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The Worrying Mystery in Children with ADHD: Autonomic Nervous System Dysregulation and Methylphenidate Use

DEHB'li Çocuklarda Endişe Verici Gizem: Otonom Sinir Sistemi Disregülasyonu ve Metilfenidat Kullanımı

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ABSTRACT

Objective: Children with attention deficit and hyperactivity disorder (ADHD) may have an increased risk of cardiovascular complications due to reduced vagal tone and increased heart rate (HR). Methylphenidate (MPH) is a frequently used drug, and its sympathomimetic effects often cause pediatricians to be concerned when making diagnostic and treatment decisions. We aimed to assess the effects of MPH on the cardiovascular system and autonomic activity of the heart using heart rate variability (HRV) in ADHD patients.

Methods: We retrospectively analyzed physical examination, blood pressure (BP), and 24-hour Holter monitoring in 33 patients (9.7±2.6 years) and 36 healthy subjects (9.54±2.8 years). The results of the examinations at the end of the first month of MPH treatment were compared with the pre-treatment findings in the patient group.

Results: Systolic and diastolic BP measurements were similar between the groups at diagnosis. The patients showed a mild increase in systolic and diastolic BP after treatment, but the differences were not statistically significant (p=0.059 and p=0.063, respectively). However, increase in heart rate and QTc duration on ECG was statistically significant in the patient group (p=0.001 and <0.001, respectively). We did not detect any significant differences in the time-domain analyses. Only the low-frequency index decreased significantly as a frequency domain parameter [871 ms2 (316.6-2198.6) vs. 788.1 ms2 (228.9-1950.3); p=0.039].

Conclusion: MPH has no significant cardiovascular side effects in ADHD. Attention should be paid when prescribing drugs that may prolong the duration of QTc; rhythm and BP should also be monitored during follow-up.

Keywords: Attention deficit and hyperactivity disorder, cardiovascular risk, variability in heart rate, methylphenidate

ÖZ

Amaç: Dikkat eksikliği ve hiperaktivite bozukluğu (DEHB) olan çocuklarda azalmış vagal tonus ve artmış kalp hızları nedeniyle kardiyovasküler komplikasyon riskinde artış gözlenebilir. Metilfenidat (MPH) sık kullanılan bir ilaçtır ve sempatomimetik etkileri çocuk doktorlarının tanı ve tedavi kararları verirken sıklıkla endişe duymalarına neden olmaktadır. Bu nedenle çalışmamızda, DEHB hastalarında kalp hızı değişkenliğini kullanarak MPH'nin kardiyovasküler sistem ve kalbin otonomik aktivitesi üzerindeki etkilerinin değerlendirmesi amaçlanmıştır.

Yöntem: Çalışmamızda 33 hasta (9,7±2,6 yıl) ve 36 sağlıklı çocuğun (9,54±2,8 yıl) fizik muayene, kan basıncı (KB) ve 24 saatlik Holter monitörizasyonu bulguları retrospektif olarak değerlendirilmiştir. Ayrıca, MPH tedavisinin birinci ayının sonundaki bulgular hasta grubunda tedavi öncesi bulgularla karşılaştırılmıştır.

Bulgular: Tanı anında sistolik ve diyastolik KB ölçümleri gruplar arasında benzerdi. Hastalarda tedavi sonrasında sistolik ve diyastolik KB'de hafif bir artış görüldü ancak istatistiksel olarak anlamlı değildi

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(sırasıyla p=0,059 ve p=0,063). Ancak, hasta grubunun kalp hızı ve QTc süresindeki artış istatistiksel olarak anlamlıydı (sırasıyla p=0,001 ve p<0,001). Zaman alanı analizlerinde anlamlı bir fark tespit edilmedi. Frekans alanı parametresi olarak sadece düşük frekans indeksi anlamlı şekilde azaldığı görüldü [871 ms^2 (316,6-2198,6) vs. 788,1 ms^2 (228,9-1950,3); p=0,039].

Sonuç: MPH tedavisinin DEHB tedavisinde önemli majör bir kardiyovasküler yan etkisi olmadığı gösterilmiştir. İlacın QTc süresini uzatabilecek diğer ilaçlarla birlikte reçete edilirken dikkat edilmesi gerekliliği; tedavi süresince ritim ve KB değerlerinin izlemi önerilmektedir.

