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The Effect of Methylphenidate Treatment on Heart Rate Variability and Cardiac Autonomic Functions in Children with Attention Deficit Hyperactivity Disorder

Dikkat Eksikliği Hiperaktivite Bozukluğu Olan Çocuklarda Metilfenidat Tedavisinin Kalp Hızı Değişkenliği ve Kardiyak Otonomik Fonksiyonlara Etkisi

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ABSTRACT

Aim: Attention deficit hyperactivity disorder (ADHD) is the most common childhood psychiatric disorder. Psychostimulant drugs are frequently used in the treatment regimen. The possible cardiac side effects of drugs are of concern. In our study, we aimed to determine possible cardiac autonomic effects with heart rate variability (HRV) in ADHD patients receiving methylphenidate (MPH).

Materials and Methods: We used a retrospective pre-post treatment study design to measure the change in HRV parameters in ADHD patients receiving MPH therapy. A total of 49 patients (mean age, 8.3±2.5 years) diagnosed with ADHAB and 30 sex- and age-matched healthy controls (mean age, 8.2±2.7 years) were examined. Rhythm Holter recordings were made for the patients before MPH treatment and in the first month of treatment and for the control group, and HRV parameters were evaluated in the computer environment.

Results: There was no difference in age, gender, weight and height in the patient and control groups ($p>0.05$). In the analysis of time-dependent HRV parameters, SDNN, SDANN, which shows the sympathetic influence, and rMSSD, which shows the parasympathetic influence, were statistically significantly lower in the patient group than in the control group ($p<0.05$). When the patients were compared before and after the treatment, SDANN increased statistically ($p<0.05$). Besides, SDNN and rMSSD increased after the treatment, although there was no statistical significance ($p>0.05$).

Conclusion: Our study showed that there was increased sympathetic and decreased parasympathetic activity in HRV parameters in ADHD patients. Both sympathetic and parasympathetic improvement was observed with MPH treatment. Although our study shows that MPH treatment has a curative effect on cardiac autonomic functions, further studies are needed.

Keywords: Attention deficit hyperactivity disorder, methylphenidate, heart rate variability

ÖZ

Amaç: Dikkat eksikliği ve hiperaktivite bozukluğu (DEHB) en sık görülen çocukluk çağı psikiyatrik hastalığıdır. Psikostümülan ilaçlar tedavi rejiminde sık kullanılmaktadır. İlaçların olası kardiyak yan etkileri endişe vericidir. Çalışmamızda metilfenidat (MPH) tedavisi alan DEHB hastalarında kalp hızı değişkenliği (HRV) ile olası kardiyak otonomik etkileri belirlemeyi amaçladık.

Gereç ve Yöntem: MPH tedavisi alan DEHB hastalarda HRV parametrelerindeki değişikliği ölçmek için retrospektif bir tedavi öncesi-sonrası çalışma tasarımı kullandık. DEHB tanısı alan toplam 49 hasta (ortalama yaş, 8,3±2,5 yıl) ve cinsiyet ve yaşları eşleştirilmiş 30 sağlıklı kontrol (ortalama yaş, 8,2±2,7 yıl) incelendi. Hastalara MPH tedavisi öncesi ve tedavinin birinci ayında ve kontrol grubuna 24 saat ritim Holter kayıtları yapılarak bilgisayar ortamında HRV parametreleri değerlendirildi.

Bulgular: Hasta ve kontrol grubunda yaş, cinsiyet, kilo ve boy açısından fark yoktu ($p>0,05$). Zaman bağımlı HRV paramatrelerinin analizinde hasta grupta kontrol grubuna göre sempatik etkilenmeyi gösten SDNN, SDANN ve parasempatik etkilenmeyi gösteren rMSSD istatistiksel açıdan anlamlı

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olarak daha düşüktü (p<0,05). Hastalarda tedavi öncesi ve sonrası karşılaştırıldığında SDANN istatistiksel açıdan anlamlı olarak yüksekti (p<0,05). Yine tedavi sonrasında SDNN, rMSSD de istatistiksel anlamlılık olmamakla birlikte yüksekti (p>0,05).

