completely resolved and they were having sexual intercourse as they wanted. Her control score of Beck depression scale was 6, and psychiatric examination was not significant for any depressive symptoms. Consequently, the treatment was stopped.

Discussion

In our case, it can be understood that the symptoms of the patient that are having no desire for sexual intercourse, having a little or no sexual fantasy, and having difficulties to start a sexual activity or to respond to her husband's intentions are acquired after a couple of years of her relation with her husband. Although these symptoms may lead to a diagnosis which is sexual arousal disorder, it cannot be ignored that the patient had also symptoms related with major depression disorder at the time she started to use medication. As she started using vortioxetine 20 mg/day and her sexual dysfunctionality started afterward, it might be likely that her symptom might have originated from the use of this medication. Although there have been sensate focus exercises applied for her treatment, it cannot be ignored that decrease the dose of the medication might be helpful for symptom alleviation.

Major depression disorder in its nature and antidepressants as side effects may cause people to have sexual dysfunction.[2] Although serotonin reuptake inhibitors have a very important role in depression treatment, they may cause sexual dysfunction as a side effect during the treatment.[1,3]

Vortioxetine is one of the antidepressants that inhibit the serotonin reuptake mechanism, and it has a strong affinity to receptors and multimodal action. Vortioxetine is an antagonist for 5-HT_3 and 5-HT_7, a partial agonist for HT_{1B} and agonist for 5-HT_{1A}.[4] In the literature, it has been shown in a few examples that it may be beneficial for sexual dysfunction to switch drugs from a selective serotonin reuptake inhibitor to vortioxetine.[5,6] Studies implied that the sexual side effects of vortioxetine are not statistically different from placebo treatment. The only significant difference was having nausea when vortioxetine treatment was compared with the placebo.[7] More reliable results might be obtained by comparing the vortioxetine treatment and placebo in groups with healthier and more regular sexual lives.[8]

Results

In this case, vortioxetine dose reduction and sexual improvement were simultaneous. Although the sensory exercises might also help the treatment of sexual dysfunction, it should not be ignored that vortioxetine may cause dose-dependent sexual side effects. Comprehensive experimental studies may further improve the knowledge about vortioxetine effects and their causes. Clinicians may consider that high doses of vortioxetine may cause sexual side effects, and they may reduce the dose for treatment of sexual impairment in clinical practice for patients having a sexual dysfunction.

Patient informed consent

Patient informed consent was obtained.

Ethics committee approval

There is no need for ethics committee approval.

Conflict of interest

There is no conflict of interest to declare.

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