It is suggested that children tend to report their internalizing symptoms more often than caregivers or teachers, and approximately two-thirds of children diagnosed with MDD have at least one comorbid psychiatric disorder[3]. As with these studies, mothers in our study usually mentioned their children's externalizing symptoms but after interviewing the children, we diagnosed depression. Also, we found that 81% of depressive children had at least one comorbid psychiatric disorder; ADHD, seperation anxiety, oppositional defiant disorder and conduct disorder were the most frequent comorbidities.

In this study, children diagnosed with depression had fewer friends and their school and social competence scores were significantly lower than in the control group. It is reported that all factors related to the school environment, like academic performance or peer relationships, have effects on child mental health, and children who have fewer friends are more likely to experience depressive symptoms[4]. Having fewer friends or lack of friends may have caused depression in the study group or could be a result of these children's behavioral problems, because these children had significantly higher scores in both internalizing and externalizing behaviors. It is reported that children who have internalizing or externalizing behavior problems could have lower social skills and thus act out more asocial behaviors among peers. Also, in this study, internalizing behavior problems were higher in depressive girls, but there was no significant difference in externalizing behavior between the sexes. These results suggest that externalizing behavior problems could be a part of childhood depression regardless of gender differences.

Another important finding of this study was that 57.1% of the children were shown to have suicidal ideation. This ratio was found to be 71% in Brenton's study[2]. Suicidal ideation is regarded as a predictor of suicide attempts. Thus, the high rates of suicide ideation in childhood depression as shown suggest that children are at risk of suicide attempts as adolescents and should be examined carefully in this regard.

Finally, in this study self-injurious behavior was detected only in depressive children. Although a study conducted with adolescents showed that self-injurious behavior is related with suicidal ideation[5], in our study this behavior was not associated with suicidal ideation or depression severity of children. We thought that self-injurious behavior in depressive children may not always be related with depression severity. Impulsivity or high comorbidity rates of childhood depression may make additional contributions to the development of this behavior. Hence the results of this study showed that self-injurious behavior was significantly associated with rule breaking, aggressive behavior, and total externalizing behavior scores.

Although the small sample size and high comorbidity rates in the study pose limitations to generalizing these results, we suggest that findings revealed in this study could contribute to the literature.

Keywords: depression, child behavior, self-injurious behavior

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[Abstract:0263] ***ADHD***

Are SSRIs and psychostimulants really safe in terms of genotoxicity?

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BACKGROUNDS AND OBJECTIVE: Attention-deficit/hyperactivity disorder (ADHD) is the most frequent psychiatric disorder in children and adolescents[2]. Depression is the most common mood disorder[4]. In the treatment of such psychiatric disorders, typically SSRI and/or methylphenidate (MPH) are used. MPH is a commonly prescribed psychostimulant in ADHD treatment[3].

El-Zein et al. have shown the genotoxic effect of a 3-month MPH treatment in 12 children[1]. In other studies, a genotoxic effect of MPH in children cannot be shown[2,3]. Additionally, in a study assessing adults, a genotoxic effect of MPH cannot be shown[3]. In the light of such information, together with a high prevalence of ADHD, increasing therapeutic usage of MPH has increased some concerns regarding its safety[5].

SSRI is widely used in the treatment of depression. In a study performed with humans, an increase in the frequency of sister chromatid exchange (SCE) via sertraline treatment has been shown. Although SSRIs are widely used in psychiatric disorders, information regarding its genotoxic effects in humans is limited[4].

In this study, we aimed to examine the effect of psychotropic drugs on early DNA damage in peripheral leucocytes by using comet analysis in adults with new depression and/or ADHD diagnoses and to evaluate their relationship with the treatment response.

METHODS: The research was executed at Pamukkale University Faculty of Medicine Department of Psychiatry and Physiology. Drugs and dosages to be taken by the patients were specified naturalistically.

According to DSM-4 diagnosis criteria, inclusion criteria are Depression and/or ADHD diagnosis, age between 18 and 60 and being literate.

Neurologic/chronic disease, mental retardation, concomitant psychiatric disorder and psychotropic usage for the last 2 months, as well as psychiatric disorders related to organic reasons are specified as exclusion criteria.

SCID-I or semi-structured socio-demographic question form was applied to the patients by the researcher. The patients were separated into 3 groups, depression, ADHD, and depression+ADHD. Clinical evaluation scales were performed according to the patient groups, and after the treatment, clinical evaluation scales were applied again according to the patient groups.

After taking blood samples from the patients before the treatment and in 2-month therapeutic doses during the treatment, these samples are evaluated via comet analysis in terms of genotoxicity.

Single cell gel electrophoresis — comet assay: 200 µl lymphocytes were placed into the centrifuge tube and 1000 µl cold PBS was added. Brakeless centrifugation was applied for 10 minutes at 200G 4˚C. 1000 µl supernatant was eliminated. 60 µl 0.5% w/v low melting point agarose (LMA) and 20 µl centrifuged cells were filled into Eppendorf vessels and placed on a lamina covered with a lamella. After storing in a refrigerator for 15 minutes, lamellas on the laminas were removed and 75 µl 0.5% w/v LMA was added at the end of the lamina and closed by unfolding another lamella. The samples was stored in the refrigerator for 15 minutes. After removing from the refrigerator, lamellas on the laminas were removed and left in the lysis solution for 2 hours. It was waited in the electrophoresis solution for 30 minutes in an electrophoresis and operated for 30 minutes at 300 ampere at 20-21 V. Laminas taken from the electrophoresis were left in the ice-cooled neutralization buffer for 5 minutes and then passed through ice-cooled distilled water. This process was repeated for 3 times. The end part of the lamina was stained with 60 µl ethidium bromide. It was left in dark for 5 minutes. Counting was done in dark environment by using a fluorescent microscope.