Sonuç: Çalışmamızda DEHB hastalarında HRV parametrelerinde artmış sempatik ve azalmış paramsempatik aktivite olduğu görüldü. MPH tedavisi ile hem sempatik hem de parasempatik iyileşme gözlendi. Çalışmamız MPH tedavisinin kardiyak otonom fonksiyonlar üzerine iyileştirici etkisi olduğunu göstermekle beraber daha ileri çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Dikkat eksikliği hiperaktivite bozukluğu, metilfenidat, kalp hızı değişkenliği

INTRODUCTION

Attention deficit and hyperactivity disorder (ADHD) is the most common neuropsychiatric disease of childhood with a rate of 9.5% in school-age children[1,2].

As ADHD causes difficulties in social and academic development in children, they also face risks such as neuropsychiatric diseases, substance abuse, and increased delinquency in adulthood[3].

The presence of hypofunction in the prefrontal cortex in the central nervous system (CNS) has been shown in the neuropathology of the disease. Different regions of the prefrontal cortex have regulatory effects on motor, sensory, behavioral and autonomic functions[4,6]. Therefore, hypofunction in the prefrontal cortex was thought to be the cause of symptoms in patients with ADHD[5,6].

The two main components of treatment are behavioral therapy and psychostimulant pharmacotherapy. Behavioral therapy is the first thing to be done, but it is often the first choice because of faster and more effective results with medical treatment[7-9]. While 50% of children with ADHD receive behavioral therapy, 75% receive psychostimulant treatment[9,10]. These drugs exert stimulating effects on the CNS by increasing the levels of norepinephrine and dopamine in the prefrontal cortex[11]. Methylphenidate (MPH) is the most used psychostimulant drug[12].

Psychostimulant drugs may cause cardiac risks such as the prolongation of cQT duration, arrhythmia and hypertension, and sudden death due to drug use has been reported[13,14]. However, this situation is controversial and some studies have not found a significant difference in terms of cardiac risks[15,16]. This may be due to the fact that the patients receiving medical treatment are children and adolescents who are cardiac healthy, and the publications are often of short duration[9]. However, in order to minimize the ultimate risks, guidelines recommend taking history, physical examination, and pre-treatment electrocardiography in evaluation[17].

Heart rate variability (HRV) in 24-hour rhythm Holter is defined as the change in heart rate from beat to beat and shows the dynamic interaction of the sinoatrial node with the autonomic nervous system (ANS)[6]. It is a simple and non-invasive method to examine the effect of ANS on the cardiovascular system (CVS)[6]. HRV is an indicator of central-peripheral neural feedback and CNS-ANS integration, and respiratory sinus arrhythmia is considered an index of cardiac vagal modulation and emotional regulation[18-20]. The standard deviation of normal sinus RR intervals (SDNN) and the standard deviation of the averages of five-minute recordings over twenty-four hours (SDANN) in the HRV analysis reflects sympathetic modulation, while the root mean square of the difference between consecutive normal RR intervals (rMSSD) and the percentage of consecutive normal sinus RR intervals that differ by more than 50 ms (pNN50) reflect parasympathetic modulation. HRV studies of ADHD show the presence of autonomic dysfunction, but the results are confusing. Although there are studies showing an increase in parasympathetic (vagal) tone, there are studies showing a decrease in vagal tone on the contrary[6,11,21].

Examination of the presence of autonomic dysfunction in children with ADHD may be useful both for a better understanding of neurobiology and for identifying patients who may be at risk for CVS[6]. As a result, treatment planning and follow-up can be done more carefully in patients at risk[6].

The aim of this study is to compare HRV with the healthy control group, assuming that children with ADHD show autonomic dysfunction, and to investigate the effect of psychostimulant MHP used in the treatment on HRV and therefore on autonomic dysfunction.