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

INTRODUCTION

Attention deficit and hyperactivity disorder (ADHD) is a neurobiological syndrome that affects approximately 5% of school-age children and often persists into adulthood.[1-5] It is more common in boys and is characterized by increased activity, an inability to concentrate, and poor school performance.[6,7]

ADHD is one of the most common psychiatric disorders in children and is also one of the most common challenges that pediatricians face during outpatient visits for various reasons (prescribing certain antibiotics or antihistamines, screening of athletes, pre-operative screening, etc.). In light of previous studies, children with ADHD might have an increased baseline risk of cardiovascular complications due to decreased vagal tone and increased heart rates (HR).[1,8,9] In addition, methylphenidate (MPH), which is the drug of choice worldwide for patients with ADHD, is also of concern to pediatricians due to its sympathomimetic effects. It has been reported that the sympathomimetic (noradrenergic and dopaminergic) effects of MPH may cause increases in systolic and diastolic blood pressure (BP) and HR, QTc prolongation, arrhythmias, and even sudden death.[10,11] Conversely, cardiovascular side effects are primarily transient, dose-dependent, and easily rectified with dosage adjustments.[6] In addition, they are considered minor from a clinical perspective, considering the level of improvement in behavior and cognitive functioning observed in most children. The primary evaluation of these patients for screening for possible adverse effects of MPH treatment involves an investigation of cardiac symptoms, physical examination, electrocardiogram (ECG), measurement of QTc duration and BP, and a detailed family history.

HR variability (HRV) is the degree of variation in the beat-to-beat differences in heart rhythm. It is a non-invasive marker of autonomic nervous system (ANS) activity based on the dynamic interplay of sympathetic and parasympathetic inputs to the sinus node.[12] High HRV indicates adaptability to environmental and physiological demands and low HRV indicates autonomic dysfunction. A sympathovagal imbalance, which is characterized by a decrease in vagal activity or an increase in sympathetic activity, is a marker of cardiovascular morbidity.[13,14] There is controversy regarding the sympathovagal imbalance in patients with ADHD, as illustrated by HRV in previous studies.[1,9,15-17] In the present study, we aimed to assess the effects of MPH treatment on the cardiovascular system and autonomic activity of the heart using HRV analysis in this patient group.

METHODS

This retrospective study evaluated 33 patients (24 males) and 36 healthy controls (21 males) using our hospital's computerized database. The patient group consisted of patients referred to the pediatric cardiology department for baseline evaluation with a diagnosis of ADHD on the criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; American Psychiatric Association 2013. We analyzed the results of physical examination, systolic and diastolic BP measurements, ECG, and 24-hour Holter monitoring in all patients and the control group. In addition, the results of physical examination, ECG, and 24-hour Holter monitoring at the end of the first month of MPH treatment were compared with the pre-treatment findings in the patient group. Subjects with congenital heart defects, dysrhythmia, systemic illness, hypothyroidism, or hyperthyroidism were excluded from the study. The confidentiality of the information was assured, and no incentives or inducements were offered to participants during the study. The study was approved by the Ankara Child Health and Diseases Oncology Training and Research Hospital Clinical Research Ethics Committee (protocol no: 2013/059, date: 22.10.2013).

QTc Interval Measurements

All standard 12-lead ECGs were acquired simultaneously at a paper speed of 25 mm/s and standardized to 1 mV/cm (0.08-35 Hz, 500 sps) using the same recorder (MAC 400; GE Medical Systems, Milwaukee, WI, USA). The ECG recordings were analyzed by a single investigator in a blinded manner. QTc intervals were measured manually using calipers to improve accuracy. QT was defined as the time from the onset of the QRS complex to the end of the T-wave, with a return to the isoelectric line. In the presence of U waves, the offset of the T wave was defined as the nadir between the T and U waves. If it was not possible to identify the end of the T wave, the lead was ruled out. Three successive QT intervals were measured, and the average was calculated for each lead.

24-h Holter Monitoring

The 24-hour Holter recordings were performed using a three-channel DMS 300-3 A Holter system (DM Software, Inc., Stateline, NV, USA). HRV analysis was based on changes in consecutive RR intervals, where measurements were performed dynamically on 24-h recordings. Abnormal beats and artifact areas were rejected. Recordings less than 18 h and those with significant arrhythmias were excluded to avoid effects caused by circadian variation in HRV. HRV was measured by calculating the time and frequency domain indices from 24-h recordings. The same qualified cardiologist carefully analyzed the Holter ECGs. Measurements of HRV were performed using only normal-to-normal intervals according to the standards of the Task Force of the European Society of Cardiology and the American Society of Pacing and Electrophysiology.[14]

The time domain indices of HRV were examined as follows: standard deviation of all normal sinus R-R intervals (SDNN); mean of the standard deviations of all normal sinus R-R intervals for all 5-minute segments of the entire recording (SDNNI); standard deviation of the averages of R-R intervals in all 5-minute segments of the entire recording (SDANN); square root of the mean of the sum of square differences between adjacent filtered RR intervals (rMSSD); and percentage of the difference between adjacent RR intervals greater than 50 milliseconds for the whole period of analysis (PNN50). Although rMSSD and pNN50 primarily reflect parasympathetically mediated changes in HR, other time domain variables reflect a mixture of parasympathetic, sympathetic, and other physiological influences.

