Cardiology in the Young

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The effect of long-term use of methylphenidate on cardiac autonomic functions and ventricular arrhythmogenesis: a prospective case–control study

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Abstract

Objective: We aimed to assess cardiac autonomic balance with heart rate variability by using 24-hour Holter electrocardiography and also to assess susceptibility to ventricular arrhythmias by using microvolt T wave alternance in children with attention deficit hyperactivity disorder. *Method:* This study was conducted with age- and gender-matched groups of 40 patients taking long-acting methylphenidate for more than a year and 55 healthy controls. Heart rate variability analysis for cardiac autonomic functions and microvolt T wave alternance measurements for susceptibility to ventricular arrhythmias were evaluated by 24-hour Holter electrocardiography. *Results:* The mean age 10.9 ± 2.7 years, mean duration of therapy 22.76 months, and mean methylphenidate doses were 37.64 mg/day. The study group had considerably higher rMSSD, higher HF, and a lower LF/HF ratio (respectively, $p : 0.02$, $p : 0.001$ and $p : 0.01$). While parasympathetic activity parameters were elevated, sympathetic activity parameters were low during the sleep period. Increase in the microvolt T wave alternance values of the study group was not found to be statistically significant ($p > 0.05$). *Conclusion:* In children taking long-acting methylphenidate, the autonomic balance was shown to be in favour of the parasympathetic system. Determination of the vulnerability to life-threatening ventricular arrhythmias has been evaluated for the first time in children with attention deficit hyperactivity disorder. Accordingly, microvolt T-wave alternance values give the notion that drug use is safe.

Attention deficit hyperactivity disorder is a neurodevelopmental condition marked by persistent symptoms of inattention, hyperactivity, and/or impulsivity. Worldwide prevalence of attention deficit hyperactivity disorder among children and adolescents is about 5–12%.[1,2]

A healthy individual's heart rate fluctuates continuously as a result of interactions between sympathetic and parasympathetic nerves, thus preserving somatic homeostasis. Some researchers believe that attention deficit hyperactivity disorder may be caused by problems with certain chemicals in the brain called catecholamines. It has been claimed that children with attention deficit hyperactivity disorder have an underactive sympathetic nervous system.[3,4]

Methylphenidate is one of the most often prescribed drugs for treating attention deficit hyperactivity disorder. Heart rate variability is a straightforward and non-invasive tool for assessing the autonomic nervous system.[5–7] To assess the relationship between microvolt T-wave alternance and ventricular arrhythmias, we examined electrocardiography parameters and findings from 24-hour Holter electrocardiography data in attention deficit hyperactivity disorder patients. Several large-scale investigations have identified microvolt T-wave alternans as an independent risk factor for sudden cardiac death and ventricular arrhythmia.[8,9] Basal regulation of heart activity by the autonomic nervous system is one potential factor modulating cardiovascular side effects of stimulants, and altered vagal and sympathetic activation levels were reported for children affected by attention deficit hyperactivity disorder.[10] Little data on the interplay between the autonomic nervous system and stimulant medication is available. Our aim was to measure microvolt T-wave alternance in order to predict ventricular arrhythmias and to evaluate the sympatovagal balance in attention deficit hyperactivity disorder patients who had been taking long-acting methylphenidate for at least 1 year.

Methods

Participants

The study included 40 children with attention deficit hyperactivity disorder and 55 age–gender-matched healthy children as the control group. All of the children with attention deficit hyperactivity disorder were using long acting methylphenidate regularly for at least 1 year. A child and adolescent psychiatrist examined children with attention deficit hyperactivity disorder between the ages of 10 and 14 to confirm the diagnosis based on DSM-5 criteria.[11] The control group were the children who were attending the paediatric cardiology clinics of Kütahya University Hospital. Children with any cardiac disease and with a history of drug use that could prolong QT intervals (antihistamines, betamimetics, etc.), electrolyte disorder, and hypothyroidism were excluded. Children who used other psychotropic medications such as antipsychotics, antidepressants, anxiolytics, hypnotics, and mood stabilisers were excluded from the study. Other exclusion criteria were having a chronic cardiac disease, using any drug, other major psychiatric disorders like schizophrenia and intellectual disability.

A socio-demographic form including age, gender, methylphenidate use, and dose was used to collect information on these parameters. All of the socio-demographic forms were filled by parents of children after psychiatric examination. Verbal assent and written consent were taken from all subjects and their families.