MATERIALS AND METHODS

Patients who applied to Tekirdağ Namık Kemal University Medical Hospital Child and Adolescent Psychiatry outpatient clinic for the first time between 1st of January, 2018 and 31th of December, 2020 and who were diagnosed with ADHD according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria were included in this retrospective study[22]. Forty-nine patients (38 boys and 11 girls, mean age 8.31±2.53 years, between 6-17 years of age) who were referred to the Pediatric Cardiology outpatient clinic were included. Chronic disorders of the CVS, pulmonary and/or other systems, hypertension, intolerance of MPH, not taking MPH for two days or longer, drug use affecting CVS and CNS, psychotic disorder and mental retardation were used as exclusion criteria. The study was planned on three groups. While the first group included the patients diagnosed with

ADHD before the treatment, the patients who were started on long-acting MPH therapy and evaluated in the first month of the treatment constituted the second group. The third group consisted of 30 age- and sex-matched healthy volunteers (21 boys and 9 girls, mean age 8.20±2.76 years, 6-17 years of age) who did not have any psychiatric disease, did not use drugs, and applied to the pediatric cardiology outpatient clinic due to an innocent murmur. For routine evaluation, physical examination, blood pressure, electrocardiography, and echocardiography were performed on the patient and control group. Twenty-four-hour rhythm Holter examination was performed twice, before the treatment and in the control examination in the first month of the treatment.

The patient group was assigned to one of three dose levels per day (10, 18, or 27 mg) based on long-acting MPH doses. Initial treatment of MPH was given at a dose of 0.3-0.6 mg/kg/day. In the second Holter treatment, the patients were inserted in the first month without increasing the dose. While rhythm Holter was inserted in 41 patients before the treatment, rhythm Holter control was performed in 27 patients in the first month of the treatment.

The study approval was obtained from the ethics committee of Tekirdağ Namık Kemal University non-interventional clinical studies (2021.189.06.19) and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practices (date: 12.11.2020, no: 2020/68).

Echocardiographic Studies

Echocardiographic examinations were performed using a 4V1c transducer with an ultrasound device (ACUSON SC2000, Siemens, Germany). Transthoracic echocardiography images were obtained in parasternal long-axis and short-axis images, and apical two- and four-chamber views using standard transducer positions. The following end-diastolic and end-systolic parameters were measured in parasternal long-axis view on M-mode echocardiography: interventricular septal thickness (IVSd and IVSs), LV dimensions (LVDd and LVDs), and LV posterior wall thickness (LVPWd and LVPWs) left ventricular ejection fraction (Ef) and fraction shortening (Fs).

Processing and Analysis of 24-hour Holter Recordings

While the patient and control groups continued their normal daily lives, rhythm recordings were made with a three-channel (medilogFD12 plus, Schiller, Switzerland) rhythm Holter monitor for 24 hours. All Holter recordings were reviewed by an experienced cardiologist after artifact recordings were deleted. HRV parameters were analyzed in a computer program. Physiological interpretation and measurement of HRV parameters were performed according to the standards set by the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology[23].

The time domain measurement of HRV determines the heart rate at any time point or the intervals between successive normal complexes. Each QRS complex is detected on the ECG, and then all intervals (NN/normal to normal intervals) between adjacent QRS complexes resulting from sinus node depolarization and instantaneous heart rate are determined. HRV measurements were calculated using normal-to-normal ranges only. SDNN, SDANN, SDNN index, RMSSD, NN50 and pNN50 were calculated in time-based HRV parameters. SDNN (ms): the standard deviation of the time (NN interval) between consecutive normal QRS complexes. SDANN (ms): the standard deviation of the averages of five-minute recordings over twenty-four hours. SDNN index (ms): the arithmetic mean of the standard deviations of the NN intervals of five-minute recordings over twenty-four hours. RMSSD (ms): the square root of the mean of the difference of the adjacent NN intervals in a 24-hour recording. NN50: the number of intervals in which the difference between consecutive NN intervals is greater than 50 ms. pNN50 (%): the ratio of the number of NN50 to the total number of NN intervals[23].

SDNN is used for the general evaluation of HRV, SDANN is used for the long-term evaluation of HRV and it reflects the effect of the sympathetic system on HRV, while rMSSD and pNN50 for the short-term evaluation reflect the effect of the parasympathetic system on HRV[23].

Statistical Analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) software, version 22.0 (SPSS Inc. IL, USA). Continuous data were indicated as mean±standard deviation, while categorical data were presented as the number of patients. The chi-square test was used to compare categorical variables, while parametric continuous variables were compared using the Student's t-test. Data were checked for normal distribution using the Kolmogorov-Smirnov test. The correlation between two variables was calculated using the Pearson's correlation coefficient (r) analysis of variance (F). A value of $p<0.05$ was considered statistically significant.