Frequency domain analysis was performed on 300-s segments selected at the time of lowest HR during the entire recording period and free of abnormal data. We determined the spectral power over three frequency regions of interest: VLF, very low-frequency index (0.017-0.05 Hz range); LF, low-frequency index (0.05-0.15 Hz range); HF, high-frequency index (0.15-0.50 Hz range). We also determined the total power (all frequencies greater than 0.017 Hz) and LF/HF ratio. HF reflects cardiac vagal activity, and LF is affected by both the vagal and sympathetic systems. LF/HF is an indicative parameter for assessing autonomic balance.

Statistical Analysis

Results were analyzed using commercial statistical software [Statistical Package for the Social Sciences (SPSS) for Windows, version 21.0; SPSS Inc, Chicago, IL, USA]. Continuous variables are presented as mean (standard deviation) or median (minimum-maximum), where appropriate, and categorical variables are presented as numbers (%). Continuous variables were compared between groups using Student's t-test or Mann-Whitney U test, depending on whether they were normally distributed or otherwise, as tested using the Shapiro-Wilk test. Statistics obtained by Wilcoxon signed rank test or Paired samples t-test for dependent variables. A value of $p<0.05$ was considered statistically significant.

RESULTS

We studied 33 children diagnosed with ADHD (24 boys, 9 girls) and 36 healthy children (21 boys, 15 girls) with a similar gender distribution (p=0.317). The mean ages of the patient and control groups were 9.72.6± and 9.542.8± years, respectively (p=0.75) (Table 1).

HR, QTc duration, and systolic and diastolic BP measurements were not significantly different between the control and patient groups at diagnosis (p=0.71, p=0.314, p=0.597, and p=0.646, respectively). After MPH treatment, the patients' systolic and diastolic BP slightly increased, but this was not statistically significant (p=0.059, p=0.063, respectively) (Table 1). However, the HR and QTc duration increase was statistically significant in the patient group (p=0.001, p<0.001, respectively). HR increased from 87±12 beats/min to 96±15 beats/min; QTc duration increased from 387±15 msec to 416±22 msec at the end of 1st month of MPH treatment. No patients required discontinuation

Table 1. Descriptive and clinical data of the patient and control groups

	Controls (n=36)	Pre-treatment (n=33)	Value	p	After treatment (n=33)	t value	p¥
Age	9.5±2.8	9.7±2.6	-0.264	0.793	N/A	N/A	N/A
Male (%)	21 (58.3)	24 (72.7)	1.002*	0.317	N/A	N/A	N/A
Heart rate (min^{-1})	92±14	87±12	-1.833	0.71	96±15	-3.598	**0.001**
QTc (ms)	391±19	387±15	-1.015	0.314	416±22	-7.820	**<0.001**
Systolic blood pressure (mmHg)	103±15	99±14	-0.532	0.597	107±13	-1.960	0.059
Diastolic blood pressure (mmHg)	61±10	60±11	-0.462	0.646	65±7	-1.924	0.063

*Chi-square value. Other values in this column indicate t-values; ¥Comparison of patient group before and after treatment.
BP: Blood pressure, N/A: Not applicable

of MPH treatment due to significant cardiovascular complaints or drug-related dysrhythmia.

24-h Holter monitoring revealed similar minimal, maximal, and average HRs between the patient and control groups upon diagnosis (p=0.849, p=0.777, and p=0.763, respectively). However, there was a slight but statistically significant increase in the average HR after MPH treatment in the patient group (p=0.044). Although rare supraventricular extrasystoles were observed in 5 patients and rare ventricular extrasystoles in 2 patients on pre-treatment Holter monitoring, similar findings were observed after MPH treatment in the patient group. In the control group, rare supraventricular extrasystoles were noted in 3 children. HRV analyses revealed no statistically significant difference between the time and frequency domain indices between the control subjects and patients with ADHD (Table 2). Similarly, these parameters were not different between the control subjects and patients in the first month of treatment. RMMSD, pNN50, and HF, which reflect predominantly parasympathetic activity in the heart, were slightly higher in the patient group than in the healthy controls before MPH treatment (p>0.05). After the first month of medical treatment, no significant difference was observed in the time domain analyses. However, only LF decreased significantly as a frequency domain parameter (993.2±510 ms^2 vs. 875.1±434 ms^2, p=0.039).