The possible DNA damage was evaluated by the "Comet assay IV system" software. In the damage evaluation, head length (HL), tail length (TL), head intensity (HI), tail intensity (TI), tail moment (TMo), and tail migration (TMi) parameters were used.

Statistical Analysis: Data was analyzed by the SPSS 21.0 package. When parametric test estimations were provided in dependent-group comparisons, significance test between two equivalents was used, and when parametric test estimations could not be provided, Wilcoxon Signed Rank Test was used. Statistical significance level (p) was accepted as 0.05.

RESULTS: Patients using MPH (n=25) were using 28.39 mg/day MPH on average. A significant difference was found between all the comet parameters evaluated before and after treatment ($p<0.05$).

A significant difference was found between all the comet parameters evaluated before and after treatment of the patients using MPH with less than 28mg/day (n=14, 18.5 mg/day) ($p<0.05$).

No significant difference was found between all the comet parameters evaluated before and after treatment of the patients using MPH with more than 28mg/day (n=11, 42.09mg/day) ($p>0.05$).

A significant difference was found between all the comet parameters evaluated before and after treatment of the patients using SSRI (n=21) ($p<0.05$).

No significant difference was found between all the comet parameters evaluated before and after treatment of the patients using Fluoxetine 20mg/day (n:8) ($p>0.05$).

DISCUSSION: According to the data of our study, MPH has shown genotoxic effect at sub-therapeutic doses. It is shown that dopamine may produce semiquinone and cause auto-oxidation in the presence of Fe^{2+}, which has a high neurodegenerative effect. Also, dopamine can be completely metabolized by monoamine oxidase, which produces highly reactive hydroxyl radicals. It is known that hydroxyl radicals cause DNA damage[5]. Such results raise the concern that DNA can be damaged by the free radicals that are produced during the oxidation of dopamine.

The results of our study are concordant with the study of El-Zein et al.[1]; in this study, 12 children had received a 20-54 mg/day MPH treatment for 3 months, and genotoxicity was shown in the peripheral blood lymphocytes by chromosome aberration test, sister chromatid exchange and micronucleus tests. In our study, different from the one mentioned, genotoxicity of MPH treatment is investigated by using the comet method in adult patients with a wider sample.

In the study by Walitza et al.[2], a genotoxic effect of MPH cannot be found. Reasons for the difference from these results may be that these studies have been conducted in children, while the study by Ponsa et al.[3] was conducted on only 7 adult patients, as well as effects of polymorphism differences, individual genetic predisposition, difference in method, and environmental factors.

In our study, a statistically significant correlation is found between the ASRS scale grade applied after the treatment and the drug dosage of the ADHD patients using MPH. Thus, it can be considered that as MPH dosage increases, it may cause a higher clinical response. Decrease of the genotoxicity of MPH with increasing dose can be related to the positive changes in the life conditions as a reason for a more significant clinical response to MPH at higher doses in ADHD patients. In addition, it can be considered that low cases numbers may have an effect on the results.

In a study performed in terms of genetic predisposition, it has been specified that carboxylesterase1 (CES1) enzyme has two undefined variants, which may cause hydrolytic activity loss against MPH. Also, it is specified that heterozygosity for recessive mutations in the genes responsible for DNA repair disorder may have increased sensitivity against genotoxic agents[3]. The difference in the results of our study may be related to this situation.

In our study, results may be different due to the polymorphous differences of the other study populations. Dopamine formation from rare amines such as tyramine is shown in hepatic microsomes. CYP2D6 is the only isoform that has a strong ability to convert p-tyramine and m-tyramine into dopamine. Thus CYP2D6 polymorphism may have caused the level of dopamine in the brain[2].

In our study, it is found that SSRI-group drugs have shown a genotoxic effect in humans. Bozkurt et al., in sertraline therapy for generalized anxiety disorder and depression patients, showed that the increase in SCE frequency was comparable to that in healthy controls. However, they specified that the results can be explained by psychogenic stress[4]. The results of our study are partially concordant with this information. Besides, in contrast to this study, it should be specified that not only sertraline is used in our study but also comorbidity is excluded.

In our study, while more significant genotoxicity is observed by MPH used in sub-therapeutic doses, it is observed that this effect disappeared in therapeutic doses. Our study is the widest attendant study in which genotoxicity assessment is performed according to MPH doses in adults. From this point of view, it is revealed that frequently used MPH should be used more carefully in therapeutic doses. According to the results of our study, it is found that SSRIs show genotoxic effects in humans. However, we did not observe a genotoxic effect of fluoxetine. Thus it can be concluded that frequently used SSRIs should be used more carefully.

For future research, it seems to be required that MPH and/or SSRI dose-based genotoxicity studies should be performed in adult ADHD, ADHD+Depression, and Depression patients with a wider sampling, in which the factors affecting DNA damage are considered. In those studies, measurement of the expression and activity of DNA repair enzymes and clarification of polymorphisms are also important.

Keywords: genotoxicity, methylphenidate, SSRI

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