RESULTS

Cohort Characteristics

A total of 49 patients with ADHD (mean age was 8.3±2.5 years; 38 boys and 11 girls) and 30 healthy controls (mean age was 8.2±2.7 years; 21 boys and 9 girls) were enrolled in this study. No significant differences were found between the two groups in terms of age, sex, weight, blood pressure systole and diastole, left ventricular end-diastolic dimension and ejection fraction

Table 1. Demographic and clinical characteristics of the study population

Parameters	Patients (n=49)	Controls (n=30)	p value
Sex (male/female)	38/11	21/9	0.51
Age (year)	8.3±2.5	8.2±2.7	0.85
Weight (kg)	31.1±12.1	29.2±7.3	0.48
Height (cm)	129.4±22.2	129.5±23.4	0.72
SBP (mmHg)	92.1±10.6	91.4±11.7	0.57
DBP (mmHg)	59.4±9.9	58.8±7.6	0,48
LVDd (cm)	3.9±0.4	3.7±0.3	0.34
Ef (%)	66.7±5.2	66.5±3.3	0.83

DBP: Diastolic blood pressure, Ef: Ejection fraction, LVDd: End-diastolic left ventricular (LV) dimension, SBP: Systolic blood pressure

Table 2. Heart rate variability parameters of the study population

Parameters	Patients (n=41)	Controls (n=30)	p value
Heart rate (beats/min.)	89.2±9.3	90.1±11.9	0.75
Mean NN (ms)	676.0±70.2	668.3±86.5	0.69
SDNN (ms)	124.0±34.1	165.6±113.3	**0.04**
SDANN (ms)	77.8±18.7	109.3±58.9	**0.01**
SDANN index (ms)	86.6±29.8	120.9±67.4	0.1
rMSSD (ms)	93.6±50.2	155.3±96.2	**0.04**
NN50 (count)	25051.3±13416.4	24196.6±14295.6	0.78
pNN50 (%)	22.1±13.7	24.6±13.6	0.47

NN50: Count of number of pairs of adjacent NN intervals differing by more than 50 ms, pNN50: Number of pairs of adjacent NN intervals differing by more than 50 ms divided by the total number of all NN intervals, rMSSD: Square root of the mean of the sum of the squares of differences between adjacent NN intervals, SDANN: The standard deviation of the mean of five-minute recordings over twenty-four hours, SDNN: Standard deviation of all NN intervals, SDNN index: The arithmetic mean of the standard deviations of the NN intervals of five-minute recordings over twenty-four hours during

(p>0.05). In the patient group, the MPH dose was 0.57±0.15 mg/kg/day. Table 1 shows the characteristics of the patient and the control groups.

Heart Rate Variability Findings

Analysis of the HRV data of the groups (Table 2) did not show any significant difference between the patient and control groups in terms of heart rate, Mean NN, SDANN index, NN50 and pNN50 (p>0.05). However, SDNN, SDANN and rMSSD were significantly lower in the patient group compared to the control group (p<0.05).

When HRV parameters in ADHD patients were compared between the pre- and post-treatment groups (Table 3), there was statistically significantly higher SDANN in the post-treatment group than in the pre-treatment group (p^2<0.05). There was no difference in other HRV parameters between the two groups. In addition, when we compared the post-treatment group with the control group, there was no difference between HRV parameters (p^1>0.05).

In the correlation analysis between age and MPH dose and HRV parameters (Table 4), there was no correlation between MPH dose and HRV parameters (p>0.05), there was a negative correlation between age and heart rate and a positive correlation between age and mean NN (p<0.05).

Study Power

The power results calculated according to the effect size values found using the numerical data of SDANN, SDANN and rMSSD in the available sample size using G*Power 3.1.9.2 software were 85%, 94%, 95% for SDNN, SDANN and rMSSD in the patient-control group, respectively. In addition, the power result was 81% for SDANN in the pre- and post-treatment group.