DISCUSSION

Although the exact mechanism of ADHD has not been completely understood, it is suggested that a genetic imbalance in catecholamine metabolism in the cerebral cortex and ANS dysregulation may play a primary role. However, reports regarding the imbalance between vagal tonus and sympathetic activity in ADHD are confusing.[1,9,18-20] In addition, several factors, including the social environment, chemicals, drugs, nutrition, and some neuro-metabolic disorders, may contribute to disease development.[5]

Inattention, hyperactivity, and emotional and behavioral abnormalities are the clinical characteristics of ADHD. The symptoms are associated with serious cognitive, academic, and social problems in affected children. It has been suggested that reduced function of the prefrontal cortex plays a significant role in the occurrence of these findings in patients with ADHD.[6] Different parts of the prefrontal cortex are responsible for various functions, including higher-order autonomic control. According to various neuropsychological and neuroimaging studies, an alteration in these functions is believed to be the neurobiological basis for the symptoms observed in ADHD patients.[21] Furthermore, it has been suggested that characteristic symptoms of ADHD reflect impairment in emotional self-regulation, which the ANS predominantly regulates.[13] Thus, it is reasonable to expect dysregulation of

Table 2. Comparison of the time- and frequency-domain HRV parameters between the patient and control groups

	Controls (n=36)	Pre-treatment (n=33)	Value	p	After treatment (n=33)	Value	p¥
Maximum HR (min^{-1})	166±17	165±12	0.285	0.777	170±14	0.285	0.077
Minimum HR (min^{-1})	51±6	52±6	-0.191	0.849	52±7	-0.191	0.586
Average HR (min^{-1})	90±12	89±9	0.303	0.763	91±9	0.303	**0.044**
SDNN (ms)	131.5±43.1	137.1±33.5	-0.601	0.550	133.7±36.5	-0.601	0.353
SDANN (ms)	112.4±41.4	121.7±32.7	-1.034	0.305	120.2±38.6	-1.034	0.737
SDNN index (ms)	64.5±19.7	65.8±18.1	-0.295	0.769	63.2±18	-0.295	0.086
RMSSD (ms)	43 (18-87)	45 (15-93)	-0.557	0.580	43 (12-97)	-0.557	0.608
PNN50 (%)	18.4±10.7	19.1±10.3	-0.278	0.782	19.2±12	-0.278	0.963
Total power (ms^2)	3881.5 (790.3-11880)	3903.1 (1070.4-10129.9)	-0.432*	0.665	3661.2 (958.9-7943)	-1.706*	0.088
VLF (ms^2)	2392.4 (450.5-8804.4)	2367.2 (694-6933)	-0.372*	0.710	2412.9 (603.7-5476.6)	-1.867*	0.062
LF (ms^2)	892.8±464	993.2±510	-0.857	0.395	875.1±434	2.150	**0.039**
HF (ms^2)	568.1±293.3	657.1±384.1	-1.075	0.286	619.6±367.1	-1.075	0.352
LF/HF	1.7 (0.9-2.8)	1.5 (0.9-5.9)	-0.877	0.384	1.5 (0.9-6.45)	-0.877	0.372

*Z-value. Other values in this column indicate t-values. ¥Comparison of patient group before and after treatment.

HR: Heart rate, SDNN: Standard deviation of all NN intervals, SDANN: Standard deviation of all 5-minute NN intervals, rMSSD: Square root of the mean of the sum of squares of differences between adjacent NN intervals, PNN50: Percentage of the difference between adjacent RR intervals that was greater than 50 milliseconds for the whole period of analysis, VLF: Very low frequency, LF: Low frequency, HF: High frequency, LF/HF: Low frequency/high frequency

cardiac autonomic functions. Most efforts to assess these effects in these patients are accomplished by evaluating autonomic regulation.