Heart rate variability

Using 24-hour Holter electrocardiogram (CardioTrak HolterSystem Version 1.4.1.3) was utilised for both data gathering and heart rate variability analysis for autonomic modulation of cardiovagal function. The heart rate variability parameters were measured and interpreted physiologically in accordance with the guidelines of the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology.[12] Time and frequency domains were utilised to categorise the heart rate variability evaluation parameters. In the time domain, the SDNN, which is the standard deviation (in milliseconds) of the normal-to-normal sinus node-initiated R–R intervals, was used to estimate the long-term parts of the heart rate variability. Statistical measurements were used to find the square root of the mean squared differences of successive normal-to-normal intervals (rMSSD).[13] As recommended by the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, short-term recordings of 5 minutes were binned into the following frequency bands: low frequency (0.05–0.15 Hz) and high frequency (0.16–0.40 Hz) components. Low frequency and high frequency power were initially recorded as absolute levels in this investigation. The total power and ratio of low frequency to high frequency (LF/HF) were derived using the absolute values of low frequency and high frequency power as single-number estimates, which are considered to indicate simultaneous modulating effects on the sympathetic and vagal systems. Since the absolute values of total power, low frequency and high frequency power were skewed, the power densities were adjusted by taking their natural logarithms in order to enable parametric statistical comparisons assuming normal distributions. The rMSSD, pNN50, and heart rate mostly represent changes in vagal tone. In addition to cholinergic and adrenergic activity, the SDNN is also impacted by other physiological inputs.

Assessing microvolt T wave alternans by using 24-hour holter recordings

In the overall sample of 95 children, 40 attention deficit hyperactivity disorder children were medicated with methylphenidate, and 55 healthy children's recordings were taken by using 24-hour electrocardiography for statistical analysis. As well as, using the time domain modified moving average approach, T wave variations in the three channels of a 24-hour Holter electrocardiography were studied. The highest T-wave alternance voltage was automatically determined from modified leads DII, V5, and V6 when the heart rate was less than 160 beats per minute.[14] When data analysis was unable due to noisy data or artifacts, corrections were made manually. The channel with the highest mean value observed on the screen was chosen and recorded.

Statistical examination

To analyse the gathered data SPSS 22.0 (IBM Corporation, Armonk, New York, United States) was used. The Kolmogorov–Smirnow test was performed to determine the conformity of the data to normal distribution. Independent-samples T and Mann–Whitney U tests were carried out to compare the study group and healthy children. A paired sample T test and Wilcoxon Signed-rank test were employed to calculate heart rate variability parameters to compare the difference between asleep and awake time in the study group. The data were analysed at a 95% confidence level and considered statistically significant at a significance level of 0.05.

Results

Patients' demographic characteristics

The study group consisted of 40 children (mean age: 10.9 ± 2.7 years, 13 female, 27 male) with ADHD who applied to an outpatient child psychiatric clinic and used long-acting methylphenidate for at least one year. In the control group, 55 healthy children (mean age: 10.3 ± 3.7, 18 female, 37 male) who presented to the cardiac outpatient clinic with the complaint of palpitations and who were followed up with a Holter electrocardiography for 24 hours without an underlying pathology are included. Duration of therapy (mean, maximum–minimum) 22.76, 12–60 and methylphenidate dosage mg/day (mean, maximum- minimum) 37.64, 10–84. There was no statistical difference in mean age or distribution of ages between patient and healthy children ($p > 0.05$) (Table 1).

Analysis of 24-hour Holter electrocardiography

Mean heart rate was significantly lower in the study group rather than the control group (Table 1). All 24-h time and frequency domain indexes were higher in the patient group than healthy subjects except pNN50; however, only rMSSD, HF, LF/HF in the patient group were found to be statistically higher than the control group. In the study group, microvolt T wave alternans was 63.6 ± 23.9 μV, whereas the microvolt T wave alternance in the control group was 56.7 ± 18.7 μV. Increase in the microvolt T wave alternance values of the study group was not found to be statistically significant ($P > 0.05$) (Table 2). During asleep period, while parasympathetic activity parameters were elevated, sympathetic activity parameters were low (Table 3).

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Table 1. Demographic characteristics and heart rate parameters of the patients and controls.