DISCUSSION

In the treatment of ADHD, the first treatment option is often the use of psychostimulant drugs such as MPH. In recent years, there has been concern about the possible CVS side effects of psychostimulant drugs. Studies on this subject are quite confusing as to whether psychostimulant drugs have a positive or negative effect on CVS. In our study, we aimed to investigate the potential benefit-harm relationship of MPH treatment in terms of CVS risks in patients with ADHD through its effect on HRV parameters, which are indicators of autonomic system dysfunction. For this purpose, 24-hour rhythm Holter recordings were analyzed in the patients before the drug and one month after they started using the drug, and in the healthy control group. When we compared the patient and healthy control groups before the treatment, SDNN and SDANN, which showed increased sympathetic effect, and rMSSD, which showed

decreased parasympathetic effect, were significantly reduced. Again, SDNN, SDANN, and rMSSD times increased in the patient group after the treatment, which showed sympathetic and parasympathetic recovery.

In a similar study, Buchhorn et al.[17] showed that rMSSD was lower in patients compared to healthy controls, supporting the decrease in parasympathetic activity, and that there was an improvement in rMSSD with MPH treatment, but this improvement was more pronounced in night HRV recordings. Similarly, Rukmani et al.[6] found rMSSD to be lower in the patient group in their study in which they compared the patient and healthy control groups. However, treatment data were not studied. There are studies reporting the opposite result. When Carvalho et al.[24] compared the patient and healthy control groups, they found rMSSD to be high in the patient group and interpreted this as an increase in parasympathetic activity. Similar results have been demonstrated in stimulant drug studies. Negrao et al.[21] found that rMSSD, which shows an increase in parasympathetic activity, increased 3 weeks after drug discontinuation in patients using MPH for ADHD. There are studies that evaluate post-treatment period, such as evaluation after treatment discontinuation. After 12 weeks of MPH treatment, Kim et al.[23] found decreased rMSSD compared to the initial values. Available data are confusing as to whether there is an increase or decrease in vagal tone with disease. The same confusion applies to how vagal healing occurs with treatment. In a recent study by Griffiths et al.[26] with a large sample (n=229 patients), although rMSSD was lower in the patient group, there was no significant difference compared to healthy controls, while low rMSSD was associated with high anxiety and social problems. Although low vagal tone has been reported in psychopathological conditions such as depression and anxiety, the relationship between this condition and ADHD appears to be weak if depression, anxiety, and mood disorders are not accompanied[27]. This may be due to the fact that ADHD is a heterogeneous group with attention deficit, hyperactivity, combined and other psychosocial disorders[27]. On the other hand, Griffiths et al.[26] showed no difference in parasympathetic activity even in ADHD subgroups in the same study. In a study evaluating short-term memory performance, children with ADHD showed excessive vagal withdrawal. If this situation is interpreted together with the study of Buchhorn et al.[17], it can be thought that there may be a daily circadian rhythm in vagal activity. This may also explain why there is a difference in vagal HRV activity at night, while there is no difference in daily measurements[28]. In a meta-analysis of eight studies (six of which were on children), Koening et al.[27] found no evidence of parasympathetic dominance or insufficiency. In our study, rMSSD values were significantly lower in the patient group compared to the healthy controls, suggesting a decrease

Table 3. Comparison of heart rate variability before and after methylphenidate treatment in ADHD (n=27)

Parameters	Controls (n=30)	Before treatment	After treatment	p^1 value	p^2 value
Heart rate (beats/min.)	90.1±11.9	88.8±9.0	89.9±10.3	0.95	0.53
Mean NN (ms)	668.3±86.5	681.2±68.1	671.4±70.1	0.88	0.40
SDNN (ms)	165.6±113.3	129.9±37.2	138.1±55.9	0.27	0.39
SDANN (ms)	109.3±58.9	80.2±19.6	107.9±74.0	0.91	**0.05**
SDANN index (ms)	120.9±67.4	91.3±32.0	98.2±58.2	0.34	0.54
rMSSD (ms)	155.3±96.2	100.7±56.7	106.4±65.8	0.19	0.68
NN50 (count)	24196.6±14295.6	26484.2±13645.6	23778.6±10235.8	0.78	0.25
pNN50 (%)	22.1±13.7	25.2±13.2	22.7±11.3	0.85	0.21

NN50: Count of number of pairs of adjacent NN intervals differing by more than 50 ms, pNN50: Number of pairs of adjacent NN intervals differing by more than 50 ms divided by the total number of all NN intervals, rMSSD: Square root of the mean of the sum of the squares of differences between adjacent NN intervals, SDANN: The standard deviation of the mean of five-minute recordings over twenty-four hours, SDNN: Standard deviation of all NN intervals, SDNN index: The arithmetic mean of the standard deviations of the NN intervals of five-minute recordings over twenty-four hours during, ADHD: Attention deficit hyperactivity disorder

p^1; Comparison of the patient group after treatment with controls.

p^2; Comparison of the patient group before and after treatment.