HRV, the beat-to-beat variation of HR, is a simple and noninvasive method for evaluating the effect of ANS on sinus nodes. Lower HRV due to sympathovagal imbalance is associated with cardiovascular morbidity, whereas higher HRV reflects good adaptability to environmental and physiological demands. It can be measured using continuous ECG, which provides information about the autonomic balance.[9,14]

MPH is one of the most preferred psychostimulants for the treatment of patients with ADHD.[6,8,11,22-25] The potential cardiovascular side effects of MPH due to its sympathomimetic effects have been a major concern for treatment. However, MPH treatment is highly effective in relieving symptoms and increasing school success, and data from clinical trials can guide the concerns of physicians and families.

In our study, contrary to previous studies, no significant difference was found between children with ADHD and healthy controls regarding the ANS indices obtained using HRV. 24-h Holter monitoring showed a slight but significant increase in average HR after MPH treatment in the patient group. Although LF decreased significantly after the first month of MPH treatment in the patient group, the clinical value of this finding should be assessed.

Buchhorn et al.[1] revealed that MPH treatment caused a significant decrease in circadian HR and increased the expression of markers reflecting vagal tone, sNN50, and rMSSD in 24-h Holter recordings. Similar findings were reported in another study using a different methodology: 5-min Holter ECG recordings from a 12-week prospective study. A meta-analysis by Robe et al.[18] concluded that the findings provide evidence for associations between ADHD and autonomic dysregulation. However, another meta-analysis presented a conflicting result. Koenig et al.[19] found no differences in short-term measures of vagally-mediated HRV, and concluded that ADHD is not associated with altered resting-state vagal tone, unlike other psychiatric disorders.

In 2006, the U.S. the Food and Drug Administration added a black box warning that stimulants may cause severe cardiovascular effects, such as increased BP and HR, severe cardiac arrhythmias, and even sudden death. However, MPH remains the treatment choice for children with ADHD, and several reports have reported conflicting results regarding side effects.[23,24] Our 24-h Holter monitoring revealed that minimal HR, maximal HR, and HRV indices reflecting sympathetic and parasympathetic influences were similar between patients and controls. In addition, we did not observe any cardiovascular side effects during treatment.

Another concern for pediatricians and child psychiatrists is the increase in BP during MPH treatment in children with ADHD. In our study, a slight increase in systolic and diastolic BP was observed in the MPH-treated patient group; however, this increase was neither statistically significant nor exceeded the 95th percentile. Although this sympathomimetic drug has the potential to cause systemic hypertension, the risk does not appear to be significant at therapeutic doses.[10,20,25] Finding et al.[20] examined the cardiovascular effects of MPH and Adderall in a clinic-based group of youth with ADHD. They found that the short-term cardiovascular effects of both drugs were modest, without any significant changes in the cardiovascular measurements. Buitelaar et al.[25] and Bhat et al.[26] reported statistically significant increases in systolic and diastolic BP 45 min after MPH administration during the daytime without any clinical symptoms. These clinically insignificant differences may be attributable to differences in the design of the studies and the number or age of subjects. Furthermore, Schelleman et al.[23] investigated cardiovascular events and mortality in children exposed to and unexposed to ADHD agents. They reported that the rate of cardiovascular events in exposed children was very low and generally not higher than that in unexposed control subjects.

Study Limitations

Our study has several limitations. First, the study has a retrospective design. Second, the number of patients in the trial was relatively small, possibly affecting the power of the study. Third, BP was measured at outpatient visits, and 24-h BP monitoring was not performed. However, we repeated the BP measurements to rule out white-coat hypertension in cases of abnormal results. Finally, medication adherence could not be checked because the patients were followed up at outpatient visits. We continued medication according to the parents' reports and excluded patients who were not adequately adherent to MPH treatment.

CONCLUSION

Children with ADHD are prevalent worldwide, and pediatricians and child psychiatrists often encounter these patients during their daily work. Although recent pediatric data demonstrate the efficacy and safety of MPH treatment, physicians still have concerns when making diagnostic and treatment decisions. This study supports the contemporary outcomes that MPH had no significant cardiovascular effects in children with ADHD, except for an increase in HR and prolongation of QTc duration. Drugs that may prolong QTc interval should be prescribed, and

rhythm and BP should be monitored regularly in patients receiving sympathomimetic agents.

Ethics

Ethics Committee Approval: The study was approved by the Ankara Child Health and Diseases Oncology Training and Research Hospital Clinical Research Ethics Committee (protocol no: 2013/059, date: 22.10.2013).

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: Ö.T., A.K., Concept: Ö.T., A.K., Design: Ö.T., A.K., Data Collection or Processing: Ö.T., A.K., Analysis or Interpretation: Ö.T., A.K., Literature Search: Ö.T., A.K., Writing: Ö.T.

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