Parameters	Study group (n:40)	Control group (n:55)	p
Age, years	10.9 ± 2.7	10.3 ± 3.7	0.43
Sex, female/male	12/27	19/37	0.74
Duration of therapy, months (mean, max-min)	22.76, 12–60		
Methylphenidate dosage, mg/day (mean, max-min)	37.64, 10–84		
Minimum heart rate, bpm (mean±SD)	51.7 ± 7.6	51.1 ± 7.7	0.71
Maximum heart rate, bpm (mean±SD)	170.1 ± 17.1	166.2 ± 19.7	0.33
Mean heart rate, bpm (mean±SD)	88.3 ± 11.2	93.2 ± 9.6	0.04

Table 2. Comparison of the 24 hours time- and freguency-domain heart rate variability (HRV) parameters and microvolt T-wave alternans.

HRV parameters	Study group (n:40)	Control group (n:55)	p
SDNN, ms	142.7 ± 31.7	138.4 ± 45.2	0.61
SDNNi, ms	70.9 ± 25.1	65.2 ± 20.9	0.23
SDANN, ms	123.8 ± 31.3	119.8 ± 42.3	0.62
rMSSD, ms	56.9 ± 34.1	44.2 ± 18.1	0.02
pNN50, %	19.1 ± 14.4	19.7 ± 12.5	0.82
TP, ms^2	4164 (4216)*	3904 (2316)*	0.67
LF, ms^2	1048 (1162)*	776 (598)*	0.09
HF, ms^2	1101 (1602)*	487 (439)*	0.001
LF/HF	1.36 ± 0.83	1.76 ± 0.7	0.01
Microvolt T Wave Alternans (μV)	63.6 ± 23.9	56.7 ± 18.7	0.14

*Data are given as median (interquartile range).

Discussion

Autonomic nervous system dysregulation has been proposed as an important factor in the mechanism of. The autonomic nervous system mainly has two branches as sympathetic and parasympathetic nervous systems which innervate and work together with every organ and this interaction is essential to maintain homeostasis of the body.

Autonomic nervous system plays an essential role in modulating physiological arousal to meet environmental changes. In mental disorders such as attention deficit hyperactivity disorder, the psychological state can influence the autonomic nervous control of the heart. Thus, heart rate variability indices, which allow us to measure sympathovagal balance, can reflect the sympathovagal balance in patients with attention deficit hyperactivity disorder.[15] Although some contradictory results, previous studies showed that patients with attention deficit hyperactivity disorder have higher LF/HF ratio and higher rMSDD and HF indices[16]. Methylphenidate is the most commonly preferred drug in the treatment of attention deficit hyperactivity disorder. Studies regarding the effect of methylphenidate, especially long-acting methylphenidate, on the heart rate variability indices are scarce. And they mainly investigated the short-term effects of methylphenidate on these indices[17]. Our study is the first to investigate the long-term effect of long-acting methylphenidate on heart rate variability, especially during awake and asleep periods. In a study, Negrao et al. showed that methylphenidate shifted the autonomic balance towards the normal levels in a short period time with 10 days usage of methylphenidate.[18] In an another study, Kim et al. showed decrease in high frequency value and rMSSD which is known as vagus-mediated of the heart compared to controls within 12 weeks.[17] This study did not show any change in other heart rate variability parameters. In contrast to studies of Negra and Kim et al., we found significantly increased rMSSD, low frequency, high frequency, and decreased LF/HF ratio compared to controls.[17,18] Also, we revealed that heart rate variability parameters increased in asleep period which we would expected to reduced with methylphenidate treatment. Our results may reveal that the effect of methylphenidate can be tolerated and reduced with overtime especially with long-term methylphenidate treatment as reported before.[19] Thus, these patients can be followed-up periodically with heart rate variability parameters in terms of development of drug tolerance. Although methylphenidate is considered safe and effective, some suspicions regarding the adverse cardiac side effects still exist. Methylphenidate may cause increases in blood pressure, arrhythmia, and even sudden cardiac death.[10] Among these side effects, especially ventricular arrhythmias are the major concern for clinicians who prescribe methylphenidate. Therefore most, of the patients with attention deficit hyperactivity disorder are sent to paediatric cardiology clinics for evaluation in terms of the arrhythmias before starting the medication. Some electrocardiographic surrogate markers such as QT and QTc dispersion which are related to tendency to ventricular arrhythmias have been evaluated in attention deficit hyperactivity disorder patients before and after methylphenidate treatment. Most of these studies concluded that methylphenidate does not have any adverse effect on the ventricular depolarisation parameters.