Table 4. Correlation between age and MPH dose with HRV variables

Parameters	Heart rate		Mean NN		SDNN		SDANN		rMSSD		NN50	
	R	p	R	p	R	p	R	p				
Age	-0.48	**0.01<**	0.49	**<0.01**	0.48	0.69	-0.06	0.95	-0.04	0.71	0.04	0.75
MPH dose	-0.95	0.59	0.08	0.63	0.09	0.60	0.32	0.06	-0.02	0.87	0.23	0.17

p value is significant if <0.05.

NN50: Count of number of pairs of adjacent NN intervals differing by more than 50 ms, pNN50: Number of pairs of adjacent NN intervals differing by more than 50 ms divided by the total number of all NN intervals, rMSSD: Square root of the mean of the sum of the squares of differences between adjacent NN intervals, SDANN: The standard deviation of the mean of five-minute recordings over twenty-four hours, SDNN: Standard deviation of all NN intervals, SDNN index: The arithmetic mean of the standard deviations of the NN intervals of five-minute recordings over twenty-four hours during, HRV: Heart rate variability, MPH: Methylphenidate

in parasympathetic activity. At the same time, although rMSSD values did not reach normal healthy control levels after treatment with MPH, they increased and were considered as parasympathetic recovery.

Studies in ADHD are mostly focused on parasympathetic involvement, and the number of studies examining sympathetic involvement is few. Similarly, results regarding whether there is an increase or decrease in sympathetic activity are mixed. Rukmani et al.[6] found low SDNN values in the patient group in their study in which they compared patients with ADHD and healthy controls, and they evaluated this situation as sympathetic dominance. A similar result was also shown in the study of Carvalho et al.[24]. The lack of screening of other sympathetic data and inclusion of a small sample were deficiencies for both studies. On the other hand, in the study of Buchhorn et al.[17] in which they compared both before and after treatment with healthy controls, there was no difference in SDNN values. On the contrary, there are studies stating that there is sympathetic insufficiency. Negrao et al.[21] found both pre- and post-treatment SDNN values higher in patients than in the healthy group and interpreted this as sympathetic insufficiency. A similar result was also found in the study of Kim et al.[25], and SDNN decreased with treatment. However, there was no comparison of healthy controls. In our study, SDNN and SDANN values were significantly lower in the patient group compared to the healthy controls, suggesting an increase in sympathetic activity. At the same time, SDNN and SDANN values, which showed sympathetic recovery, increased after treatment with MPH, and this increase was quite close to the healthy control values, especially in SDANN.

Study Limitations

The current study has some limitations. Firstly, it was conducted with a small sample size. Then, the subtypes of the patients were not evaluated, and the HRV was not reviewed again after dose increases during treatment.

CONCLUSION

As a result, the use of MPH in ADHD has a positive effect on the autonomic system with a decrease in sympathetic activity and an increase in parasympathetic activity, and it improves CVS functions. In addition, it can be said that HRV is noninvasive, reproducible and useful for possible risk assessment during treatment. Since our study was conducted with a small sample, it cannot be generalized. However, it can be a guide for larger sample studies to be done in the future.

Ethics

Ethics Committee Approval: The study approval was obtained from the ethics committee of Tekirdağ Namık Kemal University non-interventional clinical studies (2021.189.06.19) and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practices (date: 12.11.2020, no: 2020/68).

Informed Consent: Informed consent was obtained from children and their parents.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: Ö.K., S.B., Design: Ö.K., Data Collection or Processing: Ö.K., S.B., Analysis or Interpretation: Ö.K., S.B., Literature Search: Ö.K., S.B., Writing: Ö.K.

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