In recent years, some repolarisation parameters such as Tp-e interval and Tp-e/QT ratios have been evaluated in attention deficit hyperactivity disorder patients before and after methylphenidate treatment.[20] However, these studies did not follow up patients prospectively with 24-hour ECG recordings or did not evaluate the patients with electrophysiological testing.

Microvolt T-wave alternance has been found to be an important independent risk factor for ventricular arrhythmias and sudden cardiac death. Although there is no commonly accepted normal range for microvolt T-wave alternans in children. In a study, Makarov and Komoliatova found that microvolt T-wave alternans value is independent from age, gender and heart rate in healthy children. In 94% healthy children, microvolt T-wave alternans do not exceed 55 μV. However, 20–50% of children with cardiac pathology had microvolt T-wave alternans more than 55 μV. Additionally, they found that in diseases with life-threatening arrhythmias associated with night circadian type of T-wave alternans was more than 55 μV[14]. In another study, Doksoz et al. reported that patients with repaired tetralogy of Fallot have mean 95.5 μV microvolt T-wave alternans value compared to healthy controls (mean microvolt T-wave alternans value 55.5 μV).[21] Unlike QT, QTc dispersion and Tp-e interval, Tp-e/QT ratio, microvolt T-wave alternans have not been studied in children with attention deficit hyperactivity disorder who were treated with

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Table 3. Comparison of the awake time- and freguency-domain heart rate variability (HRV) parameters with the asleep time- and freguency-domain HRV parameters in the study group.

HRV parameters	Awake	Asleep	p
SDNN, ms	82.4 ± 26.2	120.5 ± 35.2	0.001
SDNNi, ms	60.2 ± 24.6	79.7 ± 34.5	0.001
SDANN, ms	52.6 ± 16.7	64.2 ± 26.8	0.02
rMSSD, ms	42.7 ± 33	72.7 ± 47.5	< 0.001
pNN50, %	7.4 (19.6)*	27.3 (34.2)*	< 0.001
TP, ms^2	1752 (2138)*	3559 (4678)*	< 0.001
LF, ms^2	584 (746)*	871 (1150)*	0.02
HF, ms^2	336 (722)*	1254 (1811)*	< 0.001
LF/HF	1.72 (1.52)*	0.82 (1.77)*	0.02

*Data are given as median (interquartile range).

methylphenidate before. In our study, we found that microvolt T-wave alternans value is increased in methylphenidate patients compared to controls. However, this increase did not reach statistically significant. Therefore, we may conclude that methylphenidate treatment is generally safe in terms of arrhythmias, which is a major concern about long-term treatment.

Our study has some limitations that should be considered, first a relatively small sample, second we did not evaluate the patients before and after the methylphenidate treatment, third we did not evaluate the patients with invasive electrophysiological testing with regards to ventricular arrhythmia.

In conclusion, our study results in terms of heart rate variability measures which reflect the cardiac autonomic balance revealed some contradictory results compared to previously reported studies in patients treated with methylphenidate.The first of these is that long-term usage of methylphenidate may lead to tolerance. Thus, our study may be a starting point to shed light on to follow-up the patients with long-term methylphenidate treatment. Another one is different from the common notion, generally methylphenidate does not lead to ventricular arrhythmias in these patients. Our study is the first to evaluate the effect of long-term use of methylphenidate in assessing the cardiac autonomic balance and tendency to ventricular arrhythmias in patients with attention deficit hyperactivity disorder. Patients who are treated with long-term methylphenidate should be monitored periodically with 24-hour ECG Holter recording to evaluate the heart rate variability for development drug tolerance and tendency for ventricular arrhythmias. Due to some limitations of our studies, further studies with large sample size and longer follow-up periods are needed to support these results.

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Conflict of interest. None.

Ethics approval. The authors assert that all procedures contributing to this work comply with the ethical standards of the national guidelines on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008, and have been approved by Dumlupinar University Clinical Researches Ethics Committee (2019-9/21). A written informed consent was taken from all participants and their legal guardians